

Antimicrobial Resistance Benchmark 2020



access to
medicine
FOUNDATION



ACKNOWLEDGEMENTS

The Access to Medicine Foundation would like to thank the following people and organisations for their contributions to this report.¹

FUNDERS

The Antimicrobial Resistance Benchmark research programme is made possible with financial support from UK AID and the Dutch Ministry of Health, Welfare and Sport.



Ministry of Health, Welfare and Sport

Expert Review Committee

Hans Hogerzeil - *Chair*
 Gregory Frank
 Nina Grundmann
 Magdalena Kettis
 Joakim Larsson
 Marc Mendelson
 Margareth Ndomondo-Sigonda
 Katarina Nedog
 Sarah Paulin (Observer)
 Andrew Singer

Research Team

Gabrielle Breugelmans
 Fatema Rafiqi
 Adrián Alonso Ruiz
 Ruth Baron
 Dulce Calçada
 Moska Hellamand

Reviewers

Christine Årdal
 Karen Gallant
 Hans Hogerzeil
 Hitesh Hurkchand
 Joakim Larsson
 Marc Mendelson
 Kevin Outtersen

Editorial Team

Anna Massey
 Deirdre Cogan
 Rachel Jones
 Emma Ross

Additional contributors

Thomas Collin-Lefebvre
 Alex Kong
 Nestor Papanikolaou

ACCESS TO MEDICINE FOUNDATION

The Access to Medicine Foundation is an independent non-profit organisation based in the Netherlands. It aims to advance access to medicine in low- and middle-income countries by stimulating and guiding the pharmaceutical industry to play a greater role in improving access to medicine.

Address

Naritaweg 227-A
 1043 CB, Amsterdam
 The Netherlands

Contact

For more information about this publication, please contact
 Jayasree K. Iyer, Executive Director
jiyer@accesstomedicinefoundation.org
 +31 (0) 20 215 35 35
www.amrbenchmark.org

¹ This acknowledgement is not intended to imply that the individuals and institutions referred to above endorse the Antimicrobial Resistance Benchmark methodology, analyses or results. Decisions regarding the final analysis were ultimately made by the Access to Medicine Foundation.

About the cover: Young woman from Brazil, where 40%-60% of infections are caused by drug-resistant bacteria.

Photo: FG Trade (Getty Images)

The fragile antibiotic market has reached a tipping point



The Antimicrobial Resistance Benchmark has evaluated for the second time how the most important players in the antibiotic market are addressing the rise of resistance and the global need for appropriate access to antibiotics. Although we can see progress — it's hanging by a thread.

We have reached a tipping point where large and prominent drugmakers have retreated from the antibiotics field and smaller innovative biotech companies have gone bankrupt due to the poor financial rewards on offer. Antibiotics are taken for short courses and the most precious products are reserved for emergencies. Only a handful of large research-based companies remain broadly engaged in developing new antibiotics, down from more than 20 in the 1980s. Losing any more big suppliers and innovators will make it extremely hard to ramp up effective drug discovery and development operations, while the tough economics of the market discourage investment in new manufacturing capacity.

This disinvestment and industry consolidation has created an increasingly fragile manufacturing and supply chain. While the top 30 companies have more than 200 sites for producing antibiotics globally, just four companies – GSK, Novartis (through its generics arm, Sandoz), Teva and Mylan – account for more than half of them. Each year, more than 90 billion packs of medicines are used worldwide to treat infections.

Antimicrobial resistance is not a future problem.

The impact of drug resistance is already being felt today. Antibiotic resistance causes more than 500,000 deaths each year, including more than 200,000 infant deaths. In India, for example, resistance exceeds 70% for many widespread bacteria. Most at risk are patients living in the poorest countries, where medicine choices are limited.

This second Benchmark provides a reality check.

Fixing the problem does not require a scientific miracle. It demands a very human solution – albeit one that is easier said than done. The tough market conditions must be replaced through a mix of public and private investment to ensure a healthy ecosystem of pharmaceutical innovation, production and supply.

We see good practice in multiple areas in 2020. More companies are stepping up – with promising ideas for tackling the toughest pathogens, and improvements in tracking resistance and safeguarding the effectiveness of existing products. We can't take their commitment for granted and wait for more companies to abandon this vital area of modern medicine. It is not too late to prevent irreparable damage to the global supply of antibiotic medicines and vaccines.

A handwritten signature in blue ink that reads "Jayasree K. Iyer".

Jayasree K. Iyer
Executive Director
Access to Medicine Foundation

Table of contents

| | | | |
|-----------|---|------------|---|
| 6 | EXECUTIVE SUMMARY | 91 | REPORT CARDS |
| 12 | BENCHMARK PERFORMANCE | 92 | Abbott Laboratories |
| 12 | Antimicrobial Resistance Benchmark - 2020 | 95 | Achaogen Inc |
| 14 | How large research-based pharmaceutical companies perform | 98 | Alkem Laboratories Ltd |
| 16 | How generic medicine manufacturers perform | 101 | Amplify Pharmaceuticals Inc |
| 18 | How small and medium-sized enterprises perform | 103 | Aurobindo Pharma Ltd |
| 20 | KEY FINDINGS | 106 | Cidara Therapeutics |
| 20 | R&D: Signs of movement in access and stewardship planning in R&D, from a low base | 108 | Cipla Ltd |
| 22 | Access: Pharma companies are missing opportunities to make antibiotics available | 111 | Debiopharm |
| 24 | Stewardship: Progress in how pharma companies tackle overselling antimicrobials | 113 | Entasis Therapeutics Inc |
| 26 | Surveillance: Pfizer is the first company to share raw data on the spread of resistance | 116 | Fresenius Kabi AG |
| 28 | PIPELINE & PORTFOLIO ANALYSIS | 119 | GlaxoSmithKline plc |
| 28 | R&D Pipelines: Which companies are developing new treatments for the most threatening bacteria and fungi? | 123 | Hainan Hailing Chemipharm Corporation Ltd |
| 29 | Portfolios: Which companies produce the most anti-bacterial and antifungal products? | 126 | Johnson & Johnson |
| 31 | RESEARCH AREAS | 130 | Melinta Therapeutics Inc |
| 33 | RESEARCH & DEVELOPMENT | 133 | Merck & Co, Inc |
| 34 | How the companies compare in Research & Development | 137 | Motif Bio plc |
| 35 | In Summary | 139 | Mylan NV |
| 36 | Small & medium-sized enterprises lead in priority research | 142 | Nabriva Therapeutics plc |
| 51 | RESPONSIBLE MANUFACTURING | 145 | Novartis AG |
| 52 | How the companies compare in Responsible Manufacturing | 149 | Otsuka Pharmaceutical Co, Ltd |
| 53 | In Summary | 153 | Pfizer Inc |
| 54 | More companies set antibacterial limits for wastewaters to minimise AMR risk | 157 | Polyphor Ltd |
| 65 | APPROPRIATE ACCESS & STEWARDSHIP | 160 | Sanofi |
| 66 | How the companies compare in Appropriate Access & Stewardship | 164 | Scynexis |
| 67 | In Summary | 166 | Shionogi & Co, Ltd |
| 68 | Progress in safeguarding use of products, yet access is still lacking in LMICs | 170 | Summit Therapeutics |
| | | 172 | Sun Pharmaceutical Industries Ltd |
| | | 175 | Tetraphase Pharmaceuticals Inc |
| | | 178 | Teva Pharmaceutical Industries Ltd |
| | | 181 | Wockhardt Ltd |
| | | 185 | APPENDICES |
| | | 186 | Appendix I: Analysis, scoring and review process |
| | | 189 | Appendix II: Limitations |
| | | 190 | Appendix III: Scoring guidelines |
| | | 196 | Appendix IV: Identifying best practices |
| | | 197 | Appendix V: Priority pathogens included for analysis in R&D |
| | | 198 | Appendix VI: Access countries |
| | | 199 | Appendix VII: Guide to Report Cards |
| | | 203 | Appendix VIII: Figures |
| | | 204 | Appendix IX: Definitions |

About this report

The second Antimicrobial Resistance Benchmark compares how a cross-section of the pharmaceutical industry is responding to the threat from drug-resistant infections. It evaluates 30 companies with a major stake in the anti-infectives space, including those with the largest R&D divisions, the largest market presence, and leading expertise in developing critically needed antibiotics and antifungals. These are among the last companies that remain invested in keeping such medicines and vaccines available and developing new ones.

The 30 companies include eight large R&D-based pharmaceutical companies, nine generic medicine manufacturers and 13 small and medium-sized enterprises. The Benchmark evaluates these companies in areas where they have the biggest potential and responsibility to limit AMR, such as R&D, managing manufacturing waste and ensuring appropriate access and stewardship.

The Antimicrobial Resistance Benchmark is used as a tool to guide and stimulate pharmaceutical companies to implement effective actions for limiting AMR and remain committed to developing new and existing medicines. It identifies the promising ideas now being implemented and maps out the opportunities to amplify current efforts to contain AMR. By publicly recognising companies' positive actions, we trigger other companies to join a 'race to do well'.

WHAT WE MEASURE

The 2020 AMR Benchmark uses a framework of 19 indicators organised into three Research Areas: Research & Development; Responsible Manufacturing; and Appropriate Access and Stewardship. These correspond to pharmaceutical companies' core responsibilities for limiting AMR: developing new medicines to replace ones that no longer work, make them accessible to those who need them, and find new ways to ensure antibiotics are produced and promoted responsibly. The Benchmark assesses company behaviour regarding diseases and product types and in a specific geographic scope, depending on the Research Area in question. Its metrics correspond to areas where experts and stakeholders agree that pharmaceutical companies can and should be taking action to limit AMR.

HOW WE MEASURE

The Benchmark evaluated data gathered via a detailed survey of company behaviour regarding AMR and from public sources. It reports company activities taking place during a period of analysis from 9 September 2017 to 21 June 2019. Data submitted by the companies or gathered from public sources was verified, cross-checked and supplemented by the Foundation's research team using public databases, sources and supporting documentation.

SECTIONS IN THIS REPORT

Benchmark Performance and four Key Findings

An analysis of how the 30 companies compare, including which companies lead and why, with Key findings in antibacterial R&D, progress in responsible promotion, and tracking the spread of resistance.

Pipeline and portfolio analysis

A breakdown of 138 R&D projects targeting the biggest bacterial and fungal threats to reveal which promising new products are being developed, and a deep dive into the 1,520 products currently on the market to highlight the biggest producers.

Three Research Areas

In-depth analyses of company activity across the three Research Areas covering topics such as: novelty in the pipeline, access planning, environmental risk-management, registration and pricing, responsible promotion and AMR surveillance.

30 Company Report Cards

Detailed overviews of how the 30 pharmaceutical companies are responding to appropriate access and the rise of AMR, including tailored opportunities for the company to do more, and a snapshot of its R&D pipeline and product portfolio.



Executive Summary

Curbing the overuse and misuse of antimicrobials is critical for slowing the spread of antimicrobial resistance (AMR) while new antibiotics are needed to ensure effective treatment options remain available. The Antimicrobial Resistance Benchmark evaluates pharmaceutical companies in areas where they have the biggest potential and responsibility to limit AMR, such as R&D, managing manufacturing waste and ensuring appropriate access and stewardship. The 30 companies evaluated include eight large R&D-based pharmaceutical companies, nine generic medicine manufacturers and 13 small and medium-sized enterprises.

Industry trends

There are signs of improvement since 2018 in how pharmaceutical companies are tackling AMR, particularly when it comes to stewardship. Examples of good or even best practice can be found in many areas. Nevertheless, the pace of change does not match the scale of the AMR challenge. A few companies deserve recognition for continuing to step up their efforts across multiple areas, yet others have rolled back good practice since 2018 or taken steps to leave the market. In most areas of R&D, the bulk of the activity is carried out by just a few companies. This concentration puts important candidates at risk should more companies withdraw from this space.

The Benchmark finds that companies are more likely to take action in response to clear priorities or external incentives, offered by, for example, civil society or public health agencies. Leading generic medicine manufacturers continue to expand beyond their conventional role as major producers, with at least one investing in R&D against priority pathogens. Meanwhile, research grants and other 'push' incentives for R&D have stimulated SMEs to become leaders in developing innovative antibacterial and antifungal medicines, but lack of sufficient returns from the market is putting some at risk of bankruptcy.

Leaders in 2020

The eight large research-based pharmaceutical companies are led by GSK, which leads in all Research Areas, despite regressing in certain metrics. It continues to have the largest pipeline targeting pathogens in scope and most of its late-stage candidates are supported by plans to ensure better access and good stewardship soon after they reach the market. GSK is followed in second place by Pfizer, which has strengthened its performance since 2018 and leads in stewardship measures, and followed by Johnson & Johnson, which maintains its focus on tuberculosis.

Cipla leads among the generic medicine manufacturers, performing strongly in all areas where it was evaluated. It is followed by Teva, then Fresenius Kabi. All three stand out for policies that will help ensure their medicines are promoted responsibly, in different ways. Cipla is one of three companies in 2020 to fully decouple its sales agents' bonuses from sales volumes. Teva is one of the few companies not to use sales agents for antibacterial and antifungal medicines, while Fresenius Kabi limits its use of sales agents and sells mainly through tenders without volume-linked bonuses.

Entasis leads the SME group, followed by Wockhardt. They stand out for targeting bacteria in the highest threat category defined by WHO and the CDC, and for supporting late-stage candidates with plans to ensure better access and good stewardship soon after launch.

Pipeline and portfolio analysis

The 2020 AMR Benchmark assessed R&D projects that target the bacteria and fungi that pose the biggest threats from AMR. Since 2018, 40 have dropped out of the pipeline and

49 have been added. Of the 138 R&D projects in the pipeline, ten are for 'novel' medicine candidates. Most of the novel clinical stage projects are being developed by SMEs. Overall, *Enterobacteriaceae* are targeted most, followed by *Mycobacterium tuberculosis*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*.

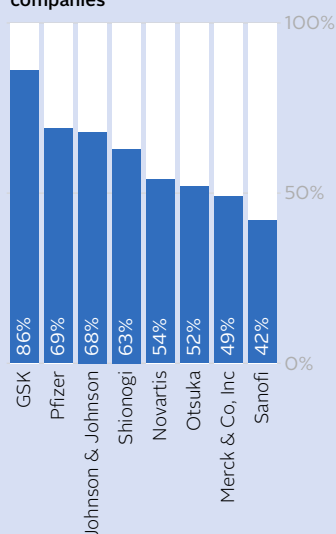
The Benchmark has also analysed the antibacterial and antifungal portfolios of the biggest players in the anti-infectives market. Out of 1,520 marketed antibacterial and antifungal medicines and vaccines in this analysis, 39 are on patent, all from large R&D-based companies. Generic medicine manufacturers have larger portfolios on average. More than 600 (40%) of the products on the market are on World Health Organization's (WHO) Essential Medicines List (EML) and thus have been identified as priorities for either better access or stricter stewardship. Generic medicine manufacturers have a greater proportion of second-line and last-resort treatments than other company groups, making their stewardship practices particularly important

KEY FINDINGS

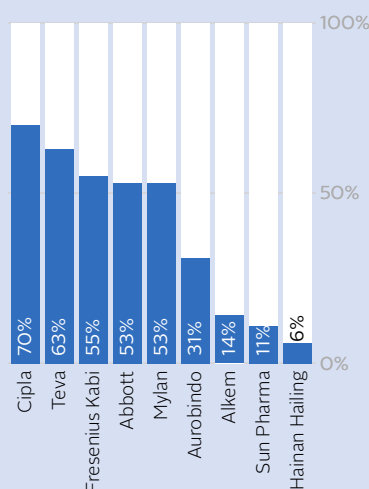
- The clinical pipeline of antibiotics for priority infections remains small, but companies have plans for access and stewardship in place for more of them than in 2018. Eight out of 32 key candidate antibiotics (25%) have such plans, up from 2 out of 28 (7%) in 2018. However, such advance planning is so far benefitting only a few diseases.
- Companies are missing opportunities to make antibiotics available, by not seeking to register new antibiotics in countries where the need is greatest and by not widely supplying to lower-income countries older antibiotics that are still clinically useful.
- There is progress in responsible promotion practices that address the overselling of antibiotics. By decoupling bonuses from sales volumes, or not using any sales staff at all, companies mitigate against overselling antibiotics and driving resistance. Ten companies now take such steps. That compares with five companies taking such action in 2018.
- More companies are supporting or running AMR surveillance programmes that track the rise and spread of resistance, and most publish the results. Pfizer has become the first company to share the raw data, publishing it on an open-access AMR online register.

ANTIMICROBIAL RESISTANCE BENCHMARK – 2020

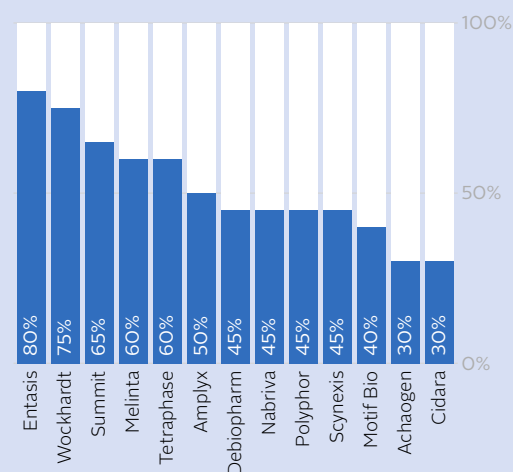
Large research-based pharmaceutical companies



Generic medicine manufacturers



Small & medium-sized enterprises



● Performance in 2020 ● Room to improve

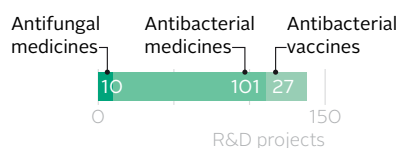
FIGURE 1

EXECUTIVE SUMMARY – FINDINGS PER RESEARCH AREA

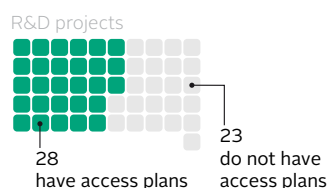
RESEARCH & DEVELOPMENT

- A total of 138 R&D projects that target infections caused by the most threatening bacteria and fungi are in development. When comparing pipelines assessed in both the 2018 and 2020 AMR Benchmark, almost one-third of projects progressed from one stage of development to another.
- Just over half (55%) of late-stage projects are supported by plans to ensure new products can rapidly be made available to patients, soon after launch. Yet only 20% of such products have stewardship plans in place to protect the effectiveness of new products.
- Almost 75% of projects are medicines targeting bacteria. Ten projects target fungal infections. All address *Candida* spp, the only priority pathogen for fungi. Most of the antifungal projects are being developed by SMEs. Five of the large R&D-based companies are active in vaccines R&D, with a total of 27 projects. No company in scope is developing an antifungal vaccine.

138 R&D projects in the pipeline



Over 55% of late-stage projects have access plans



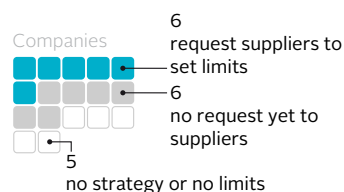
RESPONSIBLE MANUFACTURING

- Most companies have an environmental strategy to minimise the impact of their manufacturing processes in promoting resistance, with 13 showing evidence of such a strategy. Twelve of the 13 are members of the AMR Industry Alliance.
- Almost all environmental risk-management strategies include a set of discharge limits on the levels of antibacterials allowed in manufacturing discharge. Of the 12 companies that set discharge limits, seven report having assessed discharge levels against these limits at their own sites, but only half of the companies require their suppliers to set limits.
- No companies monitor antibacterial levels discharged by external, privately owned wastewater-treatment plants, nor do companies require wastewater-treatment plants to set limits for antibacterial discharge or monitor discharge levels
- No companies publish the levels of antibacterials in wastewaters discharged from their sites or the full results of audits conducted at these sites. Results of audits to suppliers' sites or the suppliers' identities are also not published.

Most companies have an environmental strategy to minimise AMR



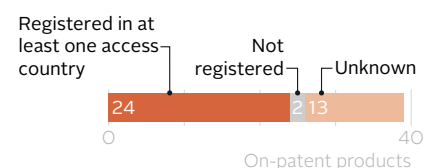
Only half of companies require suppliers to set limits



APPROPRIATE ACCESS & STEWARDSHIP

- On-patent products are filed for registration in few LMICs. Only nine out of 39 on-patent antibacterial and antifungal products are the subject of registration applications in more than 20 out of 102 countries where better access is urgently needed. Most of these are vaccines.
- Many off-patent products are unlikely to be widely available, with more than 10% of them not registered in even one access country. While most companies manufacture one or more 'forgotten antibiotics' – older, but still clinically useful antibiotics – less than half are supplied to access countries.
- Publicly sharing AMR surveillance results is common practice for the majority of companies involved. Yet one company, Pfizer, shares raw data as well as results.
- Almost half of the companies in scope take steps to promote their antibacterial and antifungal medicines responsibly, while six companies show best practice by not actively promoting such medicines or fully decoupling sales agents' bonuses from volumes.

On-patent products are registered in very few LMICs



Companies aim to prevent overselling



Not all companies are eligible for each Research Areas, as the Benchmark only evaluates companies in metrics that are relevant to its portfolio and/or pipeline.

EXECUTIVE SUMMARY – CONCLUSION

Signs of progress, but not at scale needed

The findings from the 2020 Antimicrobial Resistance Benchmark indicate that a core group of pharmaceutical companies are making progress in tackling the spread of antimicrobial resistance. However, although a few companies are expanding their efforts, change is not happening at the scale needed to radically impact the threat from drug resistance. With pharmaceutical companies leaving the anti-infectives market due to poor financial rewards, the supply of life-saving medicines is now increasingly reliant on just a handful of companies. The commitment of these companies cannot be taken for granted.

Role for companies is clear

Tackling the problem demands the concerted effort of multiple stakeholders, and the role for pharmaceutical companies is clear: to develop new medicines to replace ones that no longer work, make them available and accessible to those who need them, and find new ways to ensure antibiotics are produced and promoted responsibly.

Companies take action, but gaps remain

The continued commitment of the eight large research-based pharmaceutical companies in the Benchmark to antibacterial and antifungal markets underpins our global capacity to treat infectious diseases and drug-resistant pathogens. However, the Benchmark finds that only a few continue to expand efforts to safeguard this area of medicine, while others disengage. As companies step back, the market infrastructure becomes increasingly decentralised and patchy, raising barriers to access and availability at every step. They have clear opportunities to invest in R&D, to step up the stewardship of their products while safeguarding their supply, and to ramp up access for populations in need.

The leaders among the generic medicine manufacturers show that all such companies can take practical steps to mitigate against the risk of overselling anti-infectives. Decoupling sales bonuses from sales volumes is particularly important, as many of these companies report pursuing a low-price/high-volume business model. Plus, as major producers of antibacterials, they have a particular responsibility to strengthen their strategies for environmental risk-management in manufacturing, and to require their suppliers to comply with comparable standards. Generic medicine manufacturers also have scope to support smaller R&D-focused companies (termed small- and medium-sized enterprises (SMEs) in the Benchmark) to bring important new medicines to low- and middle-income countries by becoming co-development and manufacturing partners.

The SMEs in the Benchmark face the challenge of commercialising new products. Without existing revenue streams and as research grants expire, they have little room for error. A handful of SMEs are at risk of following Achaogen and Melinta into bankruptcy if they cannot secure the investment needed to further develop candidate products. As this group of companies bring more products through clinical development, access and stewardship planning must become standard practice, and a standard requirement from donors and investors. This will help ensure that their assets can quickly be made available to people living in low- and middle-income countries as well as those in wealthier ones and be safeguarded to ensure they remain effective for as long as possible.

2020

Antimicrobial

Resistance Benchmark

This first section of the report provides the core analyses of how the 30 companies in scope performed, with Key Findings, and a visual breakdown of their R&D pipelines and marketed products.

2020 ANTIMICROBIAL RESISTANCE BENCHMARK PERFORMANCE

- More companies join the leaders, yet progress on AMR is slow
- How large research-based pharmaceutical companies perform
- How generic medicine manufacturers perform
- How small and medium-sized enterprises perform

KEY FINDINGS

- R&D: Signs of movement in access and stewardship planning in R&D, from a low base
- Access: Pharma companies are missing opportunities to make antibiotics available
- Stewardship: Progress in how pharma companies tackle overselling antimicrobials
- Surveillance: Pfizer is the first company to share raw data on the spread of resistance

PIPELINE & PORTFOLIO ANALYSIS

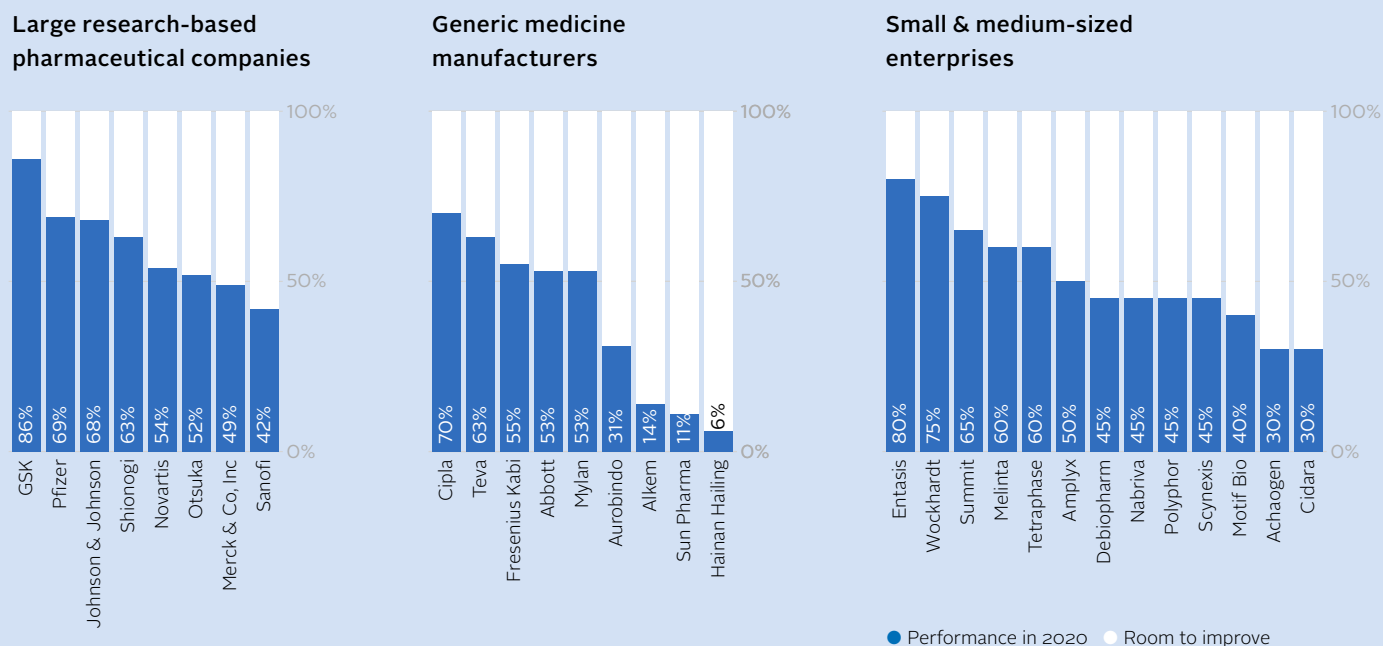
- R&D Pipelines: Which companies are developing new treatments for the most threatening bacteria and fungi?
- Portfolios: Which companies produce the most antibacterial and antifungal products?

BENCHMARK PERFORMANCE

More companies join the leaders, yet progress on AMR is slow

ANTIMICROBIAL RESISTANCE BENCHMARK – 2020

FIGURE 1



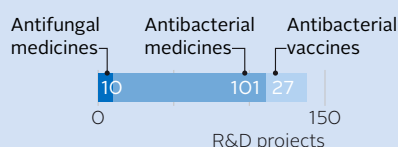
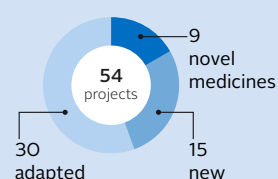
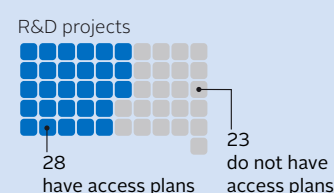
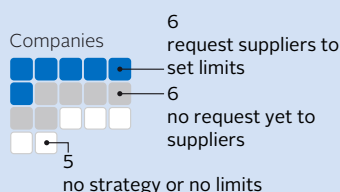
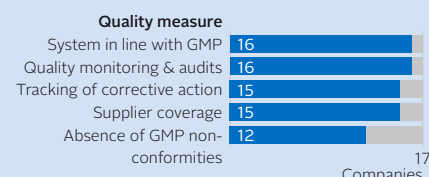
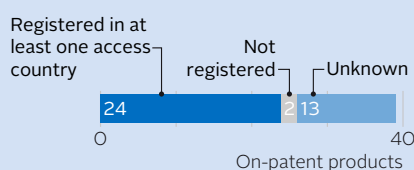
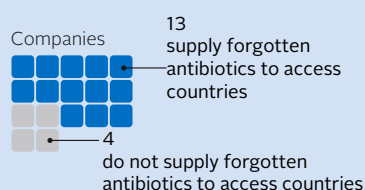
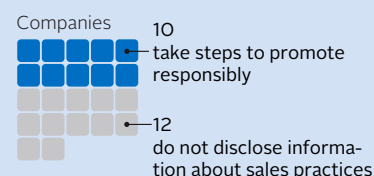
There are signs of improvement in how pharmaceutical companies are tackling antimicrobial resistance (AMR), particularly when it comes to stewardship. Disclosure, particularly among generic medicine manufacturers, has also improved.

More companies are taking steps to reduce the risk of overselling antibiotics and antifungal medicines to healthcare practitioners. Companies are also sharing what they know about resistance from their surveillance programmes, with Pfizer setting the pace by publicly sharing its raw data. Environmental risk-management strategies for manufacturing go somewhat further than in 2018, with companies also publicly committing to a comprehensive list of defined discharge limits. More clinical-stage antibiotics than in 2018 are supported by plans to ensure better access and good stewardship soon after launch. However, the development of such plans remains patchy.

Good practices are overshadowed by slow pace of change

Examples of good or even best practice can be found in all areas. Nevertheless, the pace of change does not match the scale of the AMR challenge. A few companies deserve recognition for continuing to step up their efforts across multiple areas, yet others have rolled back good practice since 2018, or have taken steps to leave the market.

The R&D pipeline for priority bacteria and fungi remains small, despite rising rates of resistance, and includes few novel candidates. In most areas of R&D, the bulk of the activity is carried out by just a few companies, for example in vaccines R&D and antifungal R&D. One company, GSK, is developing almost a fifth of all projects identified. This concentration puts important candidates at risk – there are very few companies to develop them further and bring them to market, should the current asset owners withdraw from this space. Almost all companies with antibiotics on the market are side-stepping or overlooking opportunities to

138 R&D projects in the pipeline**Few new clinical-stage medicines are novel****Over 50% of late-stage projects have access plans****Most companies have an environmental strategy to minimise AMR****Only half of companies require suppliers to set discharge limits****Quality systems align with GMP****On-patent products are registered in very few LMICs****Older, still useful antibiotics are not widely supplied****Companies aim to prevent overselling**

improve the availability of such products in high-need countries,* as reflected by low numbers of registration filings for new products, and by a lack of efforts to supply older, still useful antibiotics to low- and middle-income countries.

External incentives effective at spurring action

Companies are more likely to take action in response to clear priorities or external incentives, such as those offered by civil society or public health agencies. For example, more than a third of R&D projects target pathogens in the highest threat category defined by WHO and CDC, and companies are sharing surveillance data and results with multi-partner, multinational programmes.

Research grants and other 'push' incentives for R&D have stimulated SMEs to become leaders in developing innovative antibacterial and antifungal medicines. Companies are responding differently to the lack of acquisition interest by larger companies for successful assets. For example, in October

2019 Melinta delayed the commercial launch of its antibacterial delafloxacin (Baxdela®) so additional sources of liquidity could be secured. In December 2019, it filed for bankruptcy. Achaogen also filed for bankruptcy in 2019, despite launching an effective new antibiotic. Other small- and medium-sized companies in scope are currently at risk of going bankrupt. It is necessary to increase public and private investments to guarantee the global supply of any antibiotics emerging from the pipeline.

Generics companies expand their role

Leading generic medicine manufacturers continue to expand beyond their conventional role of major producers, with at least one company investing in R&D, and more companies now also taking steps such as strategies for affordability, licensing deals to improve availability, and measures to ensure reliable supplies. For example, Cipla acquired the rights to plazomycin from Achaogen, taking responsibility for making it available, including in LMICs.

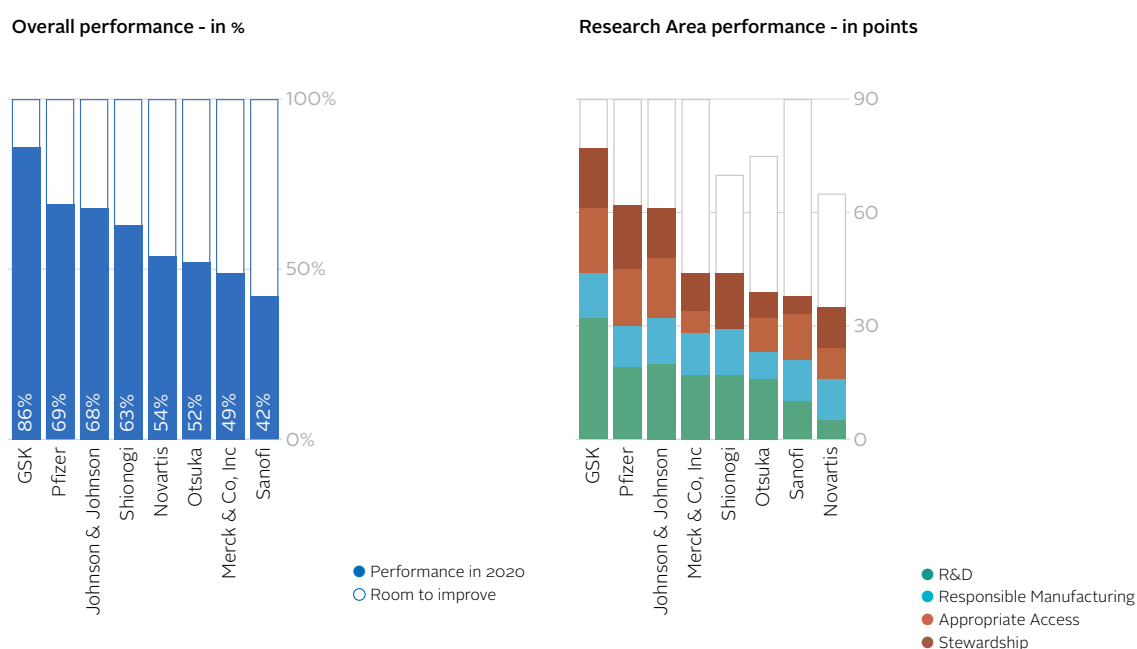
* 102 low- and middle-income countries where bacterial and fungal infectious diseases are endemic, and where populations are more likely to lack access to antibacterial and antifungal medicines.

BENCHMARK PERFORMANCE

How large research-based companies perform

BENCHMARK PERFORMANCE FOR LARGE RESEARCH-BASED PHARMACEUTICAL COMPANIES

FIGURE 2



GSK leads the group in 2020, followed closely by Pfizer and Johnson & Johnson. Shionogi has moved up, in front of Novartis and Otsuka. All companies in this group take diverse action to limit AMR. However, only a few continue to expand efforts to safeguard this critical area of modern medicine.

GSK leads in all Research Areas, despite regressing in certain metrics. It has the largest pipeline (27 projects), including the bulk of new vaccines being developed. Most of its late-stage candidates are protected by plans to ensure better access and good stewardship soon after launch. GSK discloses multiple strategies to ensure a continuous supply of antibacterials to countries where they are most needed.* These include dual sourcing for active pharmaceutical ingredients (APIs) and maintaining safety stocks. However, GSK has stepped back from fully decoupling its sales agents' bonuses

from sales volumes. It has also not fulfilled its 2018 pledge to share its raw data from resistance surveillance.

Pfizer rises to second place. It is now leading across the stewardship metrics, and is the first pharmaceutical company to publicly share raw surveillance data from its ATLAS programme. After GSK, it has one of the larger vaccine pipelines, developing an improved pneumonia vaccine, as well as new clinical-stage vaccines for *C. difficile*, Group B *Streptococcus*. Johnson & Johnson maintains a comparatively strong performance, with a focus on tuberculosis, as in 2018. For example, in stewardship, Johnson & Johnson engages in several tuberculosis-related educational programmes for healthcare professionals, taking action to mitigate conflict of interest. It also supports surveillance programmes for tuberculosis, sharing data with public health authorities.

Shionogi rises up, and invests the highest proportion of its pharmaceutical revenues in relevant R&D: USD 133 million in 2017 and 2018. It is developing several medicines that target some of the most dangerous drug-resistant pathogens.** Shionogi runs multiple AMR surveillance programmes, including one that tracks resistance of Gram-negative bacteria in 13 countries. It is the only large-research-based pharmaceutical company evaluated that fully decouples incentives for sales agents from sales volumes to help prevent the inappropriate use of all its antibacterials. Its antibacterial cefiderocol gained marketing approval in November 2019.

Since 2018, **Novartis** and **Sanofi** have licensed out or otherwise divested antimicrobial R&D assets, which contributes to their weaker performances since 2018. Both companies report a comprehensive strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at their sites, with an aim to limit AMR. Novartis reports that, including via Sandoz, it processes more than 50 antibacterial APIs across a network of 21-40 sites, and works with more than 100 suppliers of products. **Merck & Co, Inc** has the second largest pipeline in the Benchmark, including antibacterial and antifungal medicines, as well as vaccines projects. The company launched a new antibiotic in July 2019, targeting carbapenem-resistant *Enterobacteriaceae*.

WHAT NEXT

The eight companies in this group are the only large-scale multinational companies still active from development to deployment of antibacterials and antifungals. Their continued commitment to antibacterial and antifungal markets is essential for maintaining our global capacity to treat infectious diseases and drug-resistant pathogens. However, the Benchmark finds that only a few companies continue to expand efforts to safeguard the

continuous availability of effective anti-infectives – while others disengage. As companies step back in R&D or by ceasing production of antibacterials and antifungals, the market infrastructure becomes increasingly decentralised and patchy, raising barriers to access and availability at every step, from financing gaps for Phase III clinical studies, to a lack of oversight for preventing shortages. All companies who are working in the interest of health have clear opportunities to invest in R&D, to step up the stewardship of their products, while safeguarding their supply, and to ramp up access for populations in need.

* 102 low- and middle-income countries where bacterial and fungal infectious diseases are endemic, and where populations are more likely to lack access to antibacterial and antifungal medicines.

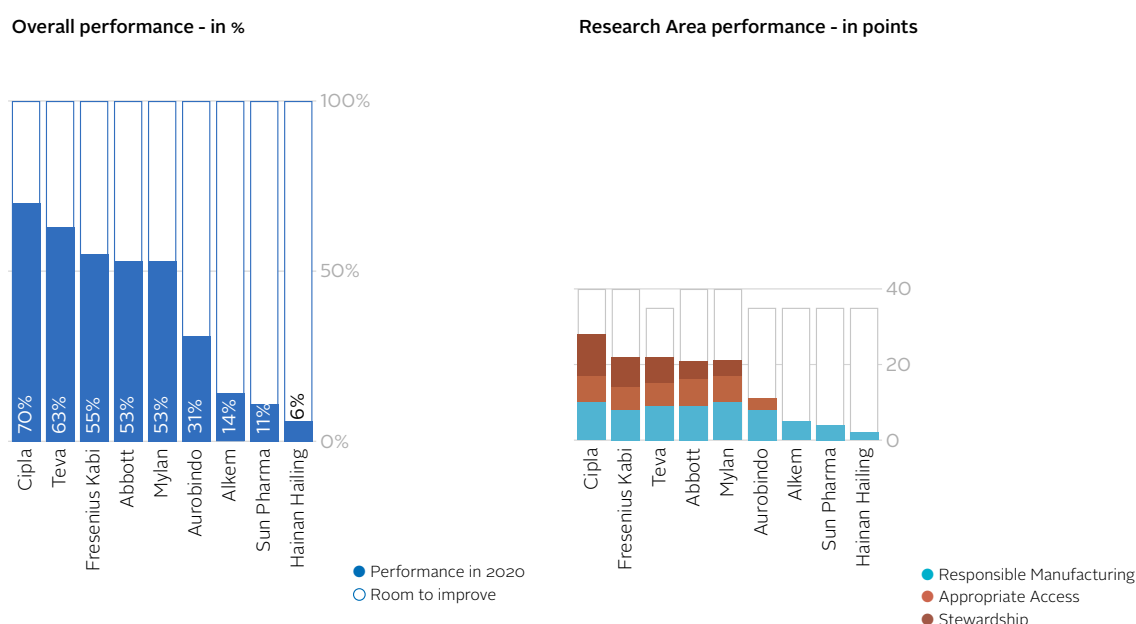
** Pathogens classed by WHO as posing a 'critical' threat, and/or by CDC as posing an 'urgent' threat to human health.

BENCHMARK PERFORMANCE

How generic medicine manufacturers perform

BENCHMARK PERFORMANCE FOR GENERIC MEDICINE MANUFACTURERS

FIGURE 3



Cipla, Teva and Fresenius Kabi take the lead in this group. All three are implementing policies that will help ensure antibacterial and antifungal medicines are promoted responsibly. Against a backdrop of greater disclosure, the leaders in this group are reported as taking additional steps against AMR compared to 2018.

Although disclosure remains comparatively low from this group, it has improved since 2018. The exceptions are Alkem, Hainan Hailing and Sun Pharma. Despite being big producers, they remain unwilling to share data and enable an evaluation of their commitment to limiting AMR.

Cipla, Teva and Fresenius Kabi take the lead, and all stand out for policies that will help ensure their medicines are promoted responsibly. Across all areas evaluated, **Mylan** and **Abbott** follow in joint fourth place. **Cipla** performs strongly in all areas where it was evaluated. It has filed all 10 of its

relevant products in countries where need is highest,* takes part in AMR surveillance,** and is one of three companies in 2020 to fully decouple its sales agents' bonuses from sales volumes, a significant step in mitigating against overselling, particularly as Cipla reports a global antibacterials sales volume of 2-3 billion units.***

Teva is one of the few companies not to use sales agents for antibacterial and antifungal medicines. It reports several strategies to ensure a continuous supply of antibacterials, including its Teva Access Initiative, which aims for a sustainable medicine supply in more countries than it currently does. The third leader in this group, **Fresenius Kabi**, takes multiple steps to mitigate the risk of conflict of interest in its educational programmes for healthcare professionals. It has also disclosed guidelines for intensive care units on the appropriate use of its intravenous antibacterials.

Mylan leads the generic medicine manufacturers when it comes to ensuring a continuous supply of medicines. It has a global supply network of over 40 sites, uses dual sourcing and maintains safety and strategic stocks. It also deploys pricing strategies that take socioeconomic conditions into account, reporting that it provided medicines to more than 165 countries in 2018.

Together with **Cipla**, **Abbott** outperforms peers in responsible manufacturing. For its own manufacturing sites, Abbott reports a comprehensive environmental risk-management strategy, including ongoing risk assessments and discharge limits for the majority of antibacterials manufactured. Abbott also expects third-party suppliers to follow its supplier guidelines. Along with Cipla, Abbott leads the group in registration filings. Its most widely filed product in this analysis is the antibacterial medicine clarithromycin, used to treat pneumonia, among other infections, which it has filed in 60 high-need countries.

WHAT NEXT

The leaders in this group show that all generic medicine manufacturers can take practical steps to mitigate against the risk of overselling anti-infectives. Decoupling sales bonuses from sales volumes is particularly important, as many of these companies report pursuing a low-price/high-volume business model. Plus, as major producers of antibacterials, they have a particular responsibility to strengthen their strategies for environmental risk-management in manufacturing, and to require their suppliers to comply with comparable standards. Generic medicine manufacturers also have the possibility to support smaller R&D-focused companies (termed small- and medium-sized enterprises in the Benchmark) to bring important new medicines to low- and middle-income countries, by becoming co-development and manufacturing partners.

* 102 low- and middle-income countries where bacterial and fungal infectious diseases are endemic, and where populations are more likely to lack access to antibacterial and antifungal medicines.

** This group of companies are not scored or evaluated in this area. The Benchmark does report on their surveillance activities, where known. From this group, Abbott, Cipla and Mylan are reported as supporting or running AMR surveillance activities.

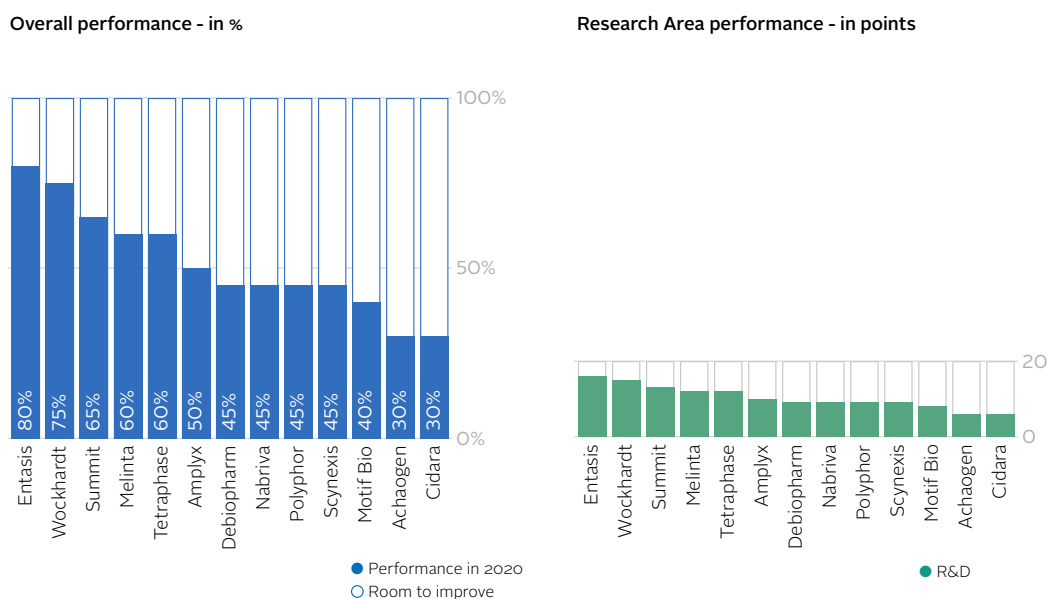
*** 'Standard units', a measure of volume defined by IQVIA to represent a dose of a particular formulation of treatment.

BENCHMARK PERFORMANCE

How small and medium-sized enterprises perform

BENCHMARK PERFORMANCE FOR SMALL AND MEDIUM-SIZED ENTERPRISES

FIGURE 4



Entasis leads, followed closely by Wockhardt. Three leaders stand out in this group for targeting bacteria in the highest threat category defined by WHO and the CDC, and for supporting late-stage candidates with plans to ensure better access and good stewardship soon after launch. Transparency in this group has improved since 2018.

The companies in this group were selected for having at least one investigational product in Phase II or beyond, which targets bacteria and/or fungi identified by WHO and/or US Centers for Disease Control (CDC) as threats to human health.* They are evaluated exclusively on their R&D activities, which means only 20 points are available to these companies. Entasis delivers the strongest performance, followed closely by Wockhardt. Summit follows in third, just ahead of Melinta (filed for bankruptcy in December 2019) and Tetrphase in joint fourth place.

Entasis' R&D pipeline of four medicines exclusively targets bacteria in the highest threat category defined by WHO and CDC. For example, its most advanced project targets *A. baumannii*, which can cause severe drug-resistant infections including pneumonia and urinary tract infections (UTIs). Entasis stands out for supporting its two late-stage projects with plans to ensure better access and good stewardship soon after launch. This includes zoliflodacin, a novel Phase II candidate targeting gonorrhoea, which is estimated to cause 78 million infections globally.¹ As a novel medicine, zoliflodacin has important differences from existing medicines, which may help to preserve its effectiveness.

Within this group, **Wockhardt** has one of the largest pipelines: four projects in clinical development, and five in pre-clinical stages. It has multiple projects that target bacteria in the highest threat

category. For example, its medicine cefepime/zidebactam, in Phase I, targets carbapenem-resistant *Enterobacteriaceae*, which causes diverse diseases including lower respiratory tract infections. Wockhardt is planning ahead to ensure rapid access to its four late-stage candidates: it commits to simultaneously filing the successful products for registration in India and other high-need countries. Although Wockhardt has a substantial generic medicine division, it was evaluated by the Benchmark alongside the small- and medium-sized enterprises. This enables a comparative analysis of its R&D activities.

Summit is developing three antibacterial medicines, including one in Phase III that is considered novel: ridinilazole, for *C. difficile* infections. Ridinilazole meets all criteria for novelty: it belongs to a new chemical class, and has a new target, mode of action and no cross-resistance. In terms of access planning, Summit has already entered into a regional licensing agreement for the medicine with Eurofarma Laboratorios, one of the largest pharmaceutical companies in Brazil and present in more than 20 countries in Latin America.

Melinta and **Tetraphase** are tied in fourth place, having performed well in different areas. Melinta filed for bankruptcy in December 2019. During the period of analysis, it had the largest pipeline in this group, with 11 projects, including eight in clinical development. It also reported access plans in place for its late-stage projects, but not stewardship plans. Tetraphase has a smaller pipeline, but it does have both access and stewardship plans in place to support its approved product, erava-cycline. This includes a licensing agreement and plans to develop a surveillance network.

WHAT NEXT

The companies in this group face the challenge of commercialising new products. Without existing revenue streams and as research grants expire,

they have little room for error. A handful of SMEs are at risk of following Achaogen and Melinta into bankruptcy if they cannot either divest existing products or secure the investment needed to further develop candidate products. Generic medicine manufacturers may prove powerful co-development and manufacturing partners for such companies.

By planning ahead during product development, pharmaceutical companies can take account of public health needs and provide swifter access to new products at more affordable prices. Companies must also integrate plans for access with plans for stewardship, so that new products can be used appropriately and remain effective over time. As this group of companies brings more products through clinical development, access and stewardship planning must become standard practice, and a standard requirement from donors and investors. This will help ensure that their assets can quickly be made available to people living in low- and middle-income countries as well as those in wealthier ones, and be safeguarded to ensure they remain effective for as long as possible.

1. Bodie M., et al. Addressing the rising rates of gonorrhea and drug-resistant gonorrhea: There is no time like the present. *Can Commun Dis Rep.* 2019;45(2-3):54–62. Published 2019 Feb 7. doi:10.14745/ccdr.v45i23a02

* The WHO identified three threat levels: critical, high and medium. These correspond to the threat levels used by the CDC: urgent, serious, concerning.

KEY FINDING 1: R&D

Signs of movement in access and stewardship planning in R&D, from a low base

Pharma companies have plans for access and stewardship for 8 out of 32 key candidate antibiotics (25%), up from 2 of 28 (7%) in 2018.

- Planning ahead while R&D projects are in clinical development accelerates access and stewardship for successful candidates.
- Clinical pipeline of antibiotics for priority infections remains small.
- With a small pipeline, the need for access and stewardship plans is more acute.

Why plan during development?

When the right antibiotics are unavailable, doctors often resort to suboptimal treatments, which gives pathogens an opportunity to develop resistance. By planning ahead – i.e., while a product is in clinical development – pharmaceutical companies can provide swifter access to new products at affordable prices, and have measures in place from day one to ensure new products are used prudently (known as stewardship).

Advance planning has been shown to improve the speed at which new medicines are made accessible. For example, Tetrphase worked with Everest, a China-based biopharmaceutical company, to register its new antibacterial eravacycline in China, receiving approval within one year of gaining market approval in the US. Eravacycline targets several drug-resistant infections.

It is well known that there are not enough antibiotics in R&D pipelines to replace those losing their effectiveness. With such small pipelines and such need, it is even more important for pharmaceutical companies to start putting access and stewardship plans in place during clinical development. The Benchmark considers that companies should know enough about a product's prospects to start planning for access and stewardship from Phase II of clinical development.

What did the Benchmark analysis find?

The 2020 Antimicrobial Resistance Benchmark identified 32 priority candidate antibiotics from the companies in scope at the stage where access and stewardship planning should be taking place. Eight of these 32 antibiotics (25%) are supported by both access and stewardship plans. This is a notable increase compared to 2018, when two out of 28 (7%) antibiotic candidates had both plans in place. Advance planning is so far benefiting only a few diseases caused by a few pathogens. Out of the eight projects, two are for tuberculosis, two are for gonorrhoea and one is a broad-spectrum antibacterial for multidrug-resistant infections.

Johnson & Johnson's paediatric bedaquiline formulation was one of only two projects recorded in 2018 as having both an access and a stewardship programme in place during clinical development. This project is still in phase II. The second project credited in 2018 was Tetrphase's eravacycline. Since the 2018 Benchmark, eravacycline was approved and Tetrphase signed its planned licensing agreement covering Southeast Asian countries, including Malaysia and Thailand.

What do access and stewardship plans look like?

There are various mechanisms that can enhance access to new medicines in low- and middle-income countries. These include licensing and affordability commitments, filing for registration in countries with a high disease burden, taking account of populations' varying ability to pay in pricing strategies, and waiving or not enforcing patent rights. Stewardship measures can include surveillance of resistance and disease, and the introduction of more appropriate marketing practices. This is particularly important in countries with high rates of drug resistance. In some cases, product development partners require such plans to be made during the development phase. This is the case for six of the eight projects supported by both access and stewardship plans in 2020.

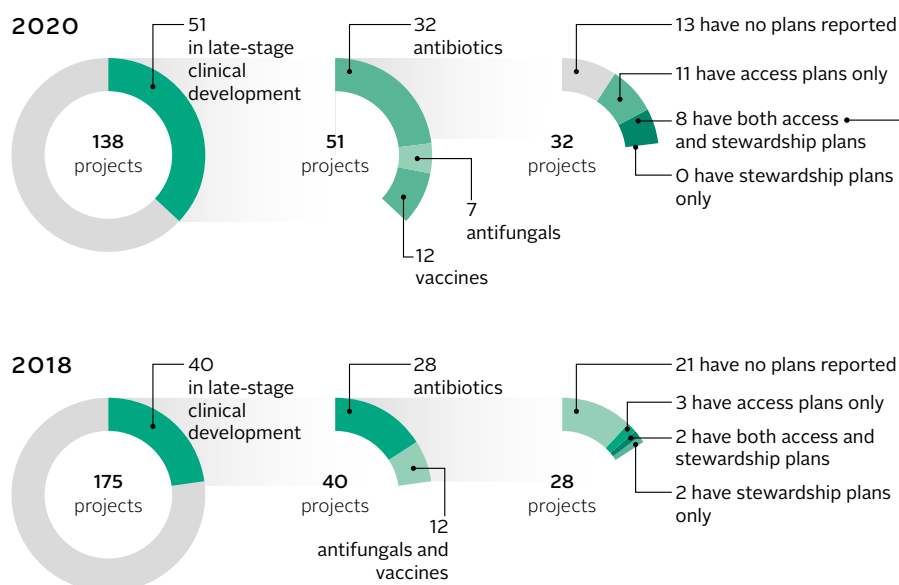
WHAT NEXT

With only a few antibiotics in development, and considering the scale of unmet need, each new antibiotic must be protected at launch by access and stewardship plans. The practice of access and stewardship planning during clinical development needs to be significantly scaled up, particularly as the 13 candidates currently without such plans include new antibiotics critically needed to combat superbugs such as *C. difficile*, *N. gonorrhoeae* and MRSA. R&D funders can play a role by including provisions for and supporting access and stewardship planning during the later stages of development, when prospects for marketing approval are becoming clear.

FIGURE 5

Eight late-stage antibiotics have both access and stewardship plans

The figure shows the proportion of late-stage antibiotics supported by access and/or stewardship plans that target bacteria and fungi posing the greatest threats to human health.

**Eight late-stage antibacterial candidates are supported by access and stewardship plans:**

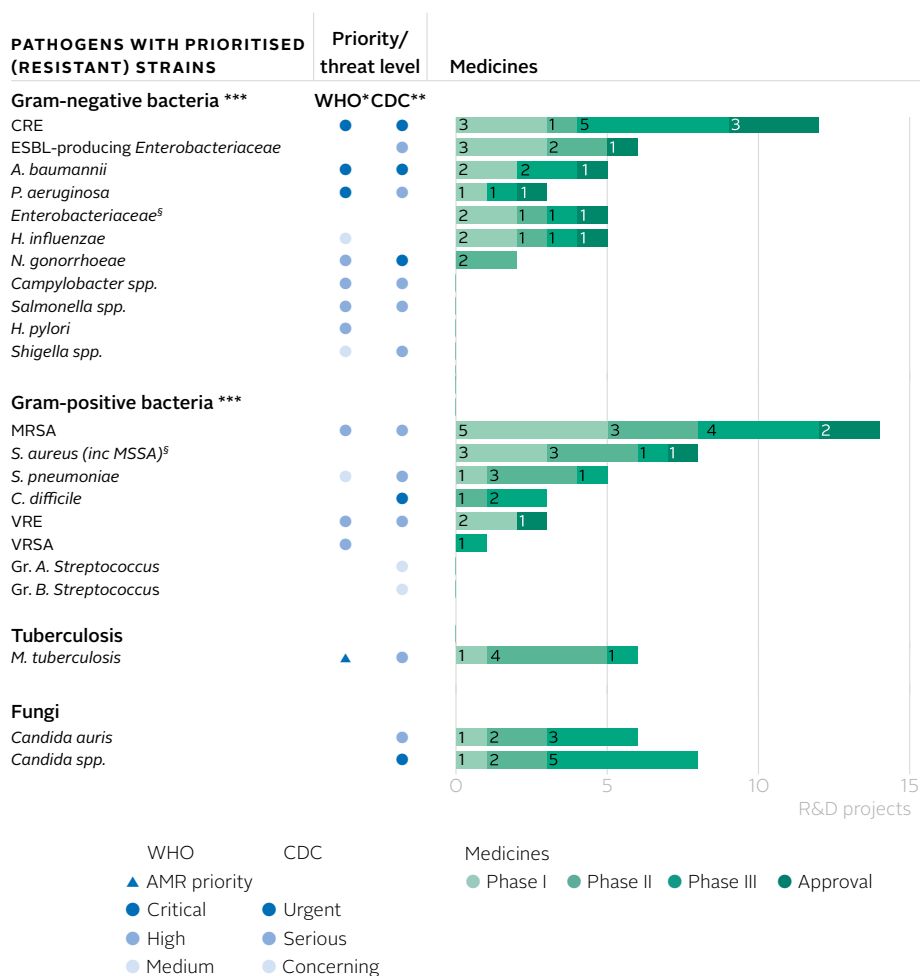
- Sulbactam/durlobactam (Entasis), a beta-lactam/beta-lactamase inhibitor (BL/BLI) combination where sulbactam is active against *A. baumannii* and durlobactam confers additional protection against betalactamases.
- Zoliflodacin (Entasis), a novel candidate for the treatment of uncomplicated gonorrhoea, developed in partnership with the Global Antibiotic Research & Development Partnership (GARDP)
- GSK-o70 (GSK) a novel candidate for the treatment of *M. tuberculosis*
- Gepotidacin (GSK), a novel candidate for the treatment of bacterial infections including *N. gonorrhoeae*
- Bedaquiline (Sirturo®) (Johnson & Johnson) paediatric studies, for the treatment of drug resistant tuberculosis in adolescents
- Aztreonam/avibactam (Pfizer), for the treatment of multidrug-resistant *Enterobacteriaceae*
- Ceftaroline fosamil (Zinforo™) (Pfizer), for MRSA as a new target indication to an expanded paediatric population
- Eravacycline (Xerava™) (Tetraphase), targeting multidrug-resistant Gram-negative and Gram-positive infections

The pipelines are not directly comparable between years, as the pathogens and companies in scope are slightly different.

FIGURE 6

Breakdown of the clinical antibiotic pipeline for priority bacteria and fungi

The figure shows how many antibiotics are in clinical development, per pathogen, from the 21 companies in scope. The bacteria and fungi receiving the most attention include *Enterobacteriaceae*, *S. aureus*, *Candida* spp. and *M. tuberculosis*. This figure excludes projects that aim to adapt existing products.



CRE = Carbapenem-resistant *Enterobacteriaceae* (CRE)

ESBL = Extended spectrum beta-lactamase

MRSA = Methicillin-resistant *Staphylococcus aureus*

MSSA = Methicillin-sensitive *Staphylococcus aureus*

VRE = Vancomycin-resistant *Enterococcus*

VRSA = Vancomycin-resistant *Staphylococcus aureus*

* WHO priority pathogens list, 2017

** CDC Antibiotic Resistance Threats list, 2019

*** Projects that target multiple pathogens are included for each relevant priority pathogen

§ Projects are listed separately where the company does not report whether or not it targets the resistant strain prioritised by CDC and/or WHO.

KEY FINDING 2: ACCESS TO ANTIBIOTICS

Pharma companies are missing opportunities to make antibiotics available

Pharmaceutical companies are not registering new antibiotics where need is greatest. Older, clinically useful antibiotics are not widely supplied.

- New medicines cannot be made widely available until companies register them.
- Only 3 of 13 on-patent antibiotics are filed for registration in more than 10 countries where better access is urgently needed (out of 102 countries).
- Older antibiotics are not widely supplied to some low-income countries.

Why access matters – to both new and older antibiotics

To reduce the threat of antimicrobial resistance (AMR), doctors must ensure that the right treatment is used to treat the infection in question. When shortages occur, doctors often resort to less optimal treatments, which poses an increased risk of AMR. The poorest countries tend to have a greater burden of infectious disease and higher rates of antibiotic resistance, making the need for better access to medicine all the more essential. Today's 'access gaps' in relation to antibiotics increase the risk that effective antibiotics cannot be made available in future.

For new on-patent medicines, patent owners or their licensees must register them for sale in a country before they can be made widely available there. Best practice in this area is for patent owners to ensure new-product dossiers are prepared for access countries in parallel to major markets, to facilitate faster registration in those access countries.

Some older, off-patent antibiotics are still clinically useful but have become 'forgotten' – they are either no longer produced or are not being supplied. This may be because they are not profitable, because there is a lack of awareness of their clinical usefulness, or because there is lack of demand, as newer alternatives have become available. A list of 'forgotten antibiotics' was first defined by Pulcini *et al* in 2017.¹

What does the Benchmark analysis show?

The 2020 Antimicrobial Resistance Benchmark has tracked the efforts of large research-based pharmaceutical companies to register on-patent antibiotics. It looks at registration filings in 102 low- and middle-income countries – referred to as 'access countries' – where the disease burden is high and access to medicine is low. It has also evaluated whether companies, including generic medicine manufacturers, are supplying older 'forgotten antibiotics' to these access countries.

Based on these analyses, the Benchmark concludes that pharmaceutical companies are missing opportunities to make either new or older antibiotics available in access countries. The companies assessed by the Benchmark have 13 new,

on-patent antibiotics. Yet, only three have been filed for registration in ten or more access countries. For four on-patent antibiotics, the Benchmark found no evidence of registration filings in any access countries. Only one company reports pursuing licensing for any of these products (Otsuka, for delamanid (Delbyta®)). In conclusion, in dozens of countries, it is fair to assume that these on-patent medicines are not available.

When it comes to older, but still effective antibiotics, the numbers are similarly bleak. For this analysis, the Benchmark looked at whether companies are supplying any of the 30 defined 'forgotten antibiotics'. The companies assessed have 24 such antibiotics in their portfolios. However, there is only evidence for 14 of these that they are being supplied to even one access country. Those 14 antibiotics tend to be ones that could be used for a broad range of infections. Half of the 14 forgotten antibiotics are on the World Health Organization Model Lists of Essential Medicines 2019 (EML).

How do companies' practices compare?

The two most widely filed on-patent products in this analysis are: ceftolozane/tazobactam (Zerbaxa®) from Merck & Co, Inc, filed in at least 30 of the 102 access countries, and bedaquiline (Sirturo®) from Johnson & Johnson for multidrug-resistant tuberculosis, filed in 28 access countries. Antibiotics that can be used to treat multidrug-resistant tuberculosis account for six of the nine products that are being registered in any of the 102 target countries.

Most of the forgotten antibiotics are produced by multiple companies. For example, Pfizer and Teva all produce benzylpenicillin and supply it to at least one access country. Benzathine benzylpenicillin, a type of benzylpenicillin supplied by Pfizer, is the only antibiotic recommended to prevent mother-to-child transmission of syphilis. Shortages in many countries have contributed to an increase in syphilis globally. Mylan and Teva each produce 15 forgotten antibiotics, and report supplying more of them to access countries than other companies evaluated (six and five forgotten antibiotics respectively, see figure 7).

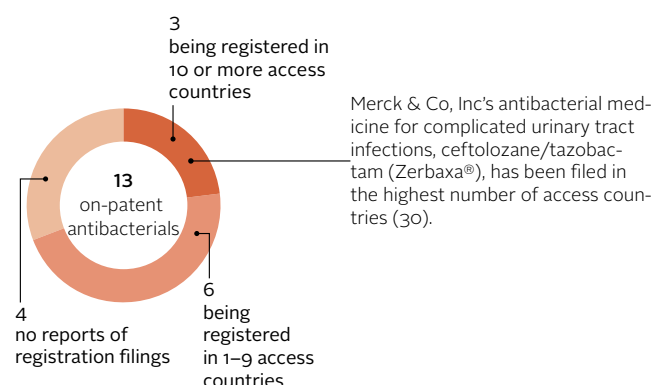
1 Pulcini C, Bush K, Craig WA, et al. Forgotten Antibiotics: An Inventory in Europe, the United States, Canada, and Australia. Clin Infect Dis. 2012;54(2):268-274. doi:10.1093/cid/cir838

FIGURE 7

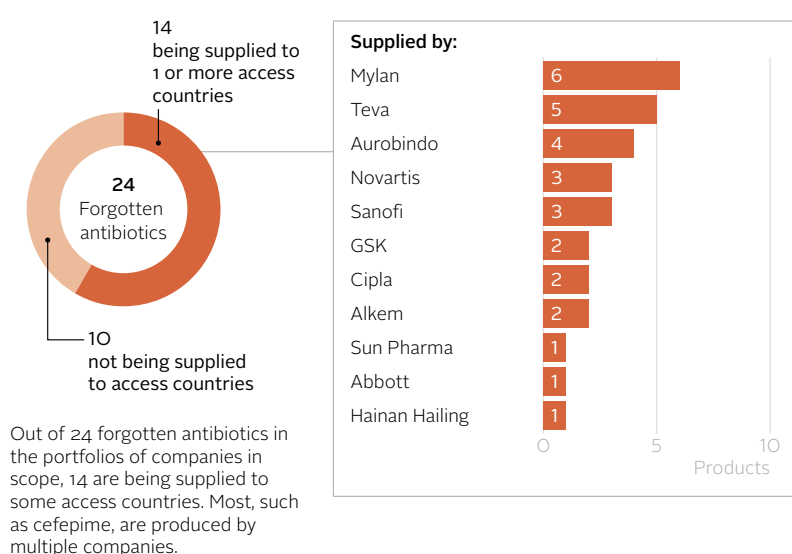
Many missed opportunities to improve access to antibiotics where need is highest

The first figure shows the proportion of on-patent antibiotics that have been filed for registration in countries with the greatest need for better access (termed access countries*). The second figure shows the proportion of forgotten antibiotics being supplied to these same countries. Both of these proportions are low, indicating many missed opportunities to improve access to antibiotics where need is highest. It seems unlikely that these antibiotics are widely available in countries with high burdens of disease and high rates of resistance.

No. of on-patent antibiotics filed in at least one access country



No. of forgotten antibiotics supplied to access countries



* 102 low- and middle-income countries with a high burden of disease and high need for greater access to medicine.

** Set of 30 older, off-patent antibiotics that are still clinically useful but have become 'forgotten', defined by Pulcini et al in 2017.¹

WHAT NEXT

For new on-patent antibiotics, companies can prioritise filing for registration in countries with the highest burden of relevant infectious diseases. Registration can be accelerated and made more cost effective if companies prepare their registration dossiers during the product development stage, and then rapidly plug them into a joint assessment or other registration or prequalification mechanism.

There are disincentives to registration in some countries, such as limited local regulatory resources, low-volume markets, political instability or conflict, and economic sanctions. Although filing for registration is under the control of companies, an enabling environment could help reduce the burden and cost and therefore facilitate this step. For example, bedaquiline went through a procedure developed by WHO that aims to facilitate and accelerate national regulatory

approvals.

To improve the availability of forgotten antibiotics and other older antibiotics, the priority is to ensure these medicines are still produced in sufficient volumes, and to put measures in place to make reliable supplies available within low- and middle-income countries. A role for non-profit medicine suppliers may also help pool demand. Colistin, for example, is a last-resort antibiotic to treat multi-drug resistant pneumonia, urinary tract infections and meningitis. It should be available and affordable in LMICs, provided there are good stewardship practices in place to prevent incidences of toxicity and reduce the risk of driving antibiotic resistance.

KEY FINDING 3: STEWARDSHIP IN SALES PRACTICES

Progress in how pharma companies tackle overselling antimicrobials

10 companies decouple bonuses from sales volume or avoid using sales agents altogether, up from 5 in 2018.

- By decoupling bonuses from sales volumes, or not using any sales staff at all, pharma companies mitigate against overselling antibiotics and driving resistance.
- Three companies have no sales agents promoting antibiotics or antifungals.
- Seven companies fully or partially decouple sales agents' bonuses from volumes.

What does the Benchmark analysis show?

The 2020 Antimicrobial Resistance Benchmark finds that responsible sales practices are gaining traction among pharmaceutical companies, when it comes to antibacterial and antifungal medicines. The number of companies engaging in responsible promotional practices has risen from five in 2018 to 10 in 2020, with six companies demonstrating best practice for at least some medicines.

What does a responsible promotional practice look like?

The Benchmark looks at whether or not pharmaceutical companies use sales agents to promote their antibacterial and antifungal medicines. By avoiding the use of sales agents, companies reduce the risk of overselling to healthcare professionals. For companies that do still have a sales force, the Benchmark looks at whether they have removed the incentive to oversell by decoupling their sales agents' financial rewards from the volume of antibacterial and/or antifungal medicines they sell.

How do the companies' practices compare?

Teva demonstrates best practice in this area, as it does not have a sales force to promote any of its antibacterial or antifungal medicines. Otsuka and Johnson & Johnson also apply this stewardship practice to their tuberculosis medicines, delamanid (Deltysba™) and bedaquiline (Sirturo®) respectively. Given the comparatively wide spread of extensively drug-resistant and multidrug-resistant tuberculosis strains, the stewardship of tuberculosis medicines is prioritised by global health and national public health bodies. As a result, tuberculosis medicines are generally not promoted by companies. Political attention and public concern about antimicrobial resistance is rising, meaning the pharmaceutical industry can anticipate this level of stewardship in the future for all antibacterial medicines.

When it comes to decoupling, three companies – Cipla, Shionogi and Wockhardt – fully decouple sales bonuses from volumes in the antibacterial and antifungal medicines space,

with Cipla as the first generic medicine manufacturer identified by the Benchmark to fully decouple. Through pilots established in 2019, Pfizer and Merck & Co, Inc have fully decoupled such bonuses in the UK. Pfizer also partially decouples bonuses from sales volumes in other countries. Novartis partially decouples bonuses, maintaining the practice it reported to the 2018 Benchmark. GSK is the only company to have regressed in this area since the 2018 Benchmark. It was a pioneer in 2013 when it fully decoupled all sales agent bonuses globally from antibacterial sales volumes, but the 2020 Benchmark reports it now embraces partial decoupling rather than full decoupling.

How can sales bonuses drive resistance rates?

One of the main drivers for the emergence of antimicrobial resistance (AMR) is the inappropriate use of antibacterial and antifungal medicines. This includes when doctors prescribe them when they are not needed. Inappropriate use has been shown to cause antimicrobials to become ineffective more rapidly. In India, for example, resistance already exceeds 70% for many bacteria, including *E. coli* and *K. pneumoniae*. The country also has one of the highest rates of antibacterial consumption. Addressing inappropriate use is one of the pillars of global efforts to curb AMR.

WHAT NEXT

Pharmaceutical companies should adopt responsible promotional practices to help ensure their antibacterial and antifungal medicines are prescribed appropriately and only when needed, in order to prolong their effectiveness. The current best practice is to stop deploying sales agents to sell antibacterials and antifungals to healthcare professionals. For companies that retain a sales force, best practice means fully decoupling agents' financial rewards from sales volumes, to remove the financial incentive to oversell. Where decoupling is policy, companies must take steps to ensure the policy is implemented in all territories.

FIGURE 8

Positive shift in pharmaceutical companies' promotional practices to improve stewardship

The chart shows how many companies are engaging in responsible promotional practices to improve stewardship and prolong the effectiveness of antibacterial and antifungal medicines. Since 2018, more companies have begun to decouple sales bonuses from sales volumes, which removes the incentive to oversell.

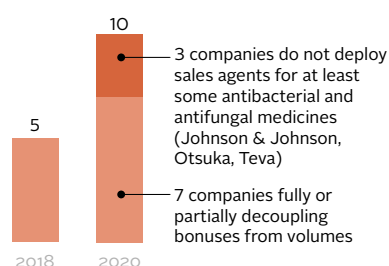


TABLE 1

How far does responsible promotion go when it comes to deploying sales staff and linking bonuses to sales volume?

By avoiding the use of sales agents to promote antibacterials or antifungals, companies mitigate the risk of overselling to healthcare professionals. For companies that do still have a sales force, the Benchmark looks at whether they are minimising the incentive to oversell by decoupling their sales agents' bonuses from sales volumes.

| Company | Portfolio size* | How far does decoupling go? |
|-------------------|-----------------|--|
| Teva | 202 | No sales force |
| Otsuka | 1 | No sales force |
| Johnson & Johnson | 25 | No sales force for Bedaquiline (Sirturo®) |
| Cipla | 72 | 100% decoupled |
| Shionogi | 19 | 100% decoupled |
| Wockhardt | 59 | 100% decoupled |
| Pfizer | 190 | Partial decoupling: 50% of variable pay** is decoupled |
| GSK | 95 | Partial decoupling: 75% of agents' pay is decoupled |
| Novartis | 154 | Partial decoupling: 72% of agents' pay is decoupled |
| Merck & Co, Inc | 26 | (UK pilot) 100% decoupled |

* Antibacterial and antifungal medicines and vaccines

** Proportion of variable pay not disclosed

Novartis and Fresenius Kabi limit use of sales-related bonuses for sales agents by selling through tenders without sales agents or volume-linked bonuses.

Pfizer has fully decoupled bonuses from volumes in a UK pilot, as has Merck & Co, Inc.

GSK and Novartis award bonuses linked to team sales targets. Pfizer goes further by linking bonuses to national sales targets.

KEY FINDING 4: AMR SURVEILLANCE

Pfizer is the first company to share raw data on the spread of resistance

Most pharma companies publish results of their surveillance programmes. Pfizer is first to share raw data.

- Surveillance is essential for monitoring and controlling the spread of diseases and the rise of antimicrobial resistance.
- 13 pharma companies, up from 9 in 2018, collect data on the spread of resistance and the effectiveness of their medicines through AMR surveillance programmes.

What type of data do pharmaceutical companies collect?

The 2020 Antimicrobial Resistance Benchmark finds that pharmaceutical companies are engaged in tracking resistance in bacterial and fungal pathogens; 13 companies are running or supporting antimicrobial resistance (AMR) surveillance programmes, compared with nine in 2018. These programmes typically monitor the prevalence of drug-resistant infections, and whether or not they can be treated with specific medicines. The Benchmark identified 20 AMR surveillance programmes, compared with 19 in 2018, including nine programmes in India, which has some of the highest resistance rates globally. The programmes cover 13 out of 18 bacterial and fungal pathogens that pose the greatest AMR threat. These include drug-resistant *S. pneumoniae*, which is the main cause of community-acquired pneumonia and meningitis in children and the elderly.

How important are these data?

Surveillance is primarily the responsibility of governments, yet through their surveillance programmes, the pharmaceutical companies involved have unique knowledge of the resistance map, particularly where their data covers countries without national surveillance efforts. Their data and insights are valuable puzzle pieces, for example for developing treatment guidelines to aid doctors in making clinical decisions.

What information are companies sharing?

As in 2018, the 2020 Benchmark finds that all companies undertaking surveillance also share the results for at least one of their programmes, or state that they intend to share them once they are available. Results are being shared in peer-reviewed journals, presentations to conferences, via public health agency reports or are being made available online. The 2020 Benchmark found that nine companies shared surveillance programme results in open-access journals or via data platforms. In a pioneering move, Pfizer has become the first company to share raw data, publishing the data from its ATLAS surveillance programme, which is active in 73

countries, on an open-access online AMR register established by the Wellcome Trust and the Open Data Institute. In 2018, GSK had reported plans to do this, but thus far has not shared its raw data with the register.

What is the practical application of surveillance data?

Insight into where resistance to specific medicines is occurring can lead to better treatment choices, by helping doctors determine which medicines are likely to be ineffective because of resistance. It can lead to more targeted pharmaceutical R&D, by guiding medicine innovators on where best to conduct clinical trials and on the best properties for the new medicines. It can support public health authorities in forecasting disease trends and planning medicine purchases.

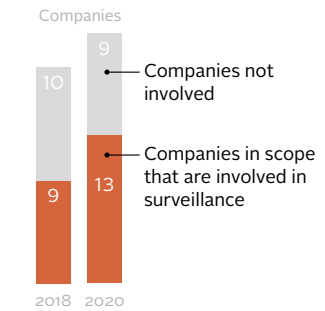
WHAT NEXT

There is significant potential for sharing raw data from other company surveillance programmes, such as GSK's SOAR programme, spanning more than 30 countries, and Merck & Co, Inc's SMART programme, which operates in 63 countries. The WHO's new Global Antimicrobial Resistance Surveillance System (GLASS) is being developed to analyse and report global data regularly. So far, GLASS has data from 87 countries. The companies evaluated in this Benchmark have data from 38 countries not covered by GLASS, and have data going back more than a decade for at least 11 programmes. Data could be contributed to the Global Burden of Disease study, published by the Institute of Health Metrics and Evaluation (IHME), which announced in 2018 that it will start including AMR morbidity and mortality in the study. In addition, the Wellcome Trust launched a Data Reuse Prize in November 2018 to reward researchers who come up with a new insight, tool or health application from data available in its AMR Register.

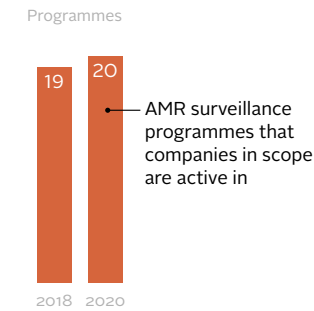
FIGURE 9
Publishing surveillance results is common practice, with sharing raw data a new gold standard

Pharmaceutical companies have unique knowledge of the resistance map. Their engagement in surveillance, and the insights that come from it, are important puzzle pieces for global efforts to control disease and preserve the lifespan of antimicrobials. The figures show that sharing results is now a standard practice. One company leads the way by also sharing raw data.

Companies involved in surveillance



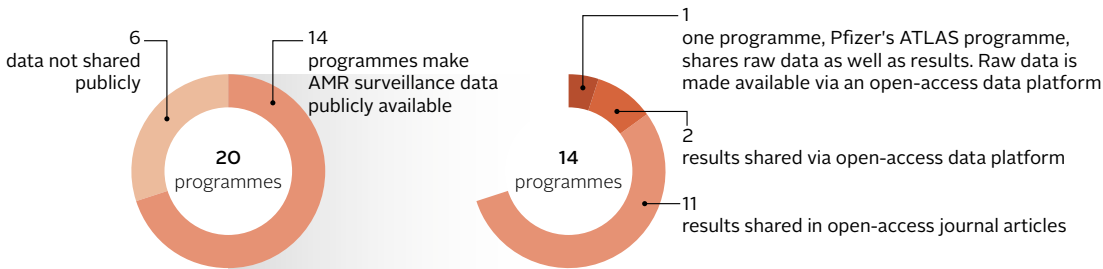
Number of surveillance programmes



HOW CAN SURVEILLANCE DATA BE USED?

- Pharmaceutical companies typically monitor the spread of disease in order to understand whether their products are effective in specific regions.
- Hospitals and governments need to know where resistance is developing so they can adapt treatment guidelines and inform prescribers of antibiotics.
- By using and combining the raw data from companies' surveillance programmes, third-party researchers can explore the potential for further research, beyond the specific questions asked by the companies themselves.

Only one company shares raw AMR surveillance data



PIPELINE & PORTFOLIO ANALYSIS

R&D Pipelines: Which companies are developing new treatments for the most threatening bacteria and fungi?

Pathogens are becoming increasingly resistant to common antibiotics, which drives an urgent need for new and novel treatment options. To reveal which promising new products are being developed, the 2020 AMR Benchmark has analysed the size and contents of 21 pharmaceutical pipelines. The Benchmark looks at R&D projects that target the biggest bacterial and fungal threats from antimicrobial resistance (AMR).

The Benchmark has identified the companies with the largest pipelines targeting these 'priority pathogens', breaking them down into medicine and vaccine projects. It identifies medicine candidates that qualify as 'novel' – meaning they are likely to be more effective against resistant pathogens. It also identifies which pathogens are most frequently targeted by the companies in scope.

138 projects targeting the biggest bacterial and fungal threats

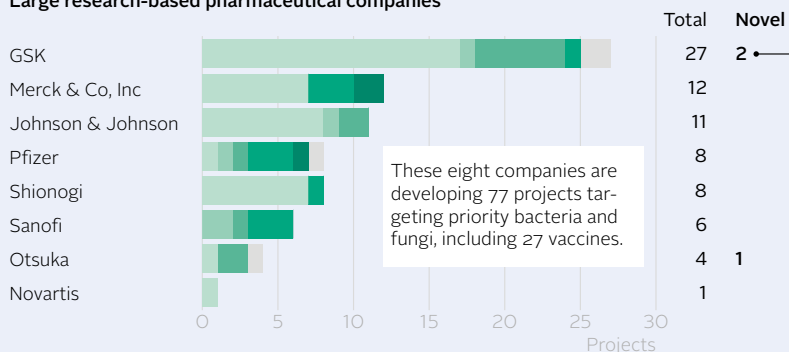
FIGURE 10

The charts below provide a breakdown of companies' R&D pipelines targeting 18 bacterial and fungal pathogens that pose a significant threat to human health (defined by WHO and the CDC). A total of 138 R&D projects are being developed by 21 companies, 54% are in clinical development or beyond.

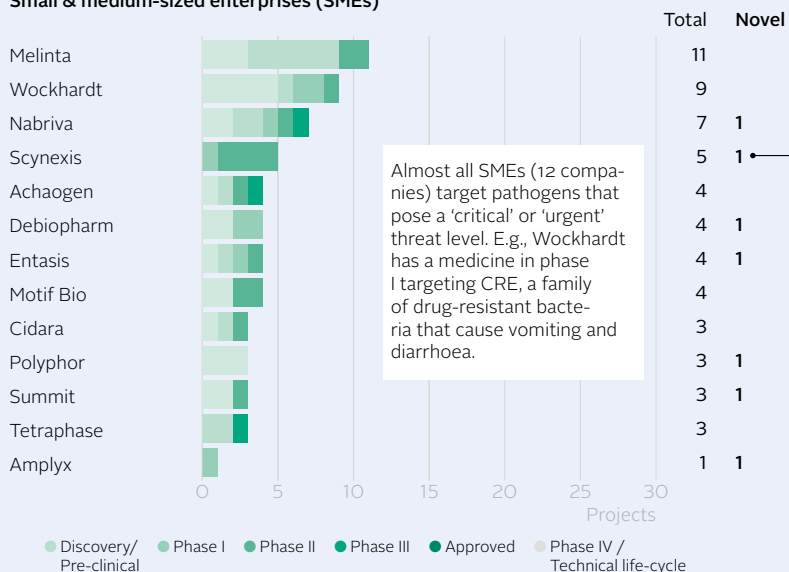
138 priority R&D projects



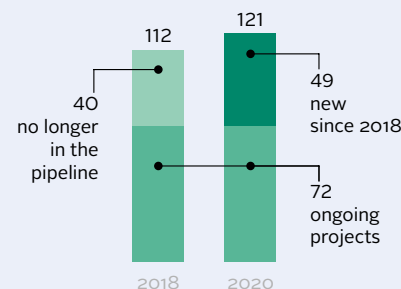
Large research-based pharmaceutical companies



Small & medium-sized enterprises (SMEs)



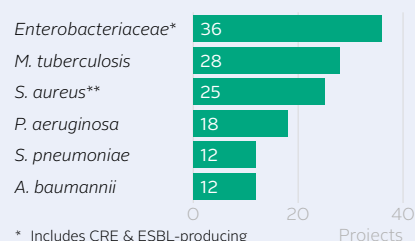
The pipeline* has grown only marginally since 2018. One third of projects advanced.



* Showing only those projects that meet criteria used in both 2018 and 2020.

Two novel medicines, from Entasis and GSK, target *N. gonorrhoeae*, which infects 78 million people each year globally.¹

Which pathogens are targeted most?



* Includes CRE & ESBL-producing

** Includes MRSA and VRSA

How urgently are new medicines needed?

New medicines are needed to replace the ones that are no longer effective. In Brazil, Indonesia and Russia, 40%-60% of infections are caused by drug-resistant bacteria.² In India, this reaches more than 70% for several common bacteria.³ In the US, 90% of *Candida auris* isolates are resistant to one antifungal (fluconazole).²

PIPELINE & PORTFOLIO ANALYSIS

Portfolios: Which companies produce the most antibacterial and antifungal products?

By using antibiotics inappropriately, we drive drug resistance rates and make these medicines less effective. Yet, millions of people around the world cannot access antibiotics when they need them. For the pharmaceutical companies that produce and supply these medicines, the challenge is to work with governments and others to make these medicines more accessible, particularly in low- and middle-income

countries, while supporting the stewardship efforts that will prevent their inappropriate use or overuse. The Benchmark has mapped the antibacterial and antifungal portfolios of the biggest players in the anti-infectives market. Out of 1,520 marketed products in this analysis, more than 600 (40%) have been flagged by the World Health Organization as priorities for either better access or stricter stewardship.

40% of products are flagged by WHO as priorities for better access and stewardship

FIGURE 11

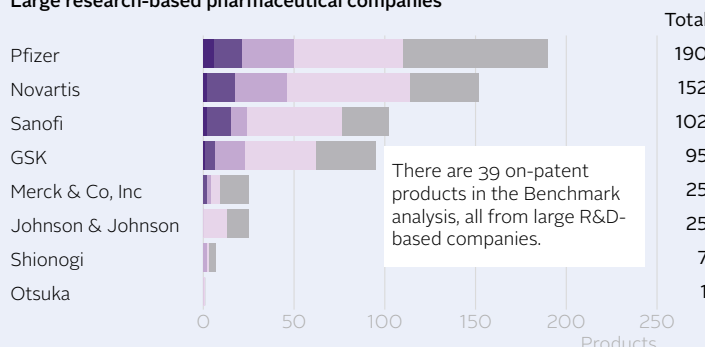
The charts below compare companies' antibacterial and antifungal portfolios.

In total, 1,520 antibacterial or antifungal medicines and/or vaccines are already available by 22 companies. More than 600 (40%) are on the WHO Model Lists of Essential Medicines, which identifies the minimum medicine needs for a basic healthcare system.

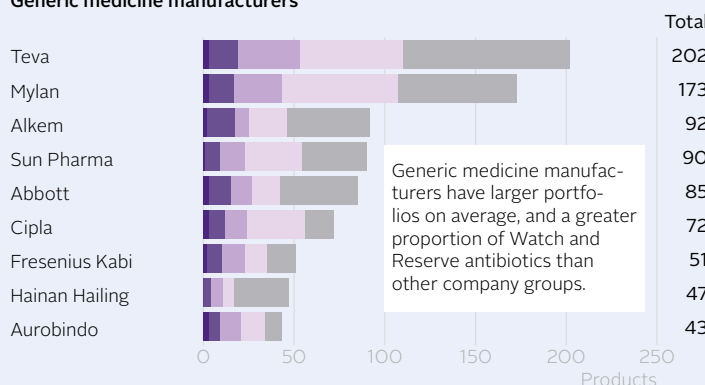
1520 antibacterial and antifungal medicines and vaccines



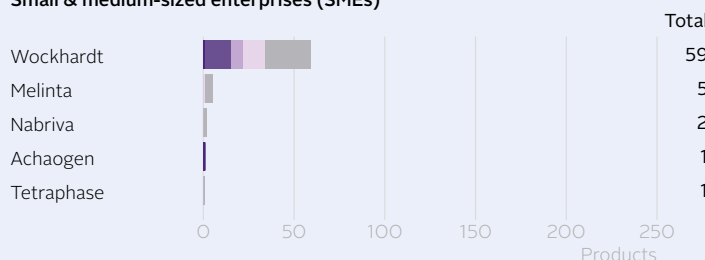
Large research-based pharmaceutical companies



Generic medicine manufacturers

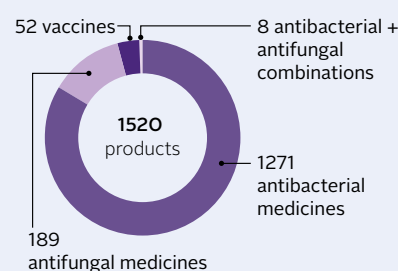


Small & medium-sized enterprises (SMEs)



On the WHO EML, category
 ● Reserve* ● Watch** ● Access ● Other*** ● Not on the WHO EML

52 products are vaccines (3.4%)



Which access tactics match the medicine?

To curb AMR while improving access, companies must ensure they match their tactics to the medicine in question. This starts with checking whether antibiotics are categorised by WHO as priorities for Access, Watch or Reserve.

- **Access antibiotics:** 1st- and 2nd-line treatments that should be widely available. For these, companies need broad strategies to improve access: e.g., registration filings, affordability measures, stronger supply chains.
- **Watch antibiotics:** To manage antibiotics in this group, companies need a nuanced approach, integrating suitable access plans with stewardship practices designed to limit misuse and overuse and to predict emerging resistance trends.
- **Reserve antibiotics:** Last-resort treatment options against the most severe, resistant infections, for when all other antibiotics fail. Companies must engage in stewardship activities that ensure their appropriate use and closely monitor resistance.

* Includes anti-TB medicines with Reserve group properties

** Includes anti-TB medicines with Watch group properties

*** Includes anti-TB medicines without Watch or Reserve group properties

REFERENCES

- 1 Bodie M., et al. Addressing the rising rates of gonorrhea and drug-resistant gonorrhea: There is no time like the present. *Can Commun Dis Rep.* 2019;45(2-3):54–62. Published 2019 Feb 7. doi:10.14745/ccdr.v45i23a02
- 2 The World Bank. Pulling Together to Beat Superbugs.;2019. <https://www.worldbank.org/> Accessed January 07, 2020.
- 3 CDDEP. Antibiotic Resistance of *Escherichia coli* in India; <https://resistancemap.cddep.org/>. Assessed January 07, 2020.

Research Areas

The 2020 AMR Benchmark uses a framework of 19 indicators organised into three Research Areas: Research & Development; Responsible Manufacturing; and Appropriate Access and Stewardship. These correspond to pharmaceutical companies' core responsibilities for limiting AMR: developing new medicines to replace ones that no longer work, make them accessible to those who need them, and find new ways to ensure antibiotics are produced and promoted responsibly. Not all companies are eligible for each Research Area, as the Benchmark only evaluates companies in metrics that are relevant to its portfolio and/or pipeline.

Each Research Area includes a ranking of how the companies performed, the leaders of each area and the drivers behind their performance and breakdown of industry activity.

Research & Development – page 33



Responsible Manufacturing – page 51



Appropriate Access & Stewardship – page 65



A RESEARCH & DEVELOPMENT

WHY THIS MATTERS

As antimicrobial medicines become less effective due to resistance, the need to develop new ones grows more pressing. New vaccines can also slow the emergence of resistance by preventing disease. To highlight the top R&D priorities, WHO and the US Centers for Disease Control and Prevention (CDC) have compiled a list of certain pathogens that pose a greater threat of resistance than others.

Once a new medicine or vaccines is approved, the challenge is to bring it to market in a way that slows the emergence of resistance. This requires advance planning while the product is still in the clinical pipeline, through licensing or pricing commitments, for example.

HOW WE MEASURE

The research presented in this area covers bacteria and fungi on R&D priority lists, such as the superbug *C. difficile*, or carbapenem-resistant *Enterobacteriaceae*. The Benchmark uses these lists to identify which companies align their R&D activities with defined global health priorities for AMR and to assess the industry' responsiveness to these calls for action. R&D priority lists include:

1. WHO global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics (2017);*
2. U.S. Centers for Disease Control and Prevention (CDC) antibiotic resistance threats in the United States (2013). **

WHAT WE MEASURE

The Benchmark uses a framework of seven metrics to analyse the R&D activities of eight large research-based pharmaceutical companies and 13 small & medium-sized enterprises SMEs across two main areas:

1. Pipelines: how many projects a company has to address priority pathogens and the degree to which products are of value for public health, judged against four criteria: novelty; medicines that can improve take-up in countries with urgent need; and vaccines in general,
2. Access and stewardship planning: companies are expected to have plans in place for pipeline projects in Phase II and beyond. The Benchmark assesses the extent to which a company creates and discloses plans to make new products swiftly accessible upon market entry and ensure they will be used appropriately.

The Benchmark does not assess the R&D activities of the generic medicine manufacturers in scope.

How companies are scored

| | Indicators | | | | | | | |
|---|------------|-------|-------|-------|-------|-----|-----|--|
| | A 1 | A 2.1 | A 2.2 | A 2.3 | A 2.4 | A 3 | A 4 | |
| Large research-based pharmaceutical companies | | | | | | | | |
| GSK | ● | ● | ● | ● | ● | ● | ● | |
| Johnson & Johnson | ● | ● | ● | ● | ● | ● | ● | |
| Merck & Co, Inc | ● | ● | ● | ● | ● | ● | ● | |
| Novartis | ● | ● | ● | ● | ● | ● | ● | |
| Otsuka | ● | ● | ● | ● | ● | ● | ● | |
| Pfizer | ● | ● | ● | ● | ● | ● | ● | |
| Sanofi | ● | ● | ● | ● | ● | ● | ● | |
| Shionogi | ● | ● | ● | ● | ● | ● | ● | |
| Small and medium-sized enterprises (SMEs) | | | | | | | | |
| Achaogen | ● | ● | ● | ● | ● | ● | ● | |
| Amplix | ● | ● | ● | ● | ● | ● | ● | |
| Cidara | ● | ● | ● | ● | ● | ● | ● | |
| Debiopharm | ● | ● | ● | ● | ● | ● | ● | |
| Entasis | ● | ● | ● | ● | ● | ● | ● | |
| Melinta | ● | ● | ● | ● | ● | ● | ● | |
| Motif Bio | ● | ● | ● | ● | ● | ● | ● | |
| Nabriva | ● | ● | ● | ● | ● | ● | ● | |
| Polyphor | ● | ● | ● | ● | ● | ● | ● | |
| Scynexis | ● | ● | ● | ● | ● | ● | ● | |
| Summit | ● | ● | ● | ● | ● | ● | ● | |
| Tetraphase | ● | ● | ● | ● | ● | ● | ● | |
| Wockhardt | ● | ● | ● | ● | ● | ● | ● | |

● Scored ● Not scored

● Scored ● Not scored

Indicators

| Indicators | Page |
|--|------|
| A.1 R&D investments | 48 |
| A.2.1 Pipeline size | 40 |
| A.2.2 Novelty | 42 |
| A.2.3 Vaccine R&D | 42 |
| A.2.4 Projects targeting critical pathogens | 40 |
| A.4 Access and stewardship planning | 46 |

* WHO priority pathogens list, 2017

** CDC Antibiotic Resistance Threats list, 2019

RESEARCH & DEVELOPMENT

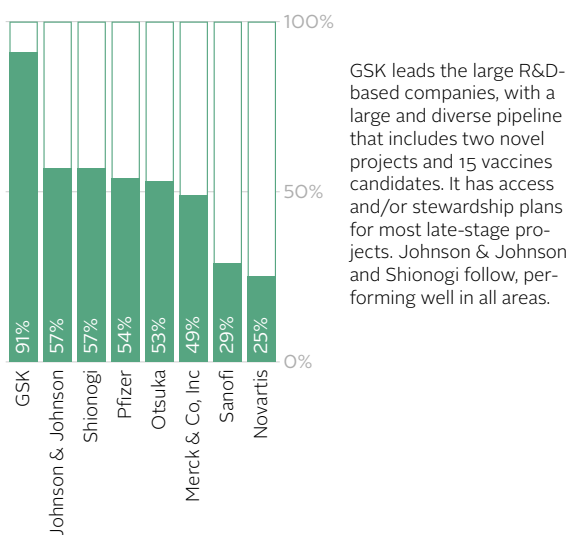
How the companies compare in Research & Development

The Benchmark analyses the R&D pipelines from eight large research-based companies and 13 pharmaceutical SMEs. It maps medicine and vaccine projects targeting priority bacterial and fungal pathogens.

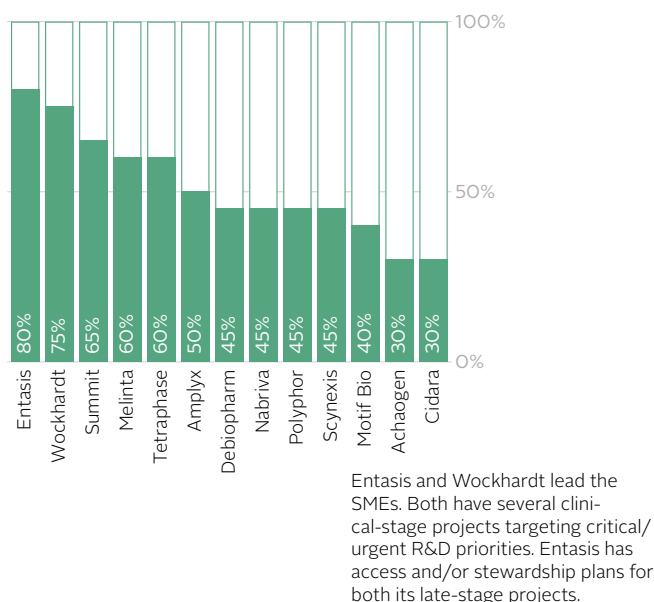
FIGURE 12

Research & Development: how the companies perform

Large research-based pharmaceutical companies



Small- and medium-sized enterprises (SMEs)



WHAT SETS THE TWO GROUPS APART?

Large, diverse pipelines, with more access & stewardship plans

Most of the eight large research-based companies are developing between six and 12 projects. GSK's pipeline is largest at 27 projects, ahead of Merck & Co, Inc with 12. These eight companies account for all vaccines projects identified, including four targeting bacteria in the highest threat category: *C. difficile* (GSK and Pfizer), *E. Coli* (Johnson & Johnson) and *N. gonorrhoeae* (GSK). Two of the eight companies have gained marketing approval for new antibacterials since 2018: Merck & Co, Inc for imipenem/cilastin/relebactam (Recarbrio™) and Pfizer for ceftaroline/fosamil (Zinforo™). This group accounts for most of the clinical-stage projects that have both access and stewardship plans in place (5/8). Five of these companies disclose their R&D investments on the basis of confidentiality, with Shionogi investing the highest proportion of its pharmaceutical revenues.

New and novel medicines targeting biggest AMR threats

The 13 pharmaceutical SMEs are largely developing between three and five projects. Only Melinta and Wockhardt's pipelines are larger (11 and nine projects respectively). Overall, the R&D activities of these 13 companies focus on bacteria and fungi in the highest threat category (31 out of 61 projects). These 13 companies account for six of the nine novel clinical-stage projects identified, including the two novel antifungals (fosmanogepix from Amplix; ibrexafungerp from Scynexis), which both target *Candida spp.*. Three of the 13 companies have gained marketing approval for new antibacterials since 2018: Achaogen, Tetraphase and Nabriva. The 13 companies are generally less likely than large research-based pharmaceutical companies to have access and/or stewardship plans in place for late-stage candidates, as they typically do not commercialise their own pharmaceuticals.

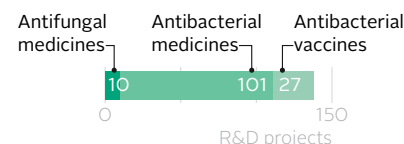
IN SUMMARY

PIPELINE SIZE

P 38

138 R&D projects in the pipeline

A total of 138 R&D projects that target infections caused by the most threatening bacteria and fungi are in development. Almost 75% of projects are medicines targeting bacteria.

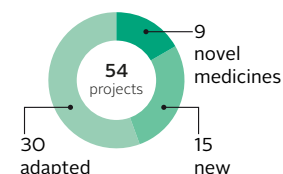


NOVELTY OF PIPELINE

P 42

Few new clinical-stage medicines are novel

Of the 138 R&D projects in the pipeline, only nine medicines in the clinical stages of development are considered novel, meaning they offer a much lower risk of resistance.



NOVELTY OF PIPELINE

P 42

Most novel candidates are being developed by SMEs

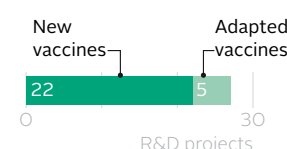
The nine novel medicines in clinical stage are being developed by six SMEs (Amplyx, Debiopharm, Entasis, Nabriva, Summit and Scynexis) and two large R&D-based companies (GSK and Otsuka).

VACCINES IN THE PIPELINE

P 42

27 vaccine projects in development

Five of the large R&D-based companies are active in vaccines R&D, with a total of 27 projects. Three companies, GSK, Johnson & Johnson and Pfizer are developing vaccines that target the most urgent pathogens. No company is developing a fungal vaccine.



CRITICAL/URGENT PATHOGENS

P 40

Highest threat pathogens are focus for many SMEs

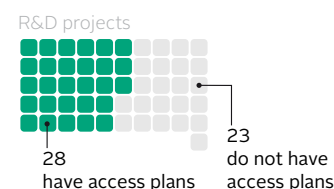
While large research-based pharmaceutical companies mostly focus on high or serious priority pathogens, most of the SMEs in scope are focused on R&D targeting the bacteria and fungi that pose the biggest threats from AMR.

WHAT'S NEW SINCE 2018?

P 44

One third of projects advanced along the pipeline

When comparing pipelines assessed in both the 2018 and 2020 AMR Benchmark, almost one-third of projects progressed from one stage of development to another.



ACCESS PLANNING

P 46

Over 50% of late-stage projects have access plans

The Benchmark evaluates whether companies are planning ahead to ensure their late-stage candidates are made available once approved. Out of 51 projects identified, 28 projects have mechanisms to enhance access to low- and middle countries.

STEWARDSHIP PLANNING

P 47

Only 20% of late-stage projects are covered by stewardship plans

The Benchmark assesses whether companies have measures in place to ensure their late-stage projects are used prudently once on the market. Out of 39 projects identified, only eight projects have such plans in place.

R&D INVESTMENTS

P 49

R&D investments vary across companies

Out of 21 companies evaluated in this area, 17 disclose their R&D investments for antibacterial and antifungal medicines and vaccines that target priority pathogens. Their investments vary from USD 30 million up to USD 370 million.

RESEARCH & DEVELOPMENT

Small & medium-sized enterprises lead in priority research

Pipelines remain small, though valuable, while efforts to plan for access and stewardship are picking up traction.

- The Benchmark examines R&D pipelines of eight large research-based pharmaceutical companies, and 13 small and medium-sized enterprises (SMEs)
- 53 out of 138 R&D projects (38%) target priority bacterial and fungal infections where the urgency/ threat is the highest
- Six new products gain approval since 2018, with a third of R&D projects advancing along the pipeline

CONTEXT

As existing antimicrobial medicines become less effective due to resistance, the need to develop new products grows more pressing. New vaccines, too, can play a part in slowing the emergence of resistance, by preventing disease and thereby averting the need for antibacterial and antifungal medicines – and, in turn, their overuse and inappropriate use. When regulatory authorities approve new antibacterial and antifungal products for sale, pharmaceutical companies should introduce them in a way that ensures they are rapidly and appropriately made accessible to the patients who need them, while also helping to conserve their use, in order to slow the emergence of AMR. Achieving these twin aims requires careful planning before products reach the market, and may only be possible at a significant financial cost with a risk of a lack of sufficient return on investments.

In this Research Area, the 2020 AMR Benchmark examines the R&D pipelines of eight large research-based pharmaceutical companies, and 13 small and medium-sized enterprises (SMEs). These companies have been selected based on criteria described in detail in the Antimicrobial Resistance Benchmark Methodology 2019. Information on the companies' pipelines was drawn from public sources, including clinical trial registers and published reports on clinical pipelines, as well as from data submissions by the 21 companies in scope. Data was captured on medicines and vaccines targeting only those bacterial and fungal pathogens that pose the greatest threat to human health from AMR (referred to as priority pathogens).

As part of the pipeline analysis, the Benchmark identifies novel antibacterials and antifungals, which are more likely to be effective for longer against resistant strains, and it assesses how companies plan ahead to ensure new products can be made available and accessible, appropriately, for patients in need. The Benchmark does not score in this Research Area those companies it categorises as generic medicine manufacturers.

PROJECTS IN THE PIPELINE

Comparing the Benchmark's antibacterial pipeline analysis to Pew and WHO research

Some bacteria have become resistant to a significant number of antibacterials due to overuse and/or inappropriate use. In the 2020 Benchmark, priority pathogens are those bacteria and fungi that have been identified and prioritised as the greatest threats to human health by the World Health Organization (WHO)¹ and the US Centers for Disease Control (CDC)² (table 3). The criteria for including R&D projects in this analysis are set out in table 2.

TABLE 2

How the Benchmark pipeline analysis complements other reports

The table gives an overview of the inclusion criteria used to select R&D projects for analysis by the 2020 AMR Benchmark, the WHO 2019 Update of Antibacterial Agents in Clinical Development and the Pew Trusts Antibiotics Currently in Global Clinical Development Sept 2019. The criteria differ slightly between reports. Benchmark analysis complements the WHO and Pew Trusts analyses by comparing specific companies on specific aspects of antimicrobial R&D.

| Inclusion criteria | 2020 AMR Benchmark | WHO analysis* | The Pew Trusts analysis† |
|---|--------------------|---------------|--------------------------|
| Company selection | ● (21) | all | all |
| New candidate products (NCE or NBE) incl combinations with at least 1 NCE) | ● | ● | ● |
| Adapted products (no NCE or NBE), label extensions, combinations without an NCE | ● | ● | ● |
| Systemic agents | ● | ● | ● |
| Topical agents | ● | ● | ● |
| Vaccines | ● | ● | ● |
| Other biologic agents (i.e., phage therapy, lysins) | ● | ● | ● |
| Gram-negative bacteria & Gram-positive bacteria | ● | ● | ● |
| Tuberculosis | ● | ● | ● |
| Fungi | ● | ● | ● |

* Update of Antibacterial Agents in Clinical Development. World Health Organization, 2019

† Tracking the Global Pipeline of Antibiotics in Development - update September 2019

TABLE 3

Priority bacterial and fungal pathogens for R&D and threats for human health

The 2020 AMR Benchmark has assessed pharmaceutical companies' R&D projects that target priority bacterial and fungal pathogens. The pathogens deemed priority by the Benchmark are listed here and comprise pathogens that are already drug-resistant, or where resistance is emerging.

| Pathogen | Prioritised for resistance to | WHO Priority List* | CDC AR Threats list** |
|---|---|--------------------|-----------------------|
| BACTERIA | | | |
| <i>Acinetobacter</i> spp. | Carbapenem | ● | ● |
| <i>Campylobacter</i> spp. | Fluoroquinolone | ● | ● |
| <i>Clostridioides difficile</i> | | | ● |
| <i>Enterobacteriaceae</i> | Carbapenem / beta-lactam / 3 rd generation cephalosporin | ● | ● / ● |
| <i>Enterococcus</i> spp. (<i>E. faecalis</i> & <i>E. faecium</i>) | Vancomycin | ● | ● |
| <i>Haemophilus influenzae</i> | Ampicillin | ● | |
| <i>Helicobacter pylori</i> | Clarithromycin | ● | |
| <i>Mycobacterium tuberculosis</i> | | ▲ | ● |
| <i>Neisseria gonorrhoeae</i> | 3 rd generation cephalosporin / fluoroquinolone | ● | ● |
| <i>Pseudomonas aeruginosa</i> | Carbapenem | ● | ● |
| <i>Salmonella</i> spp. | Fluoroquinolone | ● | ● |
| <i>Shigella</i> spp. | Fluoroquinolone | ● | ● |
| <i>Staphylococcus aureus</i> | Methicillin / Vancomycin | ● | ● |
| <i>Streptococcus</i> (group A) | Erythromycin | | ● |
| <i>Streptococcus</i> (group B) | Clindamycin | | ● |
| <i>Streptococcus pneumoniae</i> | Penicillin-non-susceptible | ● | ● |
| FUNGI | | | |
| <i>Candida</i> spp. | | | ● |
| <i>Candida auris</i> | | | ● |

Clostridioides difficile is one of the leading causes of hospital-related deaths. In the United States, it caused 250,000 cases of life-threatening diarrhoea and colitis in hospitalised patients in 2017.² The world-wide increased incidence of *C. diff* has been attributed to an increase in resistance to fluoroquinolones.⁴

WHO estimates 87 million new cases of gonorrhoea annually.³ The pathogen responsible for causing gonorrhoea, *Neisseria gonorrhoeae*, has the potential to rapidly develop antimicrobial resistance, and experts have warned that it could become resistant to all currently available antibiotics in the future.

Pseudomonas aeruginosa is a Gram-negative pathogen that can cause severe infections such as urinary tract infections. One major challenge with developing new antibacterials that are active against Gram-negative bacteria is the complex cell envelope or wall that surrounds these bacteria. The discovery of new antibacterials that can permeate this barrier is crucial.⁵

WHO CDC
 ▲ R&D priority ● Urgent
 ● Critical ● Serious
 ● High ● Concerning
 ● Medium

The threat levels of the different pathogens for AMR and/or human health have been defined and determined by WHO's R&D Priority List (2017) and by the US Centers of Disease Control's US Biggest Threat List (2019). Both WHO and CDC use three levels of prioritisation, which can be seen as comparable: critical/urgent, high/serious, and medium/concerning.

The priority pathogens where the need for new innovations is the most critical/urgent are: carbapenem-resistant *A. baumannii*, carbapenem-resistant *P. aeruginosa*, carbapenem-resistant, 3rd generation cephalosporin-resistant *Enterobacteriaceae*, *C. difficile*, *N. gonorrhoeae* and *C. auris*.

These bacteria are responsible for severe infections and high mortality and, with the exception of *N. gonorrhoeae*, most of these infections are associated with hospital or healthcare facility acquired infections⁶.

* http://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf?ua=1 (published February 2017)

** http://www.cdc.gov/drugresistance/biggest_threats.html (last reviewed 11 November 2019)

All 21 companies included in this Research Area are active in pre-clinical and/or clinical R&D, between them engaging in a total of 138 projects that target infections caused by priority bacteria and fungi (figure 13). These projects include both new product candidates in development (defined as containing at least one new component not previously approved), and adapted products that can include new treatment regimens or combinations with already approved components, label extensions (including supplemental new drug applications (sNDAs)), or new formulations of approved products.

When focusing on new product candidates in the clinical pipeline, the Benchmark analysis largely overlaps with two cornerstone antibacterial pipeline analyses conducted in recent years: by Pew Trusts⁷ and by WHO.⁸ For example, 12 of the 21 companies in the Benchmark analysis are included in the 2019 WHO update. These 12 companies have 48 projects in clinical development (Phase I-III and recent approvals), including 20 that are classified as new antibacterial treatments and are also included in 2019 WHO update. From the remaining 28 projects, 25 are not included in the WHO's pipeline analysis (see table 2) as they are either adapted projects (17), vaccines (7) or topical formulations (1). Three projects included in the WHO analysis do not feature in the Benchmark as they do not fulfil the inclusion criteria.

54 R&D projects target Gram-negative bacteria

Most of the 138 projects in the 2020 Benchmark analysis (111, or 80%) are for medicines, with 27 projects (20%) for vaccines (figure 13). Most projects target bacterial rather than fungal priority pathogens (128 out of 138). This distribution reflects that 17 out of 18 priority pathogens in scope are bacterial. The pipeline includes 28 projects that address tuberculosis.

Breaking down the pipeline further, 54% of the non-tuberculosis antibacterial projects specifically target the scientifically challenging Gram-negative bacteria (GNB) that can cause severe infections and high mortality. Due to their cell wall structure and diverse resistance mechanisms it is more difficult for antibacterials to enter the cell of a GNB compared to Gram-positive bacteria (GPB) and many GNB species have now become resistant to multiple antibacterials. There are 54 projects in the pipeline for GNB, 29 for GPB (figure 15), and 16 that target both GNB and GPB. The GNB most frequently targeted are *Enterobacteriaceae* (including carbapenem-resistant *Enterobacteriaceae*, or CRE and extended-spectrum beta-lactamase (ESBL)-producing *Enterobacteriaceae*) (36 projects) followed by *P. aeruginosa* (18 projects) and *A. baumannii* (12 projects). The GPB most frequently targeted include *S. aureus* (25 projects) and *S. pneumoniae* (12 projects).

There are no projects in the Benchmark pipeline for *Campylobacter spp.* and *H. pylori*. The same is true for *Streptococcus* group A with only one project in the pre-clinical pipeline by all 21 companies in scope. These priority pathogens are however being targeted by companies or other organisations not included in this pipeline analysis.

For example, there is currently one project in Phase I for a *Campylobacter jejuni* capsule conjugate vaccine, being developed by the US Department of Defense, while ImevaX has a vaccine in Phase I against *H. pylori*.⁹

Pipeline is evenly split between clinical and pre-clinical

The pipeline from the 21 companies in scope is evenly split between the pre-clinical and clinical stages of development (figure 14). This distribution may change with better visibility of pre-clinical projects, which are more likely to be underreported for competitive reasons. Overall, of the 138 projects in this analysis, 64 are at discovery to pre-clinical stage, and 64 are in the clinical stage of development (Phase I-III). Of these 64 clinical-stage projects, 21 are for new medicines, 13 are for new vaccines, and 30 aim to adapt existing medicines and vaccines. A further six candidates gained approval between 9 September 2017 and 16 October 2019 and four are at other post-clinical stages (Phase IV or technical lifecycle, where a company continues the development process after a product enters the market to improve the use of a medicine or vaccine, in for example, under field conditions (e.g., to address cold chain issues or thermostability).

Resistant fungal infections – targeted mostly by SMEs

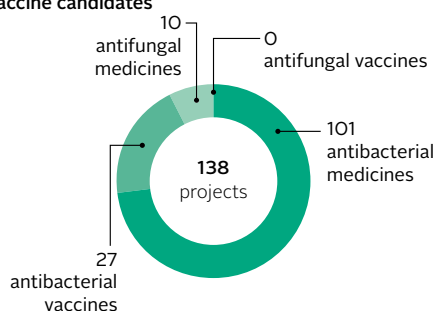
Around 1.5 million people die from invasive fungal infections each year and there is a growing resistance to antifungal agents.¹⁰ Of the 138 R&D projects in this analysis, 10 target fungal infections. All address *Candida spp.*, the only priority pathogen for fungi. The 138 projects also include six projects that target *C. auris*, which was recently classified as an urgent threat as well as other fungi such as *Aspergillus spp.*, *C. neoformans (cryptococcus)* and *P. carinii (pneumocystis)*. Between them, these four fungi account for about 90% of reported deaths caused by fungal infections.¹¹ Three SMEs (Amplifyx, Cidara and Scynexis) are focusing on developing new medicines for resistant fungal infections. These three companies have in total eight projects in clinical development. From the large research-based pharmaceutical companies, Shionogi is the only company in scope to target a priority fungal pathogen. The company has two projects in discovery.

With antifungal treatments failing due to increasing resistance¹⁰, fungal infections are emerging as a 'silent killer' in the healthcare setting.¹¹ The incidence of candidemia, a type of invasive or systemic candidiasis, is on the rise in the US and mortality rates often exceed 50%, despite use of antifungal drugs.^{12,13} This is especially true in intensive care units and in immunocompromised patients, where *Candida* bloodstream infections are estimated to impact ~400,000 patients a year globally, with an associated mortality of 46–75%.¹¹ For all these reasons, and because the hospitalisation and treatment cost of these patients is very high, CDC guidelines recommend prophylactic or pre-emptive antifungal treatment in patients considered at high risk of candidemia.¹⁴ Currently, no company in scope has a fungal vaccine in the pipeline, and the US Food and Drug Administration (FDA) and European

FIGURE 13

138 R&D projects target priority bacterial and fungal pathogens

The 2020 AMR Benchmark analysed the pipelines of 21 pharmaceutical companies and found 138 antibacterial and antifungal medicine and vaccine R&D projects.* It looked at pipelines targeting 16 bacterial pathogens and/or genuses, one fungal genus (*Candida* spp.) and one fungal pathogen (*C. auris*), identified as priorities for R&D and human health by WHO and the US CDC.

Antibacterial and antifungal medicine candidates and antibacterial vaccine candidates

* R&D projects are counted separately where the same compound is involved but targeting a different indication or adaptation.

FIGURE 14

54% of the pipeline is in clinical development or beyond

The figure shows that more than half of the R&D projects analysed by the 2020 AMR Benchmark are in clinical stages or beyond.

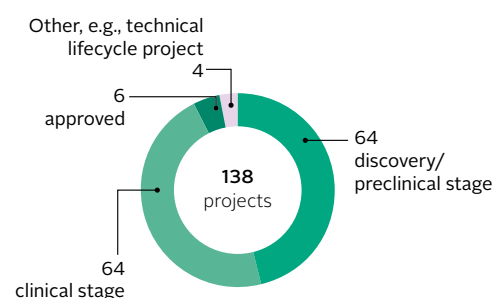
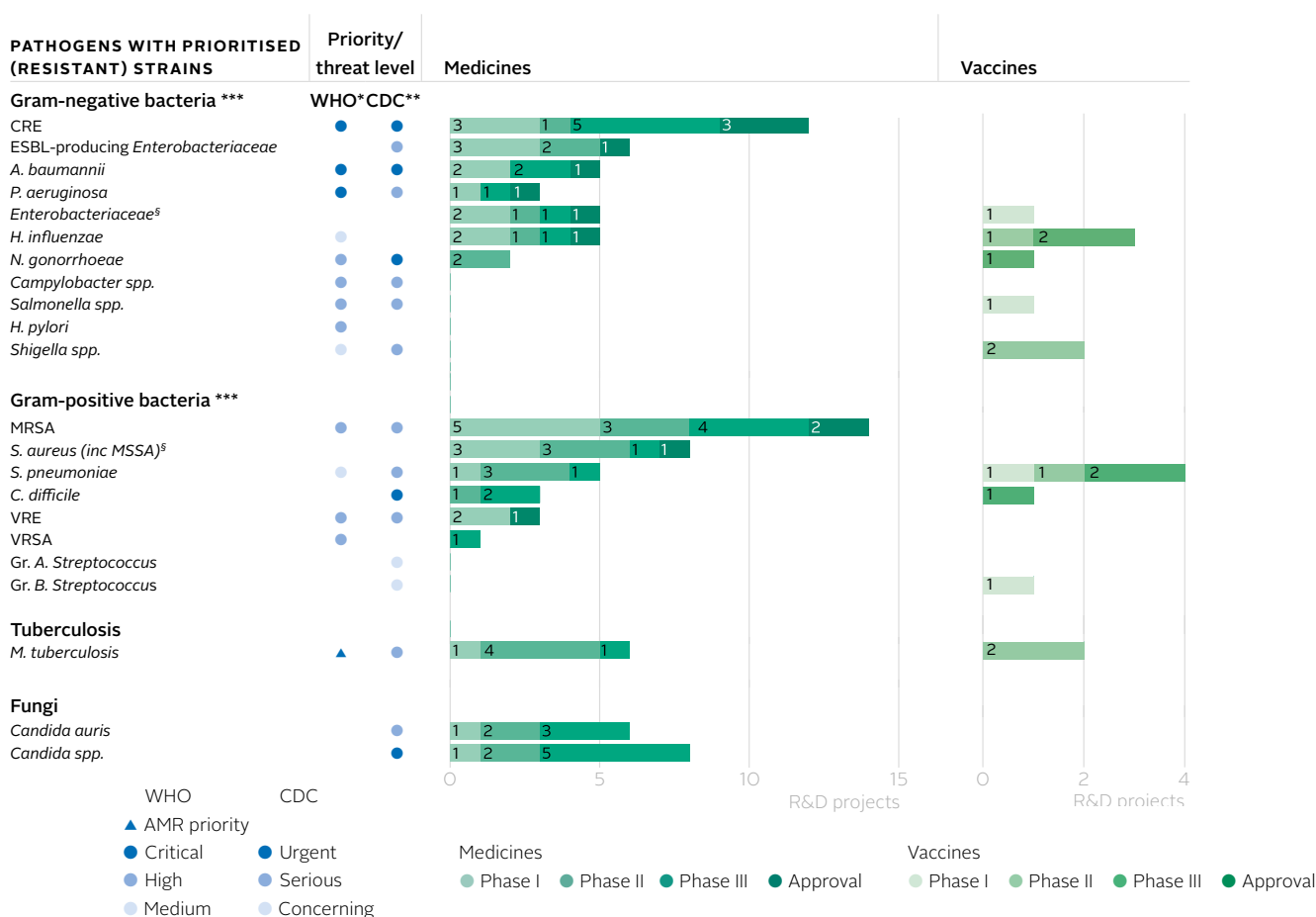


FIGURE 15

Breakdown of the clinical antibiotic pipeline for priority bacteria and fungi

The figure shows how many antibiotics are in clinical development, per pathogen, from the 21 companies in scope. The bacteria and fungi receiving the most attention include *Enterobacteriaceae*, *S. aureus*, *Candida* spp. and *M. tuberculosis*. This figure excludes projects that aim to adapt existing products.



* WHO priority pathogens list, 2017

** CDC Antibiotic Resistance Threats list, 2019

*** Projects that target multiple pathogens are included for each relevant priority pathogen

§ Projects are listed separately where the company does not report whether or not it targets the resistant strain prioritised by CDC and/or WHO.

CRE = Carbapenem-resistant *Enterobacteriaceae* (CRE)

ESBL = Extended spectrum beta-lactamase

MRSA = Methicillin-resistant *Staphylococcus aureus*

MSSA = Methicillin-sensitive *Staphylococcus aureus*

VRE = Vancomycin-resistant *Enterococcus*

VRSA = Vancomycin-resistant *Staphylococcus aureus*

Medicines Agency (EMA) have registered no such vaccines yet.¹⁵ One reason is that fungal vaccine development has complex limitations. As immunocompromised patients are the most likely patient group to acquire serious fungal infections, antifungal vaccine candidates must provide protection in these individuals. This can pose a challenge for vaccinologists because live attenuated vaccines are not recommended for use in these patients due to increased risk of infection from these vaccines.

PIPELINE SIZE PER COMPANY

Pipelines range from 1 to 27 projects

The 2020 AMR Benchmark examines the R&D pipelines of eight large research-based pharmaceutical companies, and 13 small and medium-sized enterprises (SMEs). They include antibiotic market leaders in terms of sales volume and/or value, the largest vendors of active pharmaceutical ingredients (APIs), and companies with novel clinical-stage candidates for a priority pathogens. For the 2020 Benchmark, eight new companies are in scope, reflecting changes in the available data and market dynamics.

GSK has biggest pipeline in the Benchmark

In 2020, the Benchmark finds that the eight large research-based pharmaceutical companies have a combined total of 77 projects in their R&D pipelines targeting priority bacteria and fungi. GSK has the largest R&D pipeline (figure 16), with 27 projects: 15 vaccines and 12 medicines. Most of its pipeline includes new medicine (12) or vaccine candidates (12), rather than adapted projects (3). Among GSK's twelve new medicine candidates, two are considered novel as defined by WHO¹ (see table 4). For example, one of its novel medicine candidates (GSK 3036656) includes a Phase II project that aims to develop a novel leucyl-tRNA synthetase inhibitor for the treatment of tuberculosis. Besides GSK, Otsuka is the only other large research-based pharmaceutical company to also have a novel medicine candidate in its clinical pipeline. Its candidate OPC-167832 in phase I/II is a newly synthesized carbostyryl derivative with anti-mycobacterial activity by inhibiting decaprenylphosphoryl-beta-D-ribose 2'-oxidase (DprE1), an essential enzyme for cell wall biosynthesis of *M. tuberculosis*.

Merck & Co, Inc has the second largest pipeline in scope with 12 projects (seven new and three adapted medicine candidates and two new vaccines). In July 2019, Merck & Co, Inc received a market approval for a new medicine candidate, cilastatin/meropenem/relebactam (Recarbrio®), for the treatment of complicated urinary tract and intra-abdominal infections. Shionogi is the only large research-based pharmaceutical company in scope to target fluconazole-resistant *Candida*, the only fungi identified as a priority pathogen (by the CDC).

SMEs in scope are developing 61 projects

In 2020, the Benchmark finds that small and medium-sized enterprises have in total 61 projects in their R&D pipelines targeting priority bacteria and fungi: including 36 new medicine candidates and 25 adapted medicine candidates. The 13 small and medium-sized enterprises in scope of the Benchmark are not engaged in vaccine R&D.

Melinta filed for bankruptcy in December 2019. During the period of analysis, Melinta had the largest R&D pipeline with 11 projects: three new and eight adapted medicine candidates that target priority bacteria and fungi (figure 18). Its clinical projects included a Phase I project for a paediatric indication of its approved antibacterial Vabomere® (meropenem and vaborbactam). Wockhardt has the second largest pipeline with nine projects: eight new and one adapted medicine candidate. This includes a new antibacterial project (levonadifloxacin) that recently concluded its Phase III trial in India. This broad-spectrum antibacterial is active against *S. aureus*, including multidrug-resistant strains that can cause severe skin and soft tissue infections. Nabriva's pipeline is third in size (seven projects), and includes one recently approved novel antibacterial (lefamulin) (new chemical class), one new medicine candidate in phase I (BC-7013) to address uncomplicated skin and skin structure infections, and its pleuromutilin molecule platform in discovery as well as four adapted projects to seek expanded indications for their products lefamulin and fosfomycin.

Twenty of the new medicine projects are conducted in partnerships. Twelve projects are financially supported by the global non-profit partnership Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB X) that is dedicated to accelerating antibacterial research to tackle the global rising threat of drug-resistant bacteria. Seven projects, from GSK, Johnson & Johnson, Merck & Co, Inc and Shionogi are conducted in collaboration with the TB Alliance, while Entasis has one project with the Global Antibiotic Research and Development Partnership (GARDP).

CRITICAL & URGENT PATHOGENS

Almost 40% of projects target the biggest AMR threats

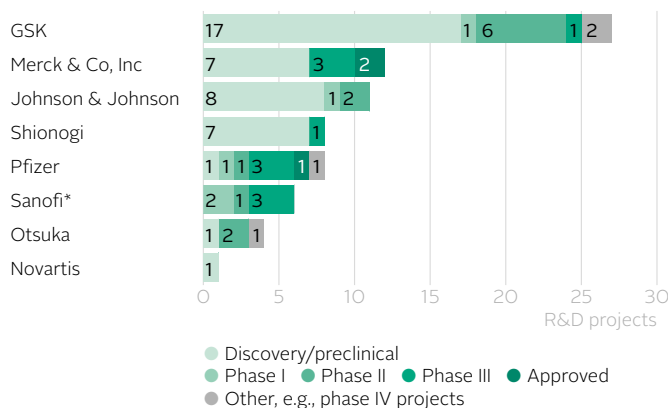
In 2020, the Benchmark identified in total 53 R&D projects targeting the bacteria and fungi that pose the biggest threats from AMR. These are five bacteria and one fungus that either WHO and/or the CDC have classified at their highest threat levels (i.e., 'critical' by WHO and 'urgent' by the CDC, table 3). For example, the fungus *Candida auris* was recently classified as urgent by CDC, because it is often multidrug-resistant, with some strains (types) resistant to all three available classes of antifungals, and can cause severe infections and spreads easily between hospitalised patients and nursing home residents.² Nineteen of the 21 companies in scope are developing new medicine candidates to target critical/urgent pathogens.

Out of these 53 projects targeting critical/urgent priorities, 22 are conducted by a large research-based pharmaceutical

FIGURE 16

GSK has largest pipeline of R&D projects targeting priority bacteria and fungi

The figure compares R&D pipelines targeting priority bacteria and fungi from eight large research-based pharmaceutical companies, including those with the biggest presence in anti-infectives markets. Overall, they are developing 77 projects that target these 18 bacterial and fungal pathogens.



* In 2018 Sanofi outsourced its early antibiotics development programmes and facility to Evotec.

FIGURE 17

Mid-level threats are main focus for large research-based pharma companies

The figure compares how companies target priority bacteria and fungi of different threat levels, as defined by WHO and the CDC. Overall, the eight large research-based pharmaceutical companies mainly target bacteria and fungi classified as 'high/serious' priorities.

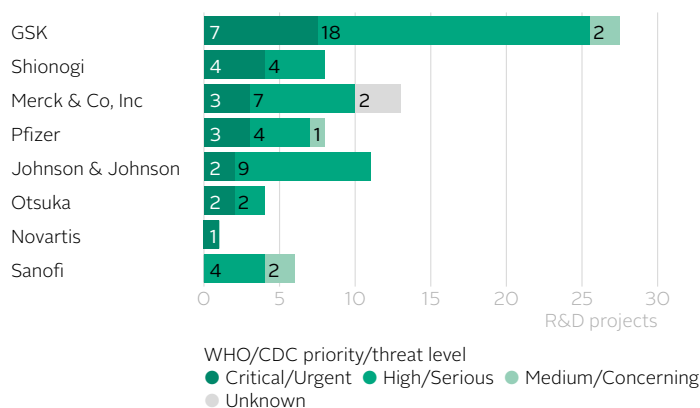
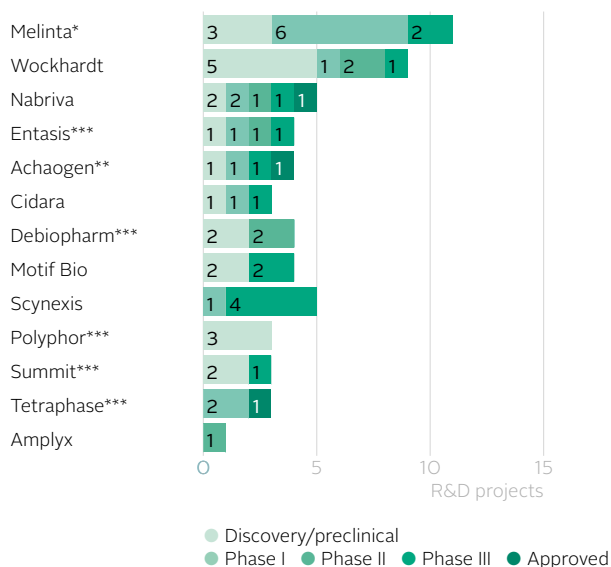


FIGURE 18

Out of 13 small and medium-size enterprises (SMEs), Melinta has largest pipeline

The figure compares R&D pipelines targeting priority bacteria and fungi from 13 small and medium-sized enterprises focused on such R&D. Overall, these companies are developing 61 projects that target these 18 bacterial and fungal pathogens.



* In 2018, Melinta closed its research and discovery programmes. It filed for bankruptcy in December 2019.

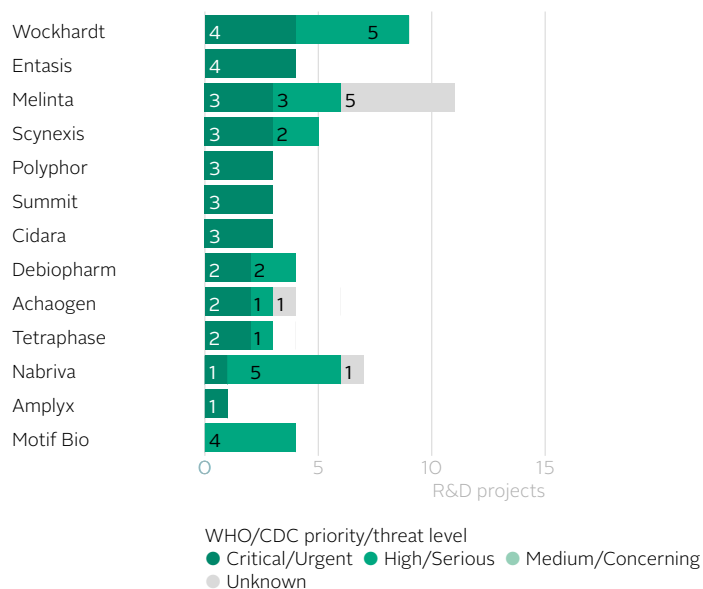
** Achaogen went bankrupt in 2018 and in 2019 came to an agreement with Cipla who acquired the company's worldwide rights, excluding Greater China, to Zemdrin® (plazomicin) as well as the worldwide right to Achaogen's C-Scape and AMP programme assets.

*** Pre-clinical and early clinical projects financially supported by CARB X.

FIGURE 19

Highest threat pathogens are focus for many SMEs

The figure compares how companies target priority bacteria and fungi of different threat levels, as defined by WHO and the CDC. Overall, the 13 small and medium-sized enterprises in scope are focused on R&D targeting 'critical/urgent' pathogens.



company (figure 17). Sanofi is the only one of these eight companies not targeting such pathogens. GSK has the most projects (7), including a second novel project that entered a phase III clinical programme in October 2019 investigating its medicine candidate gepotidacin. This is the first in a new chemical class of antibacterials (triazacacenaphthylene bacterial topoisomerase inhibitors), in patients with uncomplicated urinary tract infection and urogenital gonorrhoea. Twelve of the 13 SMEs in scope target critical/urgent pathogens, accounting for 58% (31 projects) (figure 19). Both Entasis and Wockhardt have four projects targeting such pathogens, with Entasis' pipeline being more advanced: three of its projects are in clinical development, including zoliflodacin, a novel, first-in-class oral antibiotic being developed for the treatment of uncomplicated gonorrhoea, which entered Phase III in September 2019. Entasis is also developing, in Phase III, the medicine combination sulbactam/durlobactam to treat infections caused by *A. baumannii*, including those caused by multidrug- and carbapenem-resistant isolates. Wockhardt has one medicine candidate in clinical development. Its Phase II project cefepime/zidebactam targets complicated urinary tract infections and hospital acquired bacterial pneumonia/ventilator-associated bacterial pneumonia caused by GNB and GPB (including carbapenem-resistant *Enterobacteriaceae*). Motif Bio is the only SME in scope that does not target critical/urgent pathogens. Its projects target GBP, including methicillin-resistant *S. aureus*, a high-priority pathogen.

VACCINE R&D

Three companies developing vaccines against top threats

By preventing disease, vaccines are a critical tool for slowing the spread of resistance. Of the 21 companies in this analysis, five of the large research-based pharmaceutical companies are active in vaccines R&D. Of the 27 vaccine projects in development, 22 are new candidates and five are adapted. GSK has the most vaccines in its pipeline, including one that addresses *C. difficile* in pre-clinical development. Pfizer is also developing a vaccine targeting *C. difficile*, currently in Phase III. Together with Johnson & Johnson, these are the only companies in scope developing vaccines against priority bacteria and fungi classified as 'urgent': for *C. difficile* (GSK and Pfizer), *E. coli* (Johnson & Johnson), and *N. gonorrhoeae* (GSK).

NOVELTY

Few new medicine candidates are novel

As new genes for resistance emerge, we increasingly need new antibacterials and antifungals that work in new and novel ways, and can remain effective against bacteria and fungi for as long as possible. The 2020 AMR Benchmark has identified which of the R&D projects in this analysis are new and among these, which are 'novel'. The Benchmark uses four WHO-defined criteria to determine whether an investigational clinical antibacterial or antifungal medicine is novel.¹ These criteria are: (1) new chemical class (or structure); (2) new target; (3) new mode of action; and (4) absence of cross-resistance. Novel compounds offer the best chance for new

antibacterials and antifungals to remain effective for longer because the compound is different enough from existing agents to minimise the risk of cross-resistance.

The Benchmark identified nine medicine candidates in clinical development from the companies in scope (including one recently approved candidate) that are considered novel according to the WHO criteria: seven target bacterial agents; and two target fungi (table 4).

These medicines are being developed by eight companies. Five projects meet all criteria for novelty. For example, Summit is developing ridinilazole, a bisbenzimidazole to treat infection from *C. difficile*. Amplyx has fosmanogepix, an antifungal with broad *in vitro* activity against fungal pathogens, including *Candida*, as well as *Cryptococcus*, *Aspergillus* and *Scedosporium*. The remaining four novel projects meet at least one criterion, such as Entasis' zoliflodacin and GSK's gepotidacin. Both candidates aim to treat *N. gonorrhoeae*, and each candidate has a new chemical structure and mode of action. Cross-resistance has not yet emerged for either candidate.

In addition to these nine novel medicine candidates there are 15 new clinical-stage and recently approved medicine candidates that do not fulfill the WHO criteria for innovative-ness.¹ While not fulfilling these stringent criteria, these new products (that are often medicine combinations) can still offer a significant clinical benefit against resistant infections. Examples of these new candidates include Shionogi's cefiderocol (Fetroja™) for treating complicated urinary tract infections. This is the first siderophore antibacterial approved for clinical use, having been approved by the FDA in November 2019. This new cephalosporin takes advantage of bacterial iron uptake pathways to enter cells and has demonstrated stability against beta-lactamase expressing bacteria which normally inactivate cephalosporins.¹⁶

Another example is Entasis's sulbactam/durlobactam project, which has broad-spectrum inhibitor activity against Class A, C and D beta-lactamases. Sulbactam/durlobactam is a beta-lactam/beta-lactamase inhibitor (BL/BLI) combination taking advantage of sulbactam's antibacterial activity against *A. baumannii* with durlobactam conferring additional protection against beta-lactamases.¹⁷ This improves upon existing inhibitors, which have little to no activity against Class D beta-lactamases.¹⁷

Further, there are 30 adapted projects in clinical development that do not contain a new chemical entity but that can also offer significant public health benefits. For example, Pfizer's aztreonam/avibactam combination targets carbapenem-resistant *Enterobacteriaceae*, a critical pathogen. Such products provide healthcare workers with additional options for patients that have otherwise run out of treatment options due to resistance.

FIGURE 20

SMEs have more novel medicine candidates in their pipelines

The figure shows how many new and novel candidates are in the R&D pipelines. With ten novel candidates in total, nine are in the clinical stage of development. Overall, the 13 small and medium-sized enterprises in scope have more novel medicine candidates than the large research-based companies.

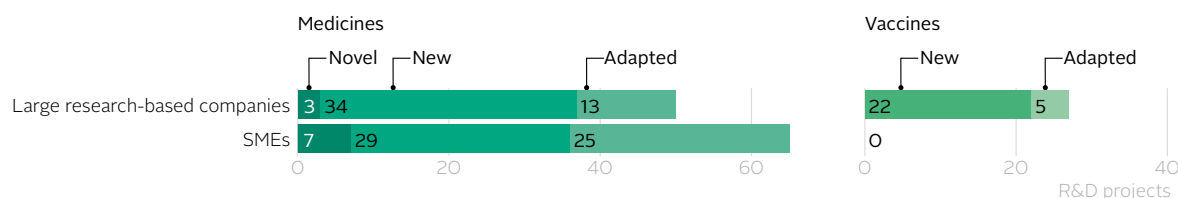
Antibacterial and antifungal medicine candidates and antibacterial vaccine candidates

FIGURE 21

Nine clinical-stage medicine candidates meet WHO criteria for innovativeness - classed as 'novel' by Benchmark

The figure shows the proportion of clinical-stage medicine projects targeting priority bacteria and fungi that meet the WHO's criteria for being a novel medicine. Novel compounds offer the best chance for new antibacterials and antifungals to remain effective for longer because there is a lower risk of cross-resistance.

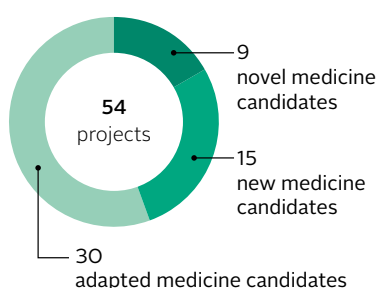
Late-stage antibacterial and antifungal medicine candidates

TABLE 4

Which medicines in clinical development are considered novel?

The table shows which of the clinical stage medicines identified by the 2020 AMR Benchmark meet one or more of the four WHO criteria for identifying a novel compound. The majority (six out of nine) are being developed by small and medium-sized enterprises (SMEs)*

| Company | R&D project and clinical phase | | Pathogen targeted | Criteria for novel compounds | | | |
|------------|--------------------------------|------------------------|-------------------|---|------------|--------------------|---------------------|
| | Antibacterial | Antifungal | | New drug class | New target | New mode of action | No cross-resistance |
| Summit | Ridinilazole | | Phase III | <i>C. difficile</i> | ● | ● | ● |
| Amplix | | Fosmanogepix(APX001) | Phase II | <i>Candida spp. (C. auris)</i> | ● | ● | ● |
| Debiopharm | Afabicin (Debio-1450) | | Phase II | <i>S. aureus</i> | ● | ● | ● |
| GSK | GSK-3036656 | | Phase II** | <i>M. tuberculosis</i> | ● | ● | ● |
| Otsuka | OPC-167832 | | Phase II | <i>M. tuberculosis</i> | ● | ● | ● |
| Entasis | Zoliflodacin (ETX0914) | | Phase II** | <i>N. gonorrhoeae</i> | ● | ● | ● |
| GSK | Gepotidacin (2140944) | | Phase II | <i>N. gonorrhoeae, Enterobacteriaceae</i> | ● | ● | ● |
| Nabriva | Lefamulin | | Approved | <i>MRSA, H. influenzae</i> | ● | | |
| Scynexis | | Ibrexafungerp(SCY-078) | Phase III | <i>Candida spp. (C. auris)</i> | ● | | |

* Polyphor's novel candidate Murepavadin against *P. aeruginosa* was in Phase III. It reverted to pre-clinical development in 2019.

** After the period of analysis, these two clinical trials moved into Phase III of clinical development.

WHAT'S NEW SINCE 2018?

One third of projects advanced along the pipeline

With resistance building and medicines becoming less effective, promising clinical candidates are closely watched to see when and whether they are likely to become available. The failure rate of pharmaceutical R&D is well known to be high. A project's movement along the pipeline from one stage to another can be an indication of multiple factors, including the specific disease target as well as technical, ethical and practical challenges. This section examines how the number of R&D projects targeting priority pathogens has changed since 2018, when the first Benchmark report was published. Sixteen companies were included in the Benchmark pipeline analyses in both the 2018 and 2020 reports: seven large research-based pharmaceutical companies and nine small and medium-sized enterprises.

In 2018, these 16 companies had 112 R&D projects to develop antibacterials and antifungals in their pipelines – which has risen to 121 projects in 2020. 49 projects were newly included in the pipeline, while 40 projects were discontinued (figure 22). In total, 72 projects that were identified in 2018 are still in the pipeline in 2020: 51 medicines and 21 vaccines. Of these, almost one third (15 medicines and 6 vaccines) have progressed to the next stage of development.

What's new in the pipeline since 2018?

The 49 new projects newly included in 2020 comprise 43 medicines and six vaccines (figure 22). Most of these (30/49) are in the discovery/pre-clinical stage and 27 are classified as new candidate projects containing at least one new component not previously approved. Such candidates are urgently needed to combat the most dangerous drug-resistant bacteria. There are 19 newly added projects in the clinical pipeline, including 16 that aim to adapt existing medicines already on the market, mostly through label extensions, and two adapted vaccines. Furthermore, it includes one new pneumococcal vaccine project from Pfizer (PF-06842433) in phase II that targets invasive and non-invasive pneumococcal infections.

Why are 40 R&D projects no longer in the pipeline?

The 40 projects that are no longer captured in this pipeline analysis comprise 34 medicines and six vaccines. The reasons include: discontinuations by companies (21 projects, due to divestments, trial futility, refunneling of resources, bankruptcy); licensing decisions (10 projects, licensed or sold to other companies); approvals (two products); lack of sufficient information (five projects); and reclassification (two projects).

In 2018 Johnson & Johnson announced that it had ended its clinical development programme for cadazolid, its phase III antibacterial for *C. difficile* infections because it had failed to meet the primary endpoint in one of its two Phase III trials.

In 2017, Novartis planned to move its clofazimine project (CLAM320B2202), for the treatment of multidrug-resistant tuberculosis, into Phase IIC/III of clinical development. The study would have provided valuable data on the safety and efficacy of clofazimine (Lamprene®). However, that same

year, WHO included clofazimine in the WHO guidelines for multidrug resistant tuberculosis, meaning that clofazimine is now considered a “standard-of-care” treatment. In response, Novartis opted to cancel the study because it was no longer possible to ethically compare clofazimine to placebo, due to the existence of an effective treatment (i.e., clofazimine itself).¹⁸ Although the trials were stopped Novartis applied for WHO prequalification and has recently entered into an agreement with the government of South Africa to make this drug available with affordable prices for patients suffering from multidrug-resistant tuberculosis. In 2018, Novartis licensed its project LYS228 to Boston Pharmaceuticals as part of a larger strategic move to discontinue antibacterial R&D.¹⁹

In 2018, Pfizer announced that it would discontinue its investigational *S. aureus* multi-antigen vaccine (PF-06290510) due to futility.

APPROVALS

What is likely to come out of pipelines next?

Six medicines have been approved since 2018 from the 21 companies evaluated in the 2020 Benchmark pipeline analyses. Four of these target priority bacteria where there is a critical/urgent need for more products on the market. Nabriva's lefamulin (Xenleta™) is noteworthy as it is the first pleuromutilin antibacterial approved for intravenous and oral administration in humans. This offers a new antibacterial class alternative for the treatment of community-acquired bacterial pneumonia.²⁰

At the time of writing, six of the 21 companies had applied for their first marketing authorisation or had entered into a pivotal phase III clinical trial. These are two large research-based pharmaceutical companies and four SMEs.

Cefiderocol from Shionogi was approved by the U.S. Food and Drug Administration's (FDA) on 14 November 2019. This is a new antibacterial for the treatment of complicated urinary tract infections (cUTI) in patients with limited or no alternative treatment options.

Gepotidacin from GSK moved to a phase III clinical trial programme on 28 October 2019. This candidate medicine is the first in a new class of antibacterials, triazaacenaphthylene bacterial topoisomerase inhibitors, and aims to treat patients with uncomplicated urinary tract infection and urogenital gonorrhoea.

Zoliflodacin, developed by Entasis and the Global Antibiotic Research and Development Partnership (GARDP), initiated a global Phase III pivotal trial in September 2019. This candidate medicine is a novel, first-in-class oral antibiotic being developed for the treatment of uncomplicated gonorrhoea.

Baxdela® (delafloxacin) from Melinta is an new antibacterial that was introduced in 2017 for the treatment of serious skin infections. Melinta filed for an additional indication: community-acquired bacterial pneumonia caused by GPB, including resistant strains. This additional indication was approved by the US FDA on 24 October 2019. However, the company is delaying the commercial launch of its products until it has secured additional sources of liquidity.²¹

TABLE 5

Approvals between 9 September 2017 – 16 October 2019

The table shows the new products approved for priority bacteria and fungi between the end of the period of analysis for the 2018 AMR Benchmark, 9 September, 2017, and 16 October, 2019.

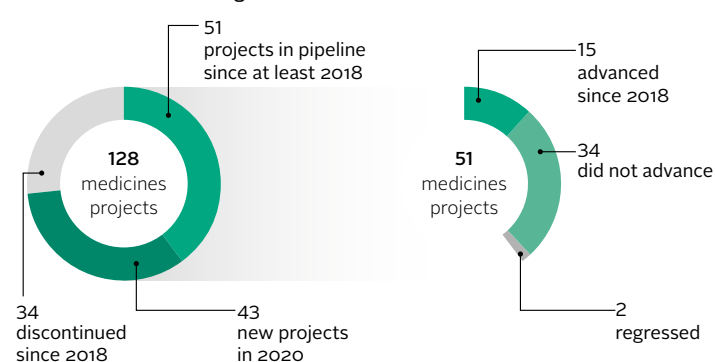
| Company | Brand name | INN | New or adaptation | Priority pathogen(s) targeted | Indication* | Approval date by stringent regulatory authority |
|-----------------|------------|-------------------------------------|----------------------------------|--|-------------------------|---|
| Achaogen | Zemdri™ | plazomicin | New | CRE and ESBL-producing <i>Enterobacteriaceae</i> | cUTI in adults | 25/06/2018 (FDA) |
| Tetraphase | Xerava™ | eravacycline | New | CRE, CRAB and other GPB | cIAI in ≥18 years | 27/08/2018 (FDA) |
| Merck & Co, Inc | Zerbaxa™ | ceftolozane and tazobactam | Adaptation – expanded indication | <i>P. aeruginosa</i> | HABP/VABP | 03/06/2019 (FDA) |
| Pfizer | Zinforo™ | ceftaroline and fosamil | Adaptation – paediatric | MRSA | cSSSTI and CAP | 28/06 2019 (EMA) |
| Merck & Co. | Recarbrio™ | imipenem, cilastatin and relebactam | New | CRE | cUTI and cIAI in adults | 16/07/2019 (FDA) |
| Nabriva | Xenleta™ | lefamulin | New | MRSA | CABP in adults | 19/08/2019 (FDA) |

* cUTI: complicated urinary tract infections;
cIAI: complicated intra-abdominal infections;
CABP: Community-acquired bacterial pneumonia;
HABP/VABP Hospital-acquired bacterial pneumonia/ventilator-acquired bacterial pneumonia

FIGURE 22

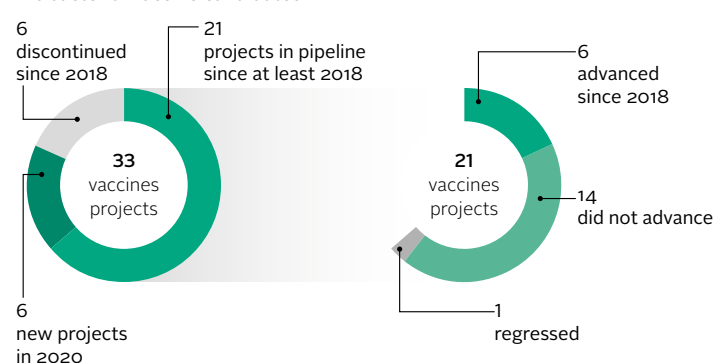
How has the pipeline changed since 2018?

The figure shows how many projects in the pipeline in 2018 have moved between phases of development or were discontinued and how many projects were newly added to the pipeline in 2020. It looks only at companies and pathogens that were in scope in both years: 18 bacterial and fungal pathogens and 16 companies resulting in 128 medicines and 33 vaccines projects.

Antibacterial and antifungal medicine candidates**What is being compared?**

Pipelines for 18 bacterial and fungal pathogens, from 16 companies assessed in both the 2018 and 2020 Benchmark. From the 112 projects in 2018, almost one-third of projects progressed from one stage of development to another between 2018 and 2020.

Since 2018, in the discovery stage/preclinical stage about the same number of projects have been discontinued (25) as have been newly added (27) to the pipeline.

Antibacterial vaccine candidates

Nabriva will resubmit its intravenous Contempo™ (IV fosfomycin) to the FDA in Q4 2019. This is an adapted antibacterial for the treatment of complicated urinary tract infections caused by ESBL-producing *Enterobacteriaceae* and other multidrug-resistant bacteria.

Motif Bio submitted a new drug application to the FDA for its most advanced antibacterial medicine candidate, iclaprim, in 2018. The medicine is developed for the treatment of acute bacterial skin and skin structure infections (ABSSSI), including infections caused by methicillin-resistant *S. aureus* (MRSA). In February 2019, the FDA informed the company that an additional Phase III trial will be required prior to granting marketing approval to address the FDA's concerns about potential liver toxicity. The company is currently deliberating on the most efficient way to bring iclaprim to the market.²²

Financial risk and uncertainty are reportedly substantial deterrents for potential participants in the antibacterial market. While this holds for any pharmaceutical company, many SMEs face particular difficulties moving from late-stage clinical trials to commercialisation. This issue is highlighted by the bankruptcy of Achaogen, an SME, that successfully launched its new antibacterial plazomicin but then failed to earn enough to stay afloat. Similarly, Melinta, another SME, delayed the launch of its new antibacterial in October 2019, in order to secure additional resources of liquidity. In December 2019, it filed for bankruptcy. To help incentivise pharmaceutical companies to develop new antibacterials for resistant pathogens, the UK government, through the National Institute for Health and Care Excellence (NICE) and NHS England and NHS Improvement, launched in July 2019 its project to develop and test the world's first 'subscription-style' model that pays pharmaceutical companies for access to antimicrobials based on their value to the NHS rather than volume of prescribing. The UK continues to promote this project internationally to encourage other countries to test similar models that, together, incentivise pharmaceutical companies to invest.

ACCESS AND STEWARDSHIP PLANNING

Eight late-stage antibiotics have both access and stewardship plans in place in 2020.

By planning ahead during product development, pharmaceutical companies can take account of public health needs and provide swifter access to new products at more affordable prices. Companies need to integrate plans for access with plans for stewardship, so that new products can be used appropriately and remain effective over time.

The 2020 AMR Benchmark evaluates whether companies are establishing access and stewardship plans for late-stage candidates (R&D medicine and vaccine projects at clinical-stage development phase II and phase III, as well as recently approved products). As with other analyses in this Research Area, the Benchmark focuses on projects that target the priority bacteria and fungi identified by WHO and the CDC. Specifically, it looks at what proportion of late-stage candidates are supported by access and stewardship plans.

The Benchmark identifies 51 late-stage R&D projects targeting pathogens in scope (figure 23). This includes 32 antibacterial medicines; eight (25%) have both an access and a stewardship plan in place. This is a notable increase since 2018, when of the 28 antibacterial medicine projects, only 2 (7%) had both an access and stewardship plans in place.

In 2020, eight out of 12 antibacterial vaccines (67%) have an access plan in place (stewardship plans are not required for vaccines). Of the seven antifungals, only one project (fosmanogepix from Amplyx) has an access plan in place, and none have a stewardship plan.

Six of the eight large research-based pharmaceutical companies evaluated have at least one specific access and/or stewardship plan in place for late-stage medicine candidates. Of the other two companies (Merck & Co, Inc and Novartis), Merck & Co, Inc reports a general commitment to expand access to its products through broad registration, to improve affordability, and to support the appropriate and responsible use of its products. Novartis has no late-stage candidates. Of the 13 SMEs in scope, only two companies, Entasis and Tetraphase, report having both (product-specific) access and stewardship plans in place for their relevant late-stage antibacterial projects: zoliflodacin and eravacycline (Xerava™) respectively. Five SMEs (Amplyx, Melinta, Motif Bio, Summit and Wockhardt) report having only access plans, and the remaining SMEs report no access or stewardship plans at all for their late stage candidates (Achaogen, Cidara, Debiopharm, Nabriva and Scynexis). However, Scynexis reports making a general commitment to expanding access through a compassionate use programme. Furthermore, after the period of analysis, Cidara entered into a partnership with Mundipharma to develop and commercialise rezafungin in markets outside of Japan and the United States. Polyphor has no late-stage candidates.

What do access and stewardship plans look like?

The eight large research-based pharmaceutical companies in scope have 26 late-stage antibacterials, split more or less evenly between medicine and vaccine candidates (12 and 14 respectively). Five of these antibacterials, developed by GSK, Pfizer and Johnson & Johnson, have both access and stewardship plans.

GSK commits publicly to equitable pricing for its medicines and vaccines via its equitable pricing strategy framework and the GSK Launch Excellence programme. GSK maintains that its sponsored clinical trials are only conducted in countries where medicines or vaccines are likely to be suitable for the country's wider community; it commits to registration in countries where it conducts clinical trials. Moreover, the GSK Launch Excellence programme starts at phase III with the development of launch plans per market, based on disease burden and regulatory requirements. Access programmes include equitable pricing strategies, distribution channel readiness, market capacity and supply readiness. GSK also commits publicly to global surveillance studies for new antibacterials to enable appropriate use and support stewardship.

FIGURE 23

Eight late-stage antibiotics have both access and stewardship plans

The figure shows the number of late-stage antibacterials that are supported by access and/or stewardship plans. The 2020 Benchmark identified 32 antibacterials in Phases II and III clinical development, or recently approved products that target bacteria posing significant threats due to AMR (according to WHO and CDC). Eight projects, up from two in 2018, have plans in place to ensure they will be accessible, yet used prudently.

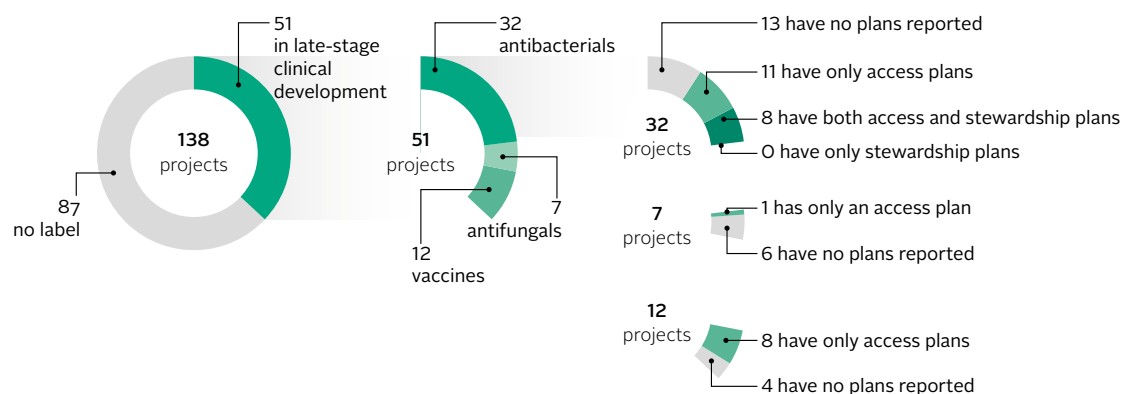
Late-stage antibacterial and antifungal medicine candidates and antibacterial vaccine candidates

TABLE 6

Recommendations for developers of new antibacterials on how to plan for access and stewardship

Overview of components and principles that can be used by public and private product developers, as they develop antibacterials and antifungals, to create comprehensive, effective plans for access and stewardship.

| | Company | ACCESS | | | | | Supply Chain Strengthening, Donations | STEWARDSHIP | | |
|---|-------------------|---|-------------------|--------------|---|---|---------------------------------------|---|--------------|---|
| | | Expanded Access; Managed Access; Compassionate Use Programmes | Equitable Pricing | Registration | Concrete provisions or other agreed-upon measures | Responsible IP arrangements, licensing arrangements | | Avoid expansion of use in unnecessary indications | Surveillance | Concrete provisions or other agreed-upon measures |
| Small and medium-sized enterprises | Amplix | ● | | | | | | | | |
| | Cidara | | | | | ● | | | ● | |
| | Entasis | | ● | ● | ● | ● | | ● | ● | ● |
| | Melinta | | | | | ● | | | | |
| | Motif Bio | | ● | ● | | | | | | |
| | Scynexis | ● | | | | | | | | |
| | Summit | | | | | ● | | ● | | |
| | Tetraphase | | ● | | | ● | | | ● | |
| | Wockhardt | | | ● | | | | | | |
| Large research-based pharmaceutical companies | GSK | | ● | ● | ● | ● | | | ● | |
| | Johnson & Johnson | ● | ● | ● | ● | | ● | | ● | ● |
| | Merck & Co, Inc | | | ● | | | | | | |
| | Otsuka | | | | ● | ● | | | | |
| | Pfizer | ● | ● | | ● | | ● | | ● | |
| | Sanofi | | ● | | | | | | | |
| | Shionogi | | ● | ● | | | | | | |

● Reports component or principle

Pfizer reports equitable pricing and supply chain commitments, including a tiered pricing approach for vaccines to ensure that countries with the least ability to afford vaccines pay a lower price in accordance with government resources, while high-income countries pay more. Pfizer partners with Gavi, the Vaccine Alliance, via the global health organisation PATH which aims to provide vaccines to the world's poorest countries. Pfizer also plans to support surveillance studies to understand the impact of vaccination programmes on reducing the burden of disease. Lastly, the company aims to launch educational initiatives on the risk of AMR and how vaccines can play a role in addressing this public health threat.

Johnson & Johnson reports that it will use the same access and stewardship plans that are currently in place for the adult formulation of bedaquiline (Sirturo™). This includes a donation programme, and it also provides the medicine at a not-for-profit price via the Stop TB Global Drug Facility (GDF).

The other three large research-based pharmaceutical companies (Otsuka, Sanofi and Shionogi) report having only access plans for their four projects in late stage-development (two medicine and two vaccine candidates). The access strategies included WHO prequalification, access provisions in partner agreements, and registration strategies.

Fewer access and stewardship plans from small and medium-sized enterprises

Small and medium-sized enterprises (SMEs) have fewer candidates with an access and/or stewardship plan. Typically these companies aim to be acquired by larger pharmaceutical companies or rely on partnerships, which means they do not establish business processes for commercialising their pharmaceuticals. Often, they seek third parties (such as regional pharmaceutical companies) to commercialise their products in other countries. This may create a different attitude toward developing access strategies. The SMEs evaluated have 25 antibacterials and antifungals in late-stage development. Only three projects have both an access and a stewardship plan (being developed by Entasis and Tetrphase).

For its novel antibacterial targeting gonorrhoea, zoliflodacin, Entasis retains all commercial rights in high-income territories while agreeing that its development partner, GARDP, has the commercial rights in low- and middle-income countries. Both GARDP and Entasis have committed to affordable and equitable pricing in their respective territories at prices equivalent to those for broad-spectrum generic antibacterials and they report a plan for tiered pricing to ensure access. Furthermore, Entasis and GARDP are also committed to supporting the responsible use and stewardship of the new product if successful. Therefore zoliflodacin will be initially developed for gonorrhoea only. For its other late stage antibacterial, sulbactam/durlobactamin, Entasis announced in 2018 a partnership with Zai Laboratories to conduct clinical trials and obtain regulatory approval in China and other countries belonging to the Association of Southeast Asian nations (ASEAN), in parallel gaining marketing approval in the US and Europe. Entasis is one of the few SMEs actively involved in

antimicrobial surveillance.

Tetrphase is the only other SME to have both access and stewardship plans in place: for its recently approved product eravacycline (Xerava™), which is to be used for complicated urinary tract infections (cUTI) caused by a range of Gram-positive and Gram-negative pathogens. Tetrphase has entered into a licensing agreement with a third party (Everest Medicine) to commercialise this product in Southeast Asia and Singapore. Tetrphase has also committed to licensing agreements in other markets and is collaborating with International Health Management Associates (IHMA), an independent laboratory with expertise in surveillance and clinical trials, to develop a surveillance network that will look at pathogens' susceptibility to eravacycline in different clinical settings. To help hospitals and researchers test the product against isolates, Tetrphase will provide the product, as well as testing strips and discs.

Nine other projects reported by SMEs (eight antibacterials and one antifungal) have access plans, but not stewardship plans. These mainly comprise equitable pricing strategies, licensing and registration plans.

While there is overall acceptance of antibacterial resistance stewardship programmes, such programmes for antifungal resistance are less established and not universally practiced, despite growing concerns about antifungal resistance.

R&D INVESTMENTS

Investments in antibacterial and antifungal R&D varies hugely across companies

Despite the urgent need for novel antimicrobial products, pharmaceutical companies have little incentive to invest in antimicrobial R&D. Such R&D involves major scientific challenges. The basic science of identifying new antibacterial molecules and mechanisms of action is difficult. The first- and second-generation discovery methods that studied natural antimicrobial activities and used high throughput biochemical assays have become less fruitful with time or have been ineffective²³. Companies must also overcome often complex regulatory hurdles to obtain market approval due to the myriad of different procedures for licensing employed by the different stringent regulatory authorities. The business model is no less problematic, requiring considerable investments in R&D, but offering dramatically lower returns than alternative areas of R&D. Notwithstanding these barriers, there is a clear public health need for novel, effective antibacterial and antifungal products. Without these, even non-infectious diseases, such as many routine surgeries, cannot be safely treated.

The Benchmark evaluates the financial resources that the companies in scope have dedicated to antibacterial and antifungal R&D, both medicines and vaccines, that target priority bacteria and fungi in the fiscal years 2017/18. This includes direct investments and R&D grants from independent funding bodies. Further, the Benchmark compares companies with products on the market on the proportion of their total revenue derived from pharmaceuticals that each invests in antibacterial and antifungal R&D for medicines and vaccines.

Of the eight large research-based pharmaceutical companies in scope, five companies disclose their R&D investments for antibacterial and antifungal medicines and vaccines that target priority pathogens (amounts were disclosed on the basis of confidentiality). Of 13 SMEs in scope, 12 report their investments. Of the large research-based pharmaceutical companies, GSK invested the most overall in antimicrobial R&D, and Johnson & Johnson the second largest amount. Of all large research-based companies, Shionogi invested the biggest proportion of its pharmaceutical revenues in R&D. In general, the SMEs in scope have small pipelines focused on late-stage antibacterial or antifungal medicines, reflecting the Benchmark's selection criteria for such companies. Their investments vary from USD 21 million up to USD 198 million. The highest investments among this group came from Achaogen, Melinta, Nabriva, Tetrphase and Wockhardt, with each investing more than USD 100 million into antibacterial or antifungal R&D over the period assessed.

While generic medicine manufacturers were not evaluated in this area, several are active in antibacterial R&D. One – Teva – reports investing in relevant R&D, which it directs towards

adapting its existing antimicrobial medicines. Aurobindo, Cipla and Mylan report investments in R&D for 2016, but do not report investments for 2017/18. Wockhardt, with relevant R&D investments approximating USD 156.1 million, is in scope in the Benchmark as a SME but also includes a generics division and maintains a portfolio of marketed medicines.

In addition to the investments made by pharmaceutical companies, one of the world's largest public-private partnerships, CARB-X, is dedicated to accelerating antibacterial research and reports investments of USD 133.5 million to date in projects that target drug-resistant bacteria as prioritised by WHO and CDC. It funds and supports projects from the early phases of pre-clinical development through the end of phase I clinical testing, and funds five SMEs in scope for the Benchmark: Debiopharm, Entasis, Polyphor, Summit and Tetrphase.

REFERENCES

- 1 WHO. Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics.; 2017. doi:10.1590/S0100-15742013000100018
- 2 Centers for Disease Control U. Antibiotic Resistance Threats in the United States, 2019.; 2019. www.cdc.gov/DrugResistance/Biggest-Threats.html. Accessed November 20, 2019.
- 3 Unemo M, Seifert HS, Hook EW, Hawkes S, Ndowa F, Dillon JAR. Gonorrhoea. Nat Rev Dis Prim. 2019;5(1). doi:10.1038/s41572-019-0128-6
- 4 Donskey CJ. Fluoroquinolone restriction to control fluoroquinolone-resistant *Clostridium difficile*. Lancet Infect Dis. 2017;17:353-354. doi:10.1016/S1473-3099(17)30052-X
- 5 'Gram-Negative Bacteria Pose a Significant Scientific Challenge' | The Pew Charitable Trusts. <https://www.pewtrusts.org/en/research-and-analysis/articles/2018/06/20/gram-negative-bacteria-pose-a-significant-scientific-challenge>. Accessed December 17, 2019.
- 6 Cassini A, Diaz Högberg L, Plachouras D, Quattrocchi A, Hoxha A, Skov Simonsen G. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. www.thelancet.com/infection. 2019. doi:10.1016/S1473-3099(18)30605-4
- 7 The Pew Charitable Trusts. Antibiotics Currently in Global Clinical Development- September 2019 Update.
- 8 World Health Organization. Antibacterial agents in clinical development- 2018 update. 2018. doi:10.1016/S1473-3099(18)30513-9 and Antibacterial agents in clinical development- 2019 update (doi not yet available)
- 9 Wellcome Trust TBCG. Vaccines to Tackle Drug Resistant Infections An Evaluation of R&D Opportunities.
- 10 Bongomin F, Gago S, Oladele RO, Denning DW. Global and multi-national prevalence of fungal diseases—estimate precision. J Fungi. 2017;3(4). doi:10.3390/jof3040057
- 11 Brown GD, Denning DW, Gow NAR, Levitz SM, Netea MG, White TC. Hidden killers: Human fungal infections. Sci Transl Med. 2012;4(165). doi:10.1126/scitranslmed.3004404
- 12 Cleveland AA, Farley MM, Harrison LH, et al. Changes in Incidence and Antifungal Drug Resistance in Candidemia: Results From Population-Based Laboratory Surveillance in Atlanta and Baltimore, 2008-2011. doi:10.1093/cid/cis697
- 13 Eliakim-Raz N, Babaoğlu R, Yahav D, Yanai S, Shaked H, Bishara J. Epidemiology, microbiology, clinical characteristics, and outcomes of candidemia in internal medicine wards—a retrospective study. 2016. doi:10.1016/j.ijid.2016.09.018
- 14 Wan Tso GH, Reales-Calderon JA, Pavelka N. The Elusive Anti-Candida Vaccine: Lessons from the past and opportunities for the future. Front Immunol. 2018;9(APR). doi:10.3389/fimmu.2018.00897
- 15 Nami S, Mohammadi R, Vakili M, Khezripour K, Mirzaei H, Morovati H. Fungal vaccines, mechanism of actions and immunology: A comprehensive review. Biomed Pharmacother. 2019;109:333-344. doi:10.1016/j.biopha.2018.10.075
- 16 Negash KH, Norris JKS, Hodgkinson JT. molecules Siderophore-Antibiotic Conjugate Design: New Drugs for Bad Bugs? 2019. doi:10.3390/molecules24183314
- 17 Tehrani KHME, Martin NI. β -lactam/ β -lactamase inhibitor combinations: an update. Medchemcomm. 2018;9(9):1439-1456. doi:10.1039/c8md00342d
- 18 Frick M, Gaudino A, Harrington M, et al. HIV, TB & HCV drugs, diagnostics, vaccines, preventive technologies, cure research, and immune-based and gene therapies in development.; 2017. www.treatmentactiongroup.org. Accessed December 17, 2019.
- 19 PORTFOLIO — Boston Pharmaceuticals. <https://www.bostonpharmaceuticals.com/portfolio>. Accessed December 17, 2019.
- 20 Novel Antibiotics | Lefamulin | Nabriva. com. <https://www.nabriva.com/pipeline-research>. Accessed December 17, 2019.
- 21 Melinta Therapeutics Announces U.S. FDA Approval of Supplemental New Drug Application for BAXDELA® (delafloxacin) for the Treatment of Community-Acquired Bacterial Pneumonia (CABP) | Melinta Therapeutics, Inc. <http://ir.melinta.com/news-releases/news-release-details/melinta-therapeutics-announces-us-fda-approval-supplemental-new>. Accessed December 17, 2019.
- 22 Motif Bio confirms receipt of FDA meeting minutes | BioSpace. <https://www.biospace.com/article/motif-bio-confirms-receipt-of-fda-meeting-minutes/>. Accessed December 17, 2019.
- 23 Hughes D, Karlén A. Discovery and pre-clinical development of new antibiotics. Ups J Med Sci. 2014;119:162-169. doi:10.3109/03009734.2014.896437

B RESPONSIBLE MANUFACTURING

WHY THIS MATTERS

Antibacterial manufacturing can contribute to antibacterial resistance in two main ways. The first is the most direct: releasing manufacturing waste that includes antibacterial residue directly into the environment. The second route relates to medicine quality: manufacturing antibacterials that contain too little of the active ingredient needed to treat infection. Both routes give bacteria opportunities to develop resistance. Pharmaceutical companies can minimise the risk of this happening by adopting environmental risk-management strategies that aim to limit AMR and by ensuring medicines meet quality standards. Companies can require suppliers to meet these same quality and environmental standards, as well as the private waste-treatment plants that are contracted to dispose of their manufacturing waste.

HOW WE MEASURE

The analysis presented in this area focuses on antibacterial manufacturing, because its potential impact on resistance is better described and understood than for other areas of antimicrobial manufacturing. The companies are selected based on their global antibacterial sales volume, which indicate that they are prominent players in multiple manufacturing chains with significant influence upon upstream suppliers.

WHAT WE MEASURE

The Benchmark uses a framework of three metrics to assess how eight large research-based pharmaceutical companies and nine generic medicine manufacturers aim to minimise the impact their manufacturing processes have on AMR. It looks at three main areas:

1. Environmental risk-management strategy: how companies manage waste that may contain antibacterial residue, resistant bacteria or resistance genes to minimise the risk that it contributes to AMR,
2. Public disclosure: how much information companies publish about these strategies,
3. High-quality production: how companies maintain high-quality production at their own sites and at third-party manufacturing sites.

The Benchmark does not assess the manufacturing activities of the small & medium-sized enterprises in scope.

Companies in scope

| | Applicable indicators | | |
|---|-----------------------|---|---|
| | 1 | 2 | 3 |
| | 1 | 2 | 3 |
| Large research-based pharmaceutical companies | | | |
| GSK | ● | ● | ● |
| Johnson & Johnson | ● | ● | ● |
| Merck & Co, Inc | ● | ● | ● |
| Novartis | ● | ● | ● |
| Otsuka | ● | ● | ● |
| Pfizer | ● | ● | ● |
| Sanofi | ● | ● | ● |
| Shionogi | ● | ● | ● |
| Generic medicine manufacturers | | | |
| Abbott | ● | ● | ● |
| Alkem | ● | ● | ● |
| Aurobindo | ● | ● | ● |
| Cipla | ● | ● | ● |
| Fresenius Kabi | ● | ● | ● |
| Hainan Hailing | ● | ● | ● |
| Mylan | ● | ● | ● |
| Sun Pharma | ● | ● | ● |
| Teva | ● | ● | ● |

● Scored ● Not scored

Indicators

| | Page |
|--|------|
| B.1 Environmental risk-management strategy | 54 |
| B.2 Disclosure of environmental risk management | 60 |
| B.3 Manufacturing high-quality antibacterials | 62 |

RESPONSIBLE MANUFACTURING

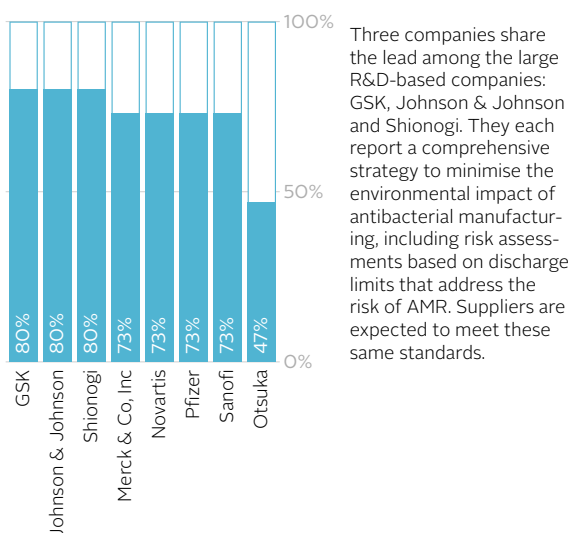
How the companies compare in Responsible Manufacturing

The Benchmark analyses how eight large research-based companies and nine generic medicine manufacturers aim to minimise the risk that antibacterial discharge released from factories contributes to AMR.

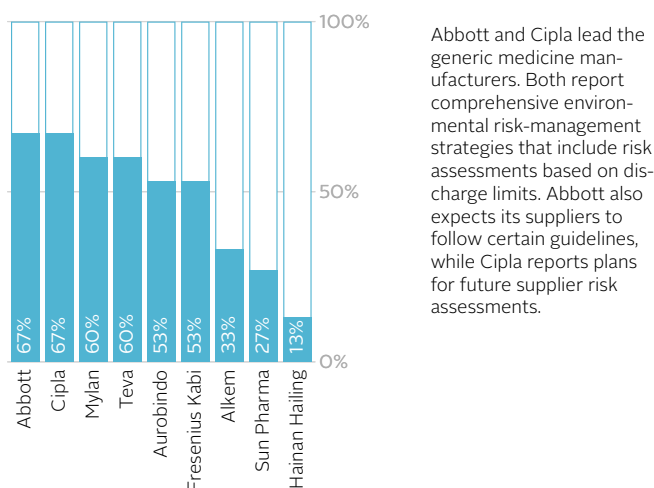
FIGURE 24

Responsible Manufacturing: how the companies perform

Large research-based pharmaceutical companies



Generic medicine manufacturers



WHAT SETS THE TWO GROUPS APART?

More likely to extend environmental risk-management strategies to suppliers and adopt discharge limits

The eight large research-based pharmaceutical companies deliver very similar performances in this area. They typically include almost all of the elements of an environmental risk-management strategy that the Benchmark looks for. These include strategies to ensure antibacterial manufacturing waste is dealt with appropriately, as well as audits. Large research-based pharmaceutical companies are more likely than generic medicine manufacturers to assess the risk that discharge exceeds limits designed to cap the concentration of antibacterials in waste that is being released into the environment. They are more likely to have completed at least one round of such risk assessments. Further, many of these companies are extending their strategies and limits to third-party suppliers of APIs and/or drug products, as well as to external private waste-treatment plants. As yet, none of these companies require these plants to limit or monitor the concentration of antibacterials being released.

Environmental risk-management strategies cover own sites, taking steps to implement discharge limits

Performances between the nine generic medicine manufacturers are more varied than among large research-based pharmaceutical companies. Two thirds of the generic medicine manufacturers report strategies to ensure antibacterial manufacturing waste is dealt with appropriately, including audits. Most of the generic medicine manufacturers with such strategies also set limits to cap the concentration of antibacterials in waste that is being released into the environment. They are more likely than large research-based pharmaceutical companies to still be completing initial risk assessments using these limits at their own sites. These companies report taking initial steps to implement the strategies with suppliers. When it comes to how generic medicine manufacturers audit external private waste-treatment sites, there is generally little information available. As yet, none of the generic medicine manufacturers require these plants to limit or monitor the concentration of antibacterials being released.

IN SUMMARY

ENVIRONMENTAL RISK-MANAGEMENT STRATEGY

P 57

Most companies have an environmental strategy to minimise AMR

Of the 17 companies assessed in this area, 13 show evidence of an environmental risk-management strategy that aims to minimise the impact of their manufacturing processes in promoting resistance. Twelve of the 13 are members of the AMR Industry Alliance.

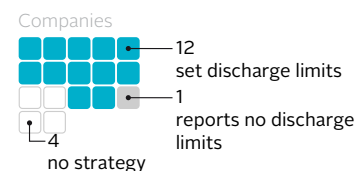


ENVIRONMENTAL RISK-MANAGEMENT STRATEGY

P 58

Companies set concentration limits on antibacterial discharge

Almost all environmental risk-management strategies include a set of discharge limits on the levels of antibacterials allowed in manufacturing discharge.



ENVIRONMENTAL RISK-MANAGEMENT STRATEGY

P 57

Seven companies report having assessed discharge against limits

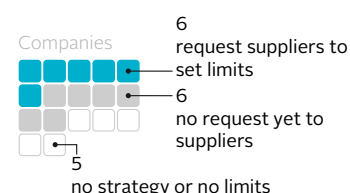
Of the 12 companies that set discharge limits as part of their strategy, seven report having assessed discharge levels against these limits at their own sites. For the five remaining, assessments have either started or are ongoing.

ENVIRONMENTAL RISK-MANAGEMENT STRATEGY

P 58

Only half of the companies with strategies require suppliers to set limits

Six companies report requesting suppliers to set discharge limits. This is done during supplier audits or via a questionnaire that asks suppliers to provide discharge levels.



ENVIRONMENTAL RISK-MANAGEMENT STRATEGY

P 59

No company assesses whether waste-treatment plants meet limits

No company monitors antibacterial levels discharged by the external privately owned wastewater-treatment plants they use, nor do companies require wastewater-treatment plants to set limits for antibacterial discharge or monitor discharge levels.

ENVIRONMENTAL RISK-MANAGEMENT STRATEGY

P 59

Some environmental strategies cover antifungal manufacturing

Of the 15 companies assessed in this area that market antifungals, seven report that they extend their environmental risk-management strategies to also cover these products.

DISCLOSURE ON ENVIRONMENTAL RISK MANAGEMENT

P 60

Public reporting on strategy components varies

Five of the companies evaluated publish some components of their overall environmental strategy, while the 12 that are members of the AMR Industry Alliance additionally publish the discharge limits they have committed to.

DISCLOSURE ON ENVIRONMENTAL RISK MANAGEMENT

P 61

No company publishes discharge levels, audit results or suppliers' identities

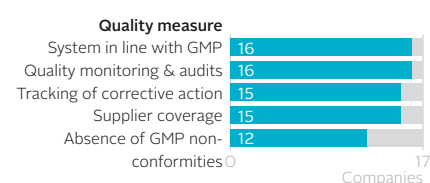
No company publishes the levels of antibacterials in wastewaters discharged from their sites or the full results of audits conducted at these sites. Results of audits to suppliers' sites or the suppliers' identities are also not published.

MANUFACTURING HIGH-QUALITY ANTIBACTERIALS

P 62

Quality systems align with GMP

Nearly all companies evaluated report having a quality system consistent with GMP standards at all antibacterial manufacturing sites. All of these, except one, report on how they track corrective actions and on how their quality systems apply to suppliers.



RESPONSIBLE MANUFACTURING

More companies set antibacterial limits for wastewaters to minimise AMR risk

Supported by the AMR Industry Alliance, companies are assessing their own and suppliers' operations to manage AMR risk from manufacturing discharge

- Most companies report an environmental risk-management strategy that includes limits
- Six companies require suppliers to set limits
- Companies publish the limits they set via the AMR Industry Alliance
- None of the companies publish discharge levels, audit results or suppliers' identities

CONTEXT

During pharmaceutical manufacturing, antibacterial residue can be released into the environment in factory wastewaters. This can contribute to the development of AMR, as bacteria naturally present in water and soil are exposed to antibacterial ingredients with the potential to trigger emergence and/or selection of resistance genes.¹⁻³ Multiple publications have reported links between high concentrations of antibacterials downstream of where factory wastewaters are released and increased levels of resistance in these locations.⁴⁻⁷ The contribution of increased resistance in the environment to the occurrence of resistant infections in humans is still an active area of investigation – an area that can benefit from greater transparency from manufacturers. Manufacturing practices that result in poor-quality products can also contribute to the development of AMR. When pathogens encounter antibacterial medicines that contain a lower than intended amount of the active ingredient, they are more likely to become resistant. Issues with quality may occur when companies' manufacturing operations do not include appropriate quality assurance systems.

Pharmaceutical companies can minimise the risk that their manufacturing operations contribute to the development of resistance through three main routes: (1) by adopting a clear environmental risk-management strategy that applies to their own manufacturing sites, to the sites of their third-party suppliers of APIs and/or drug products and to external private waste-treatment plants; (2) by publishing information on the risk-management processes they implement and their outcomes and (3) by manufacturing products of high quality, following international standards accepted by recognised authorities.

In this Research Area, the 2020 Benchmark assesses 17 companies, including large research-based pharmaceutical companies and generic medicine manufacturers, on their antibacterial manufacturing practices. Their antibacterial sales volumes/values indicate they are prominent players in multiple manufacturing chains, with significant influence on their upstream suppliers (table 7).

ENVIRONMENTAL RISK MANAGEMENT STRATEGIES

Do companies adopt clear environmental risk-management strategies?

The 2020 Benchmark assesses whether companies are adopting clear environmental risk-management strategies to minimise the impact of their manufacturing processes in promoting resistance.

It looks at whether their strategies include: processes to treat and manage waste (both liquid and solid) that may contain antibacterial residues; auditing; limits on the concentrations of antibacterials in manufacturing discharge; and discharge monitoring processes. Performance in these strategy-related dimensions is referred to by the Benchmark as depth.

The Benchmark also evaluates whether companies apply their strategies – including appropriate waste treatment, audits, limits and monitoring – solely to their own manufacturing sites, or also to third-party suppliers of antibacterial APIs and drug products, and/or to external, privately owned waste-treatment plants.* Performance in this area is referred to as breadth.

Depth and breadth of environmental risk-management strategies vary widely

The 2020 Benchmark finds that the depth and breadth of companies' environmental risk-management strategies vary widely. In 2020, the majority of companies (13 of 17 evaluated) have adopted and audit a strategy for their own sites (figure 25 and table 8). Overall, results are similar to those found by the 2018 Benchmark, which reported that 15 out of 18 companies evaluated had strategies for their own manufacturing sites, and 14 carried out strategy audits.

Almost all companies that adopt a strategy (12 of 13) set limits for manufacturing discharge (figure 25). Seven of the 12 companies that set limits on manufacturing discharge have completed risk assessments to investigate whether it is likely that discharged levels meet these limits at all manufacturing sites. Among the remaining five, risk assessments

* Off-site plants that are more than 50% owned by private parties (possibly including the companies themselves).

TABLE 7

What is the scale of pharmaceutical companies' antibacterial manufacturing operations?

The chart compares the manufacturing operations of the 17 companies evaluated in this Research Area, which include those with the largest global antibacterial sales volumes and values. These companies typically have extensive manufacturing and supply chains with significant influence on their suppliers.

Global antibacterial sales volume (SU million) *

| 1,000 - 2,000 | 2,000 - 3,000 | > 3,000 |
|---|---|--|
| 3 companies: Aurobindo, Mylan, Sanofi | 5 companies: Abbott, Alkem, Cipla, Pfizer, Teva | 3 companies: GSK, Novartis, Sun Pharma |

Number of unique antibacterial APIs processed at own sites

| 1 - 15 | 16 - 50 | > 50 |
|--|---------------------------------------|--|
| 3 companies: Johnson & Johnson, Otsuka, Shionogi | 3 companies: Aurobindo, Cipla, GSK | 4 companies: Novartis, Pfizer, Teva, 1 company undisclosed |

Number of own sites manufacturing antibacterial APIs and/or drug products

| 1 - 10 | 11 - 20 | 21 - 40 |
|---|---|---|
| 4 companies: Hainan Hailing, Johnson & Johnson, Otsuka, Shionogi | 4 companies: Aurobindo, Cipla, Fresenius Kabi, 1 company undisclosed | 4 companies: GSK, Novartis, Teva, 1 company undisclosed |

Number of suppliers of antibacterial APIs and/or drug products

| 1 - 10 | 11 - 50 | 51 - 100 | > 100 |
|--|-------------|----------------------------|---|
| 3 companies: Johnson & Johnson, Otsuka, Shionogi | 0 companies | 2 companies: Cipla, GSK | 4 companies: Novartis, Teva, 2 companies undisclosed |

* The remaining six companies have sales volumes below approximately 1,000 SU million each, based on IQVIA MIDAS® 2017 anti-infectives data. They are Fresenius Kabi, Hainan Hailing, Johnson & Johnson, Merck & Co, Inc, Otsuka and Shionogi. SU = Standard Unit

FIGURE 25

Twelve companies set limits but only six currently extend them to suppliers

The chart shows the proportion of companies that adopt environmental risk-management strategies, and whether or not strategies include limits for antibacterial discharge in manufacturing wastewaters.

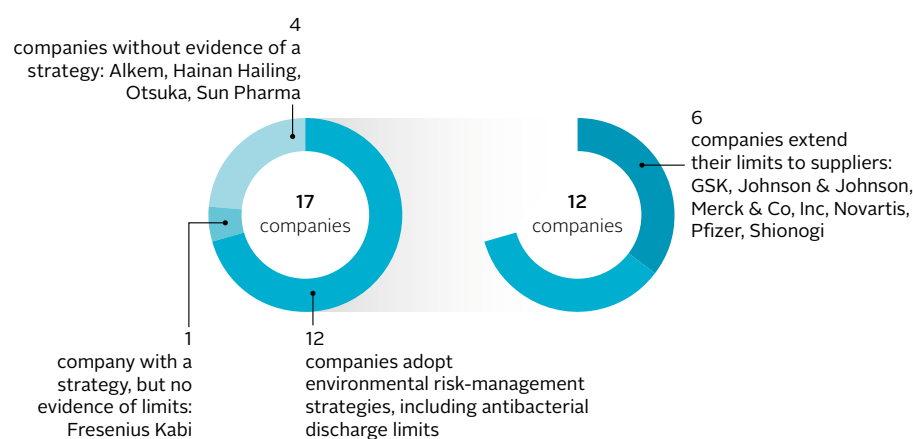


TABLE 8

Depth and breadth of environmental risk-management strategies vary widely between companies

The table shows whether companies' environmental risk-management strategies include appropriate waste treatment (labelled 'strategy'), audits, limits and monitoring of antibacterial discharge (referred to as the 'depth' of a strategy), as well as where and how companies apply these strategies ('breadth').

| | Own manufacturing sites | | Third-party suppliers of APIs and/or drug products | | External private waste-treatment plants | |
|--|-------------------------|---------------------|--|---------------------|---|---------------------|
| | Strategy & Audits | Limits & Monitoring | Strategy & Audits | Limits & Monitoring | Strategy & Audits | Limits & Monitoring |
| Large research-based pharmaceutical companies | | | | | | |
| GSK* | ● | ● | ◆ | ▼ | ■ | — |
| Johnson & Johnson* | ● | ● | ◆ | ▼ | ■ | N/A |
| Merck & Co, Inc* | ● | ● | ◆ | ▼ | ■ | N/A |
| Novartis* | ● | ● | ◆ | ▼ | ■ | — |
| Otsuka* | ● | ● | ◆ | ▼ | ■ | — |
| Pfizer* | ● | ● | ◆ | ▼ | ■ | — |
| Sanofi* | ● | ● | ◆ | ▼ | ■ | — |
| Shionogi* | ● | ● | ◆ | ▼ | ■ | N/A |
| Generic medicine manufacturers | | | | | | |
| Abbott | ● | ● | ◆ | ▼ | ■ | — |
| Alkem | ● | ● | ◆ | ▼ | ■ | — |
| Aurobindo* | ● | ● | ◆ | ▼ | ■ | — |
| Cipla* | ● | ● | ◆ | ▼ | ■ | — |
| Fresenius Kabi | ● | ● | ◆ | ▼ | ■ | — |
| Hainan Hailing | ● | ● | ◆ | ▼ | ■ | — |
| Mylan* | ● | ● | ◆ | ▼ | ■ | — |
| Sun Pharma | ● | ● | ◆ | ▼ | ■ | — |
| Teva* | ● | ● | ◆ | ▼ | ■ | — |

*Member of AMR Industry Alliance

● ● ● ● ● No or limited evidence that the company fulfills the corresponding element.

● Strategy adopted, including audits
 ● At least one round of risk assessments using limits has been completed
 ● Company has set limits but risk assessments may not yet be complete for all sites and/or antibacterials

◆ Strategy being implemented with their suppliers
 ◆ Strategy covers suppliers but has not yet been fully implemented with said suppliers
 ▼ Suppliers asked to set limits and (at a minimum) to provide discharge level information to company
 ▼ Suppliers asked to set limits but it is not clear how the company assesses whether limits are being met

■ Strategy includes audits of external private waste-treatment plants
 ■ No or less information on how external private waste-treatment plants are audited
 N/A: Three companies report not using external private plants to treat their wastewater and are therefore not evaluated with respect to limits and monitoring of discharge from these plants.

Companies that set discharge limits at their own sites (12) typically do so for all sites, including those that send wastewaters to external plants for treatment. Several of them (e.g. GSK, Novartis) report that the discharge sent to these plants should be at such a level that the final wastewater discharged by the plants meets resistance-based limits in the environment, in line with Industry Alliance methodology. No company reports monitoring or asking plants to monitor the levels of antibacterials in their discharges.

CHANGES SINCE 2018

Industry wide changes

- AMR Industry Alliance publishes Common Antibiotic Manufacturing Framework (CAMF) in Jan 2018 and list of discharge targets in Sep 2018
- Leading members of the Alliance publish article detailing methodology for discharge targets in Mar 2019
- PSCI includes AMR-specific points in its supplier questionnaire in Feb 2019

Company changes

- Cipla adopted a strategy, has completed initial own-site assessments and is developing an auditing framework in line with the CAMF.
- Aurobindo, Cipla, Merck & Co, Inc and Mylan now set limits as recommended by the AMR Industry Alliance. Based on these limits Aurobindo is starting risk assessments at its sites and Mylan and Cipla have completed them.

- Merck & Co, Inc, Novartis and Shionogi now request suppliers to set limits. Merck & Co, Inc states that limits have been provided to suppliers. Novartis states that it is asking suppliers to provide their antibacterial discharge levels and Shionogi reports that it asks suppliers to document their discharge levels for verification during ongoing on-site audits.

are ongoing, with varying levels of progress. Large research-based pharmaceutical companies are more likely than generic medicine manufacturers to monitor and assess their discharge against limits.

Overall, four large research-based pharmaceutical companies lead in this area, by covering the most depth and breadth elements with their strategies: GSK, Johnson & Johnson, Pfizer and Shionogi. In general, generic medicine manufacturers are focusing on implementing strategies at their own sites, although some report taking initial steps to implement the strategies with suppliers.

Strategies largely determined by AMR Industry Alliance framework

By implementing environmental risk-management strategies, antibacterial manufacturers can limit the risk that their manufacturing processes contribute to the emergence and spread of antimicrobial resistance.

Similar to the 2018 Benchmark, most companies evaluated (13 of 17) show evidence of an environmental risk-management strategy that aims to minimise AMR risks of antibacterial discharge (liquid and/or solid) from manufacturing processes. All 13 report auditing this strategy at their own sites manufacturing antibacterial APIs and/or drug products. Four companies (Alkem, Hainan Hailing, Otsuka and Sun Pharma) show evidence of having environmental risk-management processes but did not report a specific strategy to manage AMR risk.

Of 17 companies assessed, 12 are part of the AMR Industry Alliance, a coalition of pharmaceutical companies formed in 2016 to deliver on the commitments made in the Davos Declaration on curbing AMR. This includes all eight of the large research-based pharmaceutical companies assessed in this Research Area, together with four of the nine generic

medicine manufacturers (Aurobindo, Cipla, Mylan and Teva). As Alliance members, these companies commit to manage AMR risk from antibacterial manufacturing discharge by, for example, adopting its Common Antibiotic Manufacturing Framework (CAMF), published in January 2018.

The CAMF specifies a methodology and standards against which member companies can assess their sites, signalling that members have reached a consensus on specific steps needed to tackle AMR risk from antibacterial manufacturing.

Many Alliance members report having adopted this strategy or taken steps to align their strategies to the CAMF. As an Alliance member, Otsuka is the only one that has not yet adopted an AMR-specific strategy to support its commitment to the CAMF. Of non-Alliance companies, Abbott and Fresenius Kabi report a strategy to manage the risk of their manufacturing processes contributing to the emergence and/or spread of AMR.

Majority of companies set discharge limits at own sites and most of these assess the risk of limits being exceeded

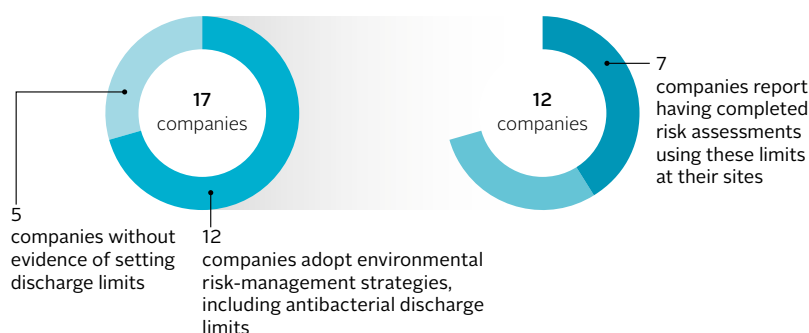
Environmental regulations do not typically set limits on the levels of antibacterials allowed in manufacturing discharge. Current initiatives in this area usually have limited scope in terms of countries and number of antibacterials covered, which hinders their effectiveness. While it is important for governments to take action and introduce relevant regulation, companies should not wait for this to happen, but voluntarily set limits to mitigate the risk of emergence and/or spread of AMR.

To manage the risk of emergence and/or spread of AMR in the environment, limits should be set, per active ingredient, either at or below the predicted no-effect concentrations (PNECs) for resistance selection. At the same time, companies should quantify their discharge levels and assess whether

FIGURE 26

Companies are assessing the risk of releasing antibacterials into the environment

The chart shows the proportion of pharmaceutical companies that have adopted environmental risk-management strategies that include discharge limits, and how many of these have conducted at least one round of risk assessment using these limits at their own sites. Most of the latter also report having a framework in place to trigger corrective action when an assessment identifies risk.



they meet these limits. Such risk assessments will enable companies to identify problematic manufacturing processes, to draft and implement appropriate remedial plans, and to define measuring and maintenance protocols.

In parallel, governments and other public institutions – as procurers of antibacterial medicines – can seek to incentivise companies to limit antibacterial discharge from manufacturing, by making environmental considerations part of their procurement policies, for example.

The Benchmark assesses whether the 17 companies evaluated in this Research Area set antibacterial discharge limits, and whether they use these to conduct risk assessments of manufacturing discharge at their own sites.

Of the 13 companies with an environmental risk-management strategy, 12 set limits for antibacterial discharge based on PNECs for resistance selection (or on more stringent PNECs). The remaining company, Fresenius Kabi, has a general strategy to minimise the impact of antibacterial discharge, but shows no evidence of setting limits.

The 12 that set limits are all, with the exception of Abbott, members of the AMR Industry Alliance (table 8). All (including Abbott) report adopting limits in line with Alliance recommendations, based on previously published scientific literature and company-generated data.^{8–11}

Of the 12 companies that set limits, seven have completed risk assessments to investigate whether discharge levels are likely to meet limits at all manufacturing sites. Among the five remaining companies, risk assessments are ongoing.

The Benchmark finds that companies are quantifying antibacterial discharge levels primarily by using a ‘mass balance’ approach, rather than taking direct measurements of antibacterial levels in factory wastewaters. Implementing technology to monitor and analyse every antibacterial manufactured is a process that is currently more expensive than using a mass balance approach.

Mass balance calculations may have a value in detecting comparably large losses of active ingredients during manufacturing.³ However, periodic sampling and measuring could be more reliable in ensuring discharge meets the limits during production activities. One company, Shionogi, reports that it plans to invest in such a framework.

Most of the companies that have conducted at least one round of risk assessment at their sites report having in place a framework to trigger corrective actions when an assessment identifies risk. Usually these actions include direct sampling and measurement, collection and incineration of

contaminated discharge close to source, and/or investigation of how the waste-treatment technologies currently deployed can be improved.

Six companies require suppliers to set antibacterial discharge limits

Pharmaceutical companies assessed by the Benchmark do not typically manufacture all the active antibacterial ingredients in the medicines they sell. They often rely on extensive networks of third parties to supply them with the antibacterial ingredients they need to manufacture medicines in their final formulation. Stakeholders expect companies to mitigate the risk of suppliers’ manufacturing operations on development of AMR in the environment, through their own environmental risk-management strategies.

The Benchmark assesses whether the 17 companies evaluated in this Research Area require their suppliers to have in place environmental risk-management strategies that are at least as stringent as their own – including audits, limits and discharge monitoring.

Of the 13 companies with environmental risk-management strategies at their own sites, 12 report that the strategies cover their suppliers of antibacterial APIs and/or drug products. Of the 12, only eight have started to implement them with said suppliers, including auditing. The remaining four (Cipla, Fresenius Kabi, Mylan and Teva) have yet to initiate supplier assessments, citing an initial focus on their own sites. Aurobindo initially reported no plans to extend its strategy to suppliers but stated, after the period of analysis, that it had conveyed the expectations of the AMR Industry Alliance CAMF to its suppliers. The company joined the Alliance in 2019.

Of the eight companies beginning to implement the strategy with suppliers, six report requesting suppliers to set limits for antibacterial discharge. Typically this is done during supplier audits, or in a questionnaire that asks suppliers to provide discharge levels. Johnson & Johnson additionally reports conducting sampling at suppliers’ sites. One company (GSK) reports plans to discontinue operations with any supplier that does not comply by 2021 with limits set.

Eight companies (GSK, Johnson & Johnson, Merck & Co, Inc, Novartis, Pfizer, Sanofi, Shionogi and Teva) are members of the Pharmaceutical Supply Chain Initiative (PSCI), an industry coalition formed to establish and promote responsible practices across members’ supply chains and, in particular, to make supplier assessments more efficient. Some of these

WHAT ARE PNECS?

Predicted no-effect concentration (PNEC) is the concentration below which no harmful effects are expected to occur from exposure to the chemical in question. To address AMR, discharge limits must be based on PNECs for resistance selection rather than, for example, toxicity to aquatic species (unless the latter PNECs are more stringent).

HOW DOES A MASS BALANCE APPROACH WORK?

Mass balance compares the amount of an active pharmaceutical ingredient (API) used during the process of making a product with the amount found in the final product. The difference between the two – the ‘mass balance’ – indicates how much API has been released into the environment.

companies (e.g. Novartis, Pfizer) report using PSCI's self-assessment questionnaire, recently updated to incorporate AMR-specific points, to evaluate suppliers. Other resources made available on the PSCI website include templates for estimation of discharge levels that can be used by suppliers to estimate whether they are meeting discharge limits.

To date, no company has shown that its supplier contracts include requirements to manage AMR-related risks, for example a requirement to meet discharge limits. This is a bar that all companies are encouraged to meet.

No company assesses whether wastewater-treatment plants meet discharge limits

Some antibacterial manufacturing sites have on-site treatment plants for their wastewaters and other waste, while others rely at least partly on external, privately owned plants to treat wastewaters and other waste from antibacterial manufacture. Both on-site and external plants have a role to play in minimising AMR risk from the discharge of antibacterials into the environment.

The Benchmark assesses whether, for antibacterial manufacturing, the 17 companies evaluated in this Research Area require external private waste-treatment plants to have in place environmental risk-management strategies that are at least as stringent as their own strategies – including audits and, for plants treating wastewater, limits and monitoring of discharge levels.

The 13 companies that have strategies covering their own sites also report having processes in place to manage

waste being treated off-site. Several report conducting initial screening of external private waste-treatment plants with respect to responsible environmental practices prior to contracting and some report that all waste sent to these plants is set to be incinerated (e.g. Shionogi). Five companies (Abbott, GSK, Johnson & Johnson, Pfizer and Shionogi) report periodic auditing of the plants. The remaining eight companies report not auditing or provide less information on how audits are carried out.

Currently, no companies require that wastewater-treatment plants set limits for antibacterial discharge, and none report monitoring (or asking plants to monitor) their discharges. Nonetheless, companies that set discharge limits at their own sites (12) typically do so for all sites, including those that send wastewaters to external plants for treatment. Several of them (e.g. GSK, Novartis) report that the discharge sent to these plants should be at such a level that the final wastewater discharged by the plants meets resistance-based limits in the environment, in line with Industry Alliance methodology.

However, some external plants – for example, those in industrial parks – receive wastewaters from multiple pharmaceutical companies, which may not all set limits, thereby undermining the success of this approach in minimising AMR risk. Companies are encouraged to engage with all external private plants, requiring them to manage AMR-related risks from wastewater discharge to the environment.

Companies' environmental policies with respect to the publicly owned waste- and wastewater-treatment plants they

SEVERAL ENVIRONMENTAL STRATEGIES ALSO COVER ANTIFUNGAL MANUFACTURING

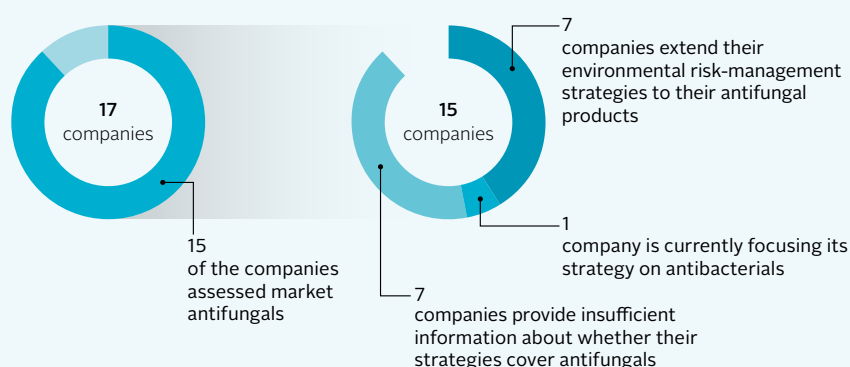
As in 2018, this Research Area focuses on antibacterials. The Benchmark has also gathered information about whether and how companies extend their environmental risk-management strategies to cover the discharge of antifungals. This is an emerging area of concern, particularly with regard to the high rate of cross-resistance between compounds employed as both broad-spectrum human antifungals and fungicides in agriculture.¹²

Fifteen of the 17 companies evaluated in this Research Area are marketing antifungal medicines. Of these, seven report a strategy that covers antifungal manufacturing, and one indicates an exclusive focus on antibacterials, with potential future extension to antifungals. Regarding discharge limits, the list published by the AMR Industry Alliance includes limits for both antibacterial and antifungal products, though only a handful of the latter. Moving forward, companies can build on this list and ensure that limits apply to all antifungal products they manufacture and/or market.

FIGURE 27

Seven companies extend environmental risk-management strategies to antifungal production

The chart shows the proportion of companies in scope that market antifungals and extend their environmental risk-management strategies to also cover these products.



use were not evaluated by the Benchmark. This is because companies may have less power to negotiate contractual terms with these plants, given national and/or regional regulations.

DISCLOSURE OF ENVIRONMENTAL RISK MANAGEMENT

Do companies publish their environmental risk management strategies and their outcomes?

As companies implement specific strategies to manage environmental risks relating to AMR, experts and stakeholders expect them to publish certain elements of these strategies, as well as their outcomes. Publication can allow independent third parties to analyse and compare companies' processes and performance. Publication can also promote the dissemination of good practice and give procurers (such as governments and other public institutions) the information necessary to identify companies that manufacture responsibly.¹³ The Benchmark measures whether the 17 companies evaluated in this Research Area publish: (1) their overall environmental risk-management strategies; (2) the limits set for antibacterial discharge at their sites; (3) the results of strategy audits and discharge levels at company sites; (4) the results of strategy audits to third-party suppliers of antibacterial APIs, drug products and waste treatment services; and (5) the identities of such third parties.

All 17 companies evaluated publish some of the elements looked for by the Benchmark (figure 28). Five companies publish only some components of their overall environmental risk-management strategies. The other 12 are members of the AMR Industry Alliance, which has published a list of recommended antibacterial discharge limits. Yet, no company publishes its discharge levels, audit results or the identities of

third-party suppliers.

Public reporting on strategy components varies

The Benchmark assessed whether pharmaceutical companies published components of their overall environmental risk-management strategies (independently of whether AMR is taken into account).

All 17 companies evaluated publish components of their environmental risk-management strategies. These include policy documents; sections in corporate responsibility reports describing environmental management systems, programmes and/or progress (demonstrated by, e.g., Pfizer and Sanofi); and disclosures to public reporting initiatives (demonstrated by, e.g., Novartis to the CDP, formerly known as the Carbon Disclosure Project). Importantly, 12 companies have made a public commitment to assess their own and suppliers' sites through the AMR Industry Alliance's Common Antibiotic Manufacturing Framework (CAMF), a publicly available document that provides strategic recommendations on handling and treatment of antibacterial waste, risk assessment and auditing to minimise AMR risk from antibacterial manufacturing. Being publicly available, the CAMF allows independent experts to assess the appropriateness of such recommendations.

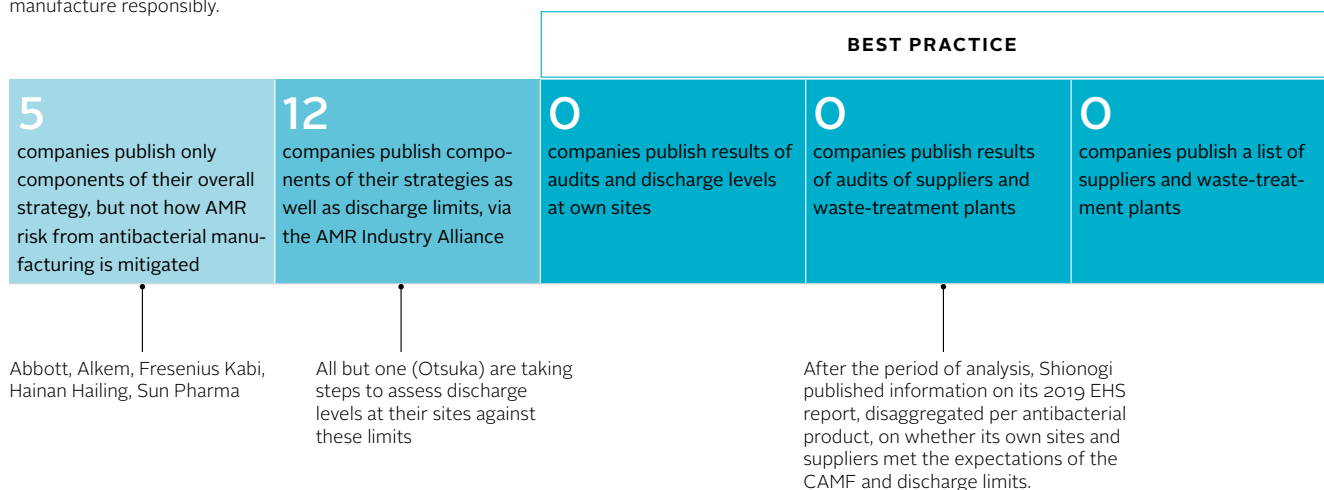
Companies publish limits via AMR Industry Alliance

By publishing the antibacterial discharge limits they set, companies allow independent experts to assess whether such limits are appropriate for minimising the risk of AMR in the environment. The Benchmark assessed whether companies published the limits they set for antibacterial discharge at their manufacturing sites (independently of whether such limits

FIGURE 28

Which elements of their environmental risk-management strategies are published by 17 companies?

The chart shows how many companies publish each piece of information about their environmental risk-management practices that the Benchmark seeks. Publishing this information can allow independent third parties to analyse and compare companies' processes and performance, promote dissemination of good practice and give medicine procurers (such as governments) the information necessary to identify companies that manufacture responsibly.



are being met).

Twelve companies have made a public commitment to the limits recommended by the AMR Industry Alliance, published in September 2018. The other five companies (of the 17 evaluated) are not Alliance members and do not publish limits for antibacterial discharge: Abbott, Alkem, Fresenius Kabi, Hainan Hailing and Sun Pharma.

Three companies (Mylan, Pfizer and Shionogi) publicly report using the limits recommended by the Alliance to conduct risk assessments on their official websites or sustainability reports. Others (e.g. GSK, Johnson & Johnson) report that their updated policy documents will reflect this information in the future. All companies, including members of the AMR Industry Alliance, are encouraged to use official company sources (such as websites or annual reports) to publish the limits they set, and describe how these are used in practice. This description could include, for example, whether a company prioritises certain antibacterials for assessment against specific limits; and the processes a company follows for antibacterials that do not yet have AMR-related limits.

No company publishes actual antibacterial discharge levels

Pharmaceutical companies are expected to be able to publish their strategy audits, including levels of antibacterial residue found to have been discharged in wastewaters. Disclosures of these levels, and of the protocols used for quantification, can support governments and researchers as they work to understand the relationships between antibacterial discharge, development of resistance in the environment, and the occurrence of resistant infections in humans.¹⁴

Of the 17 companies evaluated in this Research Area, none publish results of audits of their own manufacturing sites, and none disclose the levels (concentrations) of antibacterials discharged in these sites' wastewaters. Several companies state that they consider this information to be proprietary and

confidential.

Yet some companies, in corporate responsibility reports, publish levels of wastewater quality indicators not specific to antibacterials, such as chemical oxygen demand (e.g. Sanofi) and biological oxygen demand (e.g. Abbott).

Experts and stakeholders expect companies to publish full audits and/or risk assessments of their own sites, on a per site basis, including levels (concentrations) of individual antibacterials discharged, and the quantification protocols.¹⁵

No company publishes audits of suppliers' sites or waste-treatment plants

In publishing audit results from suppliers' sites and waste-treatment plants, pharmaceutical companies provide a measure of progress achieved and the challenges remaining in ensuring that the entire supply chain manages AMR-related risks.

None of the 17 companies evaluated in this Research Area publish results of their audits at supplier sites or waste-treatment plants. Some companies report these to be confidential, saying current contractual agreements prevent such disclosure. While companies sometimes disclose overall results of environmental audits in their corporate responsibility reports (e.g. Johnson & Johnson in its Health for Humanity report), these do not show AMR-specific supplier performance. After the period of analysis, Shionogi published information in its 2019 Environmental Health and Safety report, on whether its own sites and suppliers met the expectations of the CAMF and discharge limits, disaggregated per antibacterial product. This is a positive step, although the actual level of antibacterial discharge and suppliers' identities were not published.

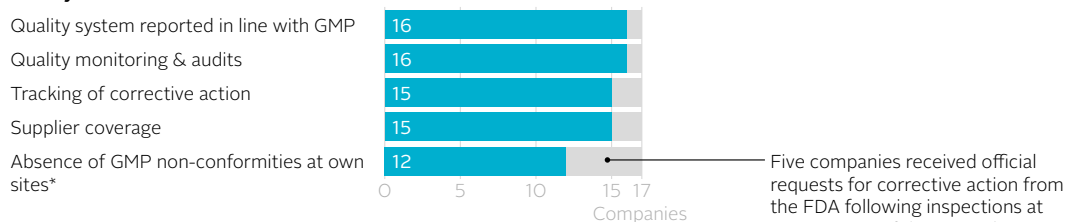
In general, the companies that the Benchmark assesses are dominant players in their manufacturing chains, with power to influence standards and practices, and to negotiate terms. This might include renegotiating contracts to facilitate the publication of results of supplier audits. Existing collaborative

FIGURE 29

Broad adherence to GMP

The chart shows how many companies have the five quality aspects that the Benchmark assesses in place. Typically, companies report having quality management systems that follow GMP guidance, including provisions for quality monitoring and auditing, tracking of corrective and preventive actions (CAPAs), and oversight of suppliers.

Quality measure



platforms, such as the AMR Industry Alliance or the PSCI, can also be used to coordinate public disclosure of audit results.

No company discloses suppliers or waste-treatment plants

By publishing which suppliers and waste-treatment plants they engage with, companies can increase accountability along the supply chain, even if audit results are not made available. Disclosing lists of suppliers allows independent third parties to investigate whether such suppliers have in place environmental risk-management strategies that minimise AMR-related risks.

Of the 17 companies evaluated in this Research Area, none yet publish lists of suppliers or of external, private waste-treatment plants. As with audits, some companies report this information to be confidential, with current contractual agreements preventing public disclosure.

By contrast, some SMEs with antibacterial products on the market – SMEs included in the 2020 Benchmark but not evaluated in this Research Area – do publish information about their suppliers. Nabriva, in particular, publishes information about its commercial suppliers for lefamulin (Xenleta™) and fosfomycin (Contepo™). In its annual report, it published the identities of all API and drug products suppliers it contracts for manufacturing these products.

By publishing the identities of third-party suppliers, Nabriva enables governments, researchers and others to assess the impact of its manufacturing chain on the emergence of antibacterial resistance.

MANUFACTURE OF HIGH-QUALITY ANTIBACTERIALS

Quality systems align with Good Manufacturing Practice

Pharmaceutical companies are expected to produce their antibacterials using the highest standards to ensure quality, such as standards of Good Manufacturing Practice (GMP). By using these standards, companies help to minimise the risk that patients are exposed to sub-therapeutic levels of antibacterials, which drive AMR.¹⁶

The Benchmark reports on the systems companies have in place to ensure high-quality production in own and third-party facilities used to manufacture antibacterial APIs and drug products. The Benchmark evaluates how companies maintain consistency with international GMP standards, how they monitor and audit quality, and how they implement and track corrective actions. Publicly available GMP non-compliance reports are also considered in the assessment.

Of the 17 companies evaluated in this Research Area, 16 report having a quality system consistent with international GMP standards at all sites manufacturing antibacterial APIs and/or drug products. This includes provisions for quality monitoring, testing and/or periodic auditing (figure 29). The 17th company, Hainan Hailing, publishes very limited information about its quality system, but the Benchmark has been able to determine that it operates in markets under FDA and EU (EMA) purview. During the period of analysis, Hainan Hailing has not received any FDA requests for

official corrective action or non-compliance reports from EU member states, as reported publicly in the FDA's Inspection Classification Database and the EMA EudraGMP database, respectively.

With the exception of Sun Pharma, all companies report on how they track corrective and preventive action (CAPA) plans, and on how their quality systems apply to suppliers, as well as to their own manufacturing sites. With regard to the quality standards and systems that companies require suppliers to implement, most companies evaluated report that they assure the use and maintenance of such standards through (1) quality agreements established in (or as part of) commercial contracts and (2) periodic audits. Five companies (Cipla, Fresenius Kabi, GSK, Johnson & Johnson and Mylan) also report collaborating with suppliers to design improvement plans, which in some cases (Fresenius Kabi, Johnson & Johnson, Mylan) may entail placing company personnel at a supplier site on a temporary basis.

For 12 of the 17 companies assessed in this area, the Benchmark finds no publicly available evidence of important GMP non-compliance reports in the FDA or EMA databases. For the other five, one or more of the companies' manufacturing sites (or subsidiaries' sites) received an inspection result of 'Official Action Indicated' (OAI) by the FDA during the period of analysis^{**}; for Aurobindo, Mylan, Pfizer^{***} and Teva, the reports refer to sites at which antibacterials are manufactured. Teva reports that oral antibacterial products produced at the site were not affected by the observations raised by the FDA. For Alkem, it cannot be determined from the available reports whether or not the site produces antibacterials.[†]

Strong quality management systems and practices are essential in guaranteeing that patients receive quality antibacterial medicines, which minimises the risk of resistance developing. Regulatory authorities must be supported to guide and inspect pharmaceutical companies as they establish and maintain quality management systems and adhere to standards. To support public health, inspection information needs to be published. This encourages compliance and enables healthcare professionals to make informed choices in prescribing antibacterial medicines, and aids procurement agencies during product selection.

^{**} 9 September 2017 to 21 June 2019, inclusive.

^{***} Production has been discontinued at one of the sites.

[†] Nevertheless, the OAI report by the FDA was taken into account, since it suggests potential risks regarding how the company's reported quality system is being implemented at sites producing antibacterials; for Teva, the warning letter issued by the FDA included observations on systems that may potentially affect antibacterial products, in addition to more specific observations focusing on a non-antibacterial.

REFERENCES

- 1 Larsson DGJ. Pollution from drug manufacturing: Review and perspectives. *Philos Trans R Soc B Biol Sci*. 2014;369(1656). doi:10.1098/rstb.2013.0571
- 2 Singer AC, Shaw H, Rhodes V, Hart A. Review of Antimicrobial Resistance in the Environment and Its Relevance to Environmental Regulators. *Front Microbiol*. 2016;7:1728. doi:10.3389/fmicb.2016.01728
- 3 Initiatives for Addressing Antimicrobial Resistance in the Environment: Current Situation and Challenges.; 2018. <https://wellcome.ac.uk/sites/default/files/antimicrobial-resistance-environment-report.pdf>.
- 4 Karkman A, Pärnänen K, Larsson DGJ. Fecal pollution can explain antibiotic resistance gene abundances in anthropogenically impacted environments. *Nat Commun*. 2019;10(1). doi:10.1038/s41467-018-07992-3
- 5 Kristiansson E, Fick J, Janzon A, et al. Pyrosequencing of antibiotic-contaminated river sediments reveals high levels of resistance and gene transfer elements. *PLoS One*. 2011;6(2). doi:10.1371/journal.pone.0017038
- 6 Bielen A, Šimatović A, Kosić-Vukšić J, et al. Negative environmental impacts of antibiotic-contaminated effluents from pharmaceutical industries. *Water Res*. 2017;126:79-87. doi:10.1016/j.watres.2017.09.019
- 7 Li D, Yang M, Hu J, Ren L, Zhang Y, Li K. Determination and fate of oxytetracycline and related compounds in oxytetracycline production wastewater and the receiving river. *Environ Toxicol Chem*. 2008;27(1):80-86. doi:10.1897/07-080.1
- 8 Bengtsson-Palme J, Larsson DGJ. Concentrations of antibiotics predicted to select for resistant bacteria: Proposed limits for environmental regulation. *Environ Int*. 2016;86:140-149. doi:10.1016/j.envint.2015.10.015
- 9 Le Page G, Gunnarsson L, Snape J, Tyler CR. Integrating human and environmental health in antibiotic risk assessment: A critical analysis of protection goals, species sensitivity and antimicrobial resistance. *Environ Int*. 2017;109:155-169. doi:10.1016/j.envint.2017.09.013
- 10 Brandt KK, Amézquita A, Backhaus T, et al. Ecotoxicological assessment of antibiotics: A call for improved consideration of microorganisms. *Environ Int*. 2015;85:189-205. doi:10.1016/j.envint.2015.09.013
- 11 Tell J, Caldwell DJ, Häner A, et al. Science-based Targets for Antibiotics in Receiving Waters from Pharmaceutical Manufacturing Operations. *Integr Environ Assess Manag*. 2019;15(3):312-319. doi:10.1002/ieam.4141
- 12 Verweij PE, Chowdhary A, Melchers WJG, Meis JF. Azole Resistance in *Aspergillus fumigatus*: Can We Retain the Clinical Use of Mold-Active Antifungal Azoles? *Clin Infect Dis*. 2016;62(3):362-368. doi:10.1093/cid/civ885
- 13 Larsson DGJ, Fick J. Transparency throughout the production chain—a way to reduce pollution from the manufacturing of pharmaceuticals? *Regul Toxicol Pharmacol*. 2009;53(3):161-163. doi:10.1016/j.jrtp.2009.01.008
- 14 Larsson DGJ, Andreumont A, Bengtsson-Palme J, et al. Critical knowledge gaps and research needs related to the environmental dimensions of antibiotic resistance. *Environ Int*. 2018;117:132-138. doi:10.1016/j.envint.2018.04.041
- 15 Nijssingh N, Munthe C, Joakim Larsson DG. Managing pollution from antibiotics manufacturing: Charting actors, incentives and disincentives. *Environ Heal A Glob Access Sci Source*. 2019;18(1). doi:10.1186/s12940-019-0531-1
- 16 Weinstein ZB, Zaman MH. Evolution of Rifampin Resistance in *Escherichia coli* and *Mycobacterium smegmatis* Due to Substandard Drugs. *Antimicrob Agents Chemother*. 2018;63(1). doi:10.1128/AAC.01243-18

C APPROPRIATE ACCESS & STEWARDSHIP

WHY THIS MATTERS

Rising antimicrobial resistance (AMR) poses twin challenges: excess and access. The rise of AMR is being accelerated by excessive or inappropriate antibacterial and antifungal use (stewardship), while millions of people currently live without reliable access to such products. Both issues are closely interlinked as the need to enhance access where necessary must be balanced with that of ensuring optimal and appropriate use. Pharmaceutical companies can influence both access and stewardship. To ensure access, they can put in place strategies, relating to product registration, affordability and improving supply chains. Regarding stewardship, the role for pharmaceutical companies spans a range of areas such as surveillance and ensuring sales practices take account of the risks of overuse and misuse.

HOW WE MEASURE

This analysis uses global antibiotic sales volumes to inform its selection of companies to analyse. The Benchmark assesses 17 companies in this Research Area: all eight large research-based pharmaceutical companies and all nine generic medicine manufacturers. The scale of these companies' sales volumes suggests that their policies and practices can likely have a significant impact on AMR.

WHAT WE MEASURE

The Benchmark uses a framework of nine metrics to assess companies' access strategies for antibacterial and antifungal products in 102 low- and middle-income countries, alongside their global stewardship initiatives. It looks across the following areas:

1. Registration: whether companies file both on- and off-patent products in the countries that need them the most,
2. Pricing: how companies are setting prices, at a country level and for populations within a given country,
3. Supply: do companies implement mechanisms to prevent and stock-outs and shortages,
4. Surveillance: whether companies monitor, track and share data on consumption and resistance trends,
5. Promotion: how companies ensure their products are used appropriately,
6. Education: how conflicts of interest are mitigated if companies engage in educational activities aimed at healthcare professionals,
7. Packaging adaptations: whether companies have adapted their product brochures and packaging to encourage appropriate use.

The Benchmark does not assess the activities of the 13 small & medium-sized enterprises in scope so as to preserve the comparability of this group. Most of these companies have no products on the market. However, the Benchmark highlights the relevant activities of these companies where possible.

Companies in scope

| | Applicable indicators | | | | | | |
|--|-----------------------|-------|-----|-------|-----|-------------|-----|
| | Access | | | | | Stewardship | |
| | C.1 | C.1.2 | C.2 | C.2.2 | C.3 | C.4 | C.5 |
| Large research-based pharmaceutical companies | | | | | | | |
| GSK | ● | ● | ● | ● | ● | ● | ● |
| Johnson & Johnson | ● | ● | ● | ● | ● | ● | ● |
| Merck & Co, Inc | ● | ● | ● | ● | ● | ● | ● |
| Novartis | ● | ● | ● | ● | ● | ● | ● |
| Otsuka | ● | ● | ● | ● | ● | ● | ● |
| Pfizer | ● | ● | ● | ● | ● | ● | ● |
| Sanofi | ● | ● | ● | ● | ● | ● | ● |
| Shionogi | ● | ● | ● | ● | ● | ● | ● |
| Generic medicine manufacturers | | | | | | | |
| Abbott | ● | ● | ● | ● | ● | ● | ● |
| Alkem | ● | ● | ● | ● | ● | ● | ● |
| Aurobindo | ● | ● | ● | ● | ● | ● | ● |
| Cipla | ● | ● | ● | ● | ● | ● | ● |
| Fresenius Kabi | ● | ● | ● | ● | ● | ● | ● |
| Hainan Hailing | ● | ● | ● | ● | ● | ● | ● |
| Mylan | ● | ● | ● | ● | ● | ● | ● |
| Sun Pharma | ● | ● | ● | ● | ● | ● | ● |
| Teva | ● | ● | ● | ● | ● | ● | ● |

● Scored ● Not scored

Indicators

| | Page |
|---|------|
| C.1.1 On-patent registration | 69 |
| C.1.2 Off-patent/generic registration | 72 |
| C.2 Pricing | 73 |
| C.3 Continuous supply | 77 |
| C.4 Conflicts of interest mitigation | 86 |
| C.5 Responsible promotional practices | 84 |
| C.6 Brochure and packaging adaptations | 88 |
| C.7 AMR surveillance | 80 |

APPROPRIATE ACCESS & STEWARDSHIP

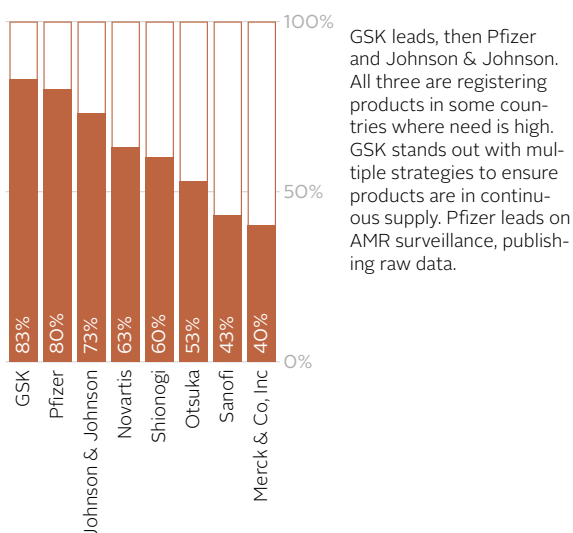
How companies compare in Appropriate Access & Stewardship

In this area, the Benchmark evaluates eight large research-based pharmaceutical companies and nine generic medicine manufacturers including in product registration and pricing, supply, AMR surveillance and responsible promotion.

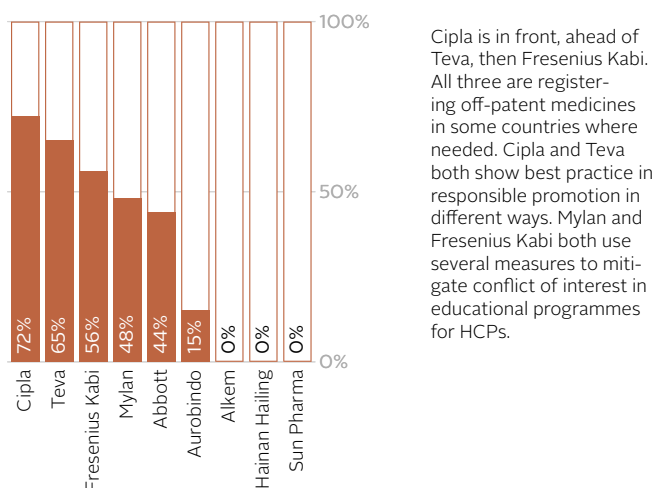
FIGURE 30

Appropriate Access & Stewardship: how the companies perform

Large research-based pharmaceutical companies



Generic medicine manufacturers



WHAT SETS THE TWO GROUPS APART?

Portfolios include vaccines and on-patent products; companies take more diverse steps in access and stewardship

The eight companies in this group have at least 598 relevant products, including the 39 on-patent products evaluated in the registration and pricing analyses. On-patent products are not being registered particularly widely (only nine, mainly vaccines, are filed in more than 20 out of 102 access countries*). These companies account for six of the 10 off-patent medicines evaluated that are being registered in more than 20 access countries. On affordability, large research-based pharmaceutical companies generally report a more diverse range of pricing strategies than generic medicine manufacturers. They are also slightly more likely to be involved in AMR surveillance (6/8 companies), and often publish results in open-access journals. On responsible promotion, three companies from this group either do not promote antimicrobial medicines, or fully decouple its sales incentives from sales volumes (Johnson & Johnson, Otsuka and Shionogi).

Larger portfolios, all off-patent medicines; most companies take some steps, with less variation in the group

The nine companies in this group have at least 855 relevant products. They account for around half of the off-patent products that are being registered in more than five access countries (19 out of 36 products), but a lower proportion of those products being filed in more than 20 access countries (four out of 10 products). Compared to large research-based companies, a smaller proportion of these companies use pricing strategies to address affordability. They use a less diverse range of strategies, often applying for tenders. When it comes to stewardship, four of the nine companies in this group engage in educational programmes for healthcare professionals. On responsible promotion, two companies from this group either do not promote antimicrobial medicines, or fully decouple sales incentives from sales volumes (Cipla and Teva).

* 102 low- and middle-income countries where better access to medicine is most needed. See Appendix VI.

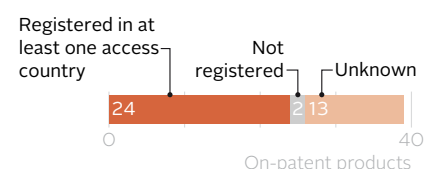
IN SUMMARY

ON-PATENT REGISTRATION

P 70

On-patent products are registered in very few LMICs

Out of 39 on-patent antibacterial and antifungal products assessed, 24 are registered in at least one country where better access is urgently needed (termed access countries); but only 9 in more than 20 access countries.



OFF-PATENT REGISTRATION

P 72

Many off-patent products are unlikely to be widely available

Over 10% of off-patent products are not registered in even one access country. For a further 30%, it is unknown if these products have been registered in any access countries.

PRICING

P 74

Companies address pricing in different ways

Most companies report that they apply a diverse range of pricing strategies to relevant on- and off-patent products, ranging from tiered pricing, tenders to licensing agreements.

CONTINUOUS SUPPLY

P 77

Companies prevent falsified medicines entering supply chain

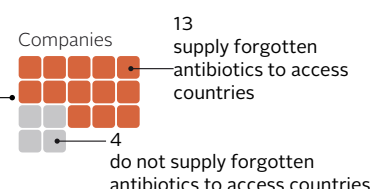
Companies' supply strategies mostly aim to prevent the production or supply of falsified medicines: e.g., auditing warehouses or track-and-trace coding.

FORGOTTEN ANTIBIOTICS

P 79

Older, still useful antibiotics are not widely supplied

While most companies manufacture one or more 'forgotten antibiotics' - older, but still useful antibiotics - less than half are supplied to access countries.

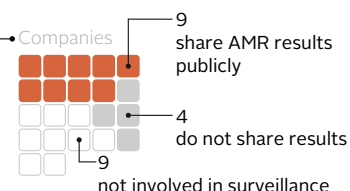


ANTIMICROBIAL SURVEILLANCE

P 82

Companies share AMR surveillance results

Publicly sharing AMR surveillance results is common practice for the majority of companies involved. Yet one company, Pfizer, shares raw data as well as results.



RESPONSIBLE PROMOTIONAL PRACTICES

P 84

Companies aim to prevent overselling

Almost half of the companies in scope take steps to promote their antibacterial and antifungal medicines responsibly, while six companies go further by fully decoupling sales agents' bonuses from volumes or not actively promoting such medicines.



EDUCATIONAL STEWARDSHIP ACTIVITIES

P 86

Most AMR educational programmes avoid conflicts of interest

The majority of companies are involved in AMR-related educational programmes aimed at healthcare professionals. Most companies aim to mitigate conflicts of interest that may arise from providing information about how their products should be used.

STEWARDSHIP-ORIENTED PACKAGING ADAPTATIONS

P 88

Product packaging is improved to ensure correct use

Some companies report adaptations in their brochures and/or packaging to improve likelihood of appropriate use, and so limit AMR. Language is the most common adaptation.

APPROPRIATE ACCESS & STEWARDSHIP

Progress in safeguarding use of products, yet access is still lacking in LMICs

Urgently needed products, are not yet widely accessible, but companies' efforts to track the spread of resistance is progressing.

- Both new and older antibacterial and antifungal medicines are unlikely to be widely available to low- and middle-income countries.
- Leading companies take new steps in monitoring resistance and ensuring responsible promotion practices.

CONTEXT

Antibacterial and antifungal medicines and vaccines are essential tools for treating infectious diseases worldwide. Yet antimicrobial resistance or AMR is increasingly threatening their effectiveness. One of the main drivers for AMR is the excessive use of antibacterial and antifungal medicines. This issue of excess is now firmly at the top of global health agendas, yet another vital component deserving of the same attention is the issue of access.

People living in less developed and resource-limited settings are on the frontlines for AMR. They generally face higher rates of resistance and infectious diseases yet often struggle to access antibacterials and antifungals medicines when they need them. In fact, millions of people currently live without reliable access to these medicines or to good information on how to use them. These two sides are referred to as 'access' and 'stewardship'. Both issues are closely interlinked as the need to enhance access where necessary must be balanced with that of ensuring optimal and appropriate use to prolong their effectiveness.

A 2015 study by the Centers for Disease Dynamics and Control found that global antibiotic consumption had increased by 65% in the past 15 years (from 21.1 billion to 34.8 billion defined daily doses).¹ This was driven by rising consumption in low- and middle-income countries. In India, for example, antibacterial consumption reached 4,950 defined daily doses per 1,000 people in 2015, up from 2,645 in 2000.² Nevertheless, the burden of infectious diseases in India remains extremely high. Lower respiratory infections, diarrhoeal diseases and tuberculosis are among the ten deadliest diseases in India.³ Out of every 100,000 children aged under five in 2016, 258 died due to pneumonia, diarrhoea or another common infectious disease.⁴ Today, it has one of the highest AMR rates in the world with more than 50% resistance against 14 out of 16 bacteria measured in the Benchmark.⁵ Although infectious disease burdens are also linked to safe water, hygiene and sanitation, these numbers indicate a clear unmet need for access to appropriate antibacterial and antifungal medicines and

vaccines, and stewardship policies that delay the emergence of resistance.

To improve access, pharmaceutical companies can implement strategies that relate to fast and broad product registration, affordability to address the needs of different populations and improving supply for the long term. This applies to both products controlled by companies (on-patent) and where generic versions are available (off-patent). Regarding stewardship, the role for pharmaceutical companies spans areas such as the surveillance of rates of infectious disease and resistance, informing healthcare professionals about effective stewardship of their own products, via education programs on resistance and adequate product information. This also includes the use of more effective diagnostics, and the adaptation of ensuring marketing and promotional practices are set up to prevent overuse/misuse of products.

The 2020 AMR Benchmark assesses 17 large manufacturers of antibacterial and antifungal products across these aspects of appropriate access and stewardship. These comprise eight large research-based pharmaceutical companies and nine generic medicine manufacturers. Each company is assessed in those metrics where it has relevant products. In this chapter, the Benchmark first reports its findings in areas relating to access. Its findings on stewardship practices begin on page 72.

Sources

- 1 Klein, E. Y., et al. Global increase and geographic convergence in antibiotic consumption between 2000 and 2015. *Proc. Natl. Acad. Sci. U. S. A.* 115, E3463–E3470 (2018).
- 2 CDDEP. Antibiotic Use Resistance Map. Available at: <https://resistancemap.cddep.org/AntibioticUse.php>.
- 3 Agrawal, G. Health transition in India: does data on causes of death reveal trends, patterns and determinants? *Int. J. Hum. Rights Healthc.* 8, 92–109 (2015).
- 4 Institute for Health Metrics and Evaluation. GBD Compare. Available at: <http://www.healthdata.org/data-visualization/gbd-compare>.
- 5 Committee for Development Policy of ECOSOC Least Developed Country (LDC) list (as of March 2018) <https://www.un.org/development/desa/dpad/least-developed-country-category.html>

ACCESS

Much room for improvement in making key products available to countries in need

The 2020 AMR Benchmark measures how pharmaceutical companies address access to antibacterial and antifungal medicines and vaccines in countries where better access is most needed. The Benchmark has identified 102 such countries, which it refers to as 'access countries'. These are low- and middle-income countries where bacterial and fungal infectious diseases are endemic, and where populations are more likely to lack access to antibacterial and antifungal medicines. The Benchmark analyses on-patent and off-patent/generic products separately, recognising that companies must apply different registration and pricing strategies to these two categories of product. The registration and pricing analyses in this chapter cover 156 products in total from 17 companies.

ON-PATENT REGISTRATION

Registration is the first step in making products available

Registering a product with a country's regulatory authority is a key step to making a medicine or vaccine available there for the people that need it. Once approved, the product can then be offered for sale. For new medicines and vaccines, pharmaceutical companies should file for registration in low- and middle-income countries as rapidly as possible after first market launch in order to make them widely available.

In this section, the Benchmark assesses the registration filings of antibacterial and antifungal medicines and vaccines from the pharmaceutical companies in scope. It looks first at registration filings for on-patent products, followed by filings for off-patent/generic products.

Registration of on-patent products

Of the companies in scope, six large research-based pharmaceutical companies have products eligible for this analysis: i.e., on-patent antibacterial and antifungal medicines and vaccines. These companies have 39 such products in total: 13 antibacterial medicines, 19 antibacterial vaccines and seven antifungal medicines (figure 33).

WHICH COUNTRIES URGENTLY NEED ACCESS TO PRODUCTS?

The 2020 Benchmark measures how companies address access to antibacterial and antifungal medicines and vaccines in countries where better access is most needed. 102 such countries were identified based on countries' level of income; the scale of inequality in each country; and their bacterial and fungal disease burden.¹⁻⁴ These countries are referred to as 'access countries.'

FIGURE 31

102 low- and middle-income countries need better access to medicine.

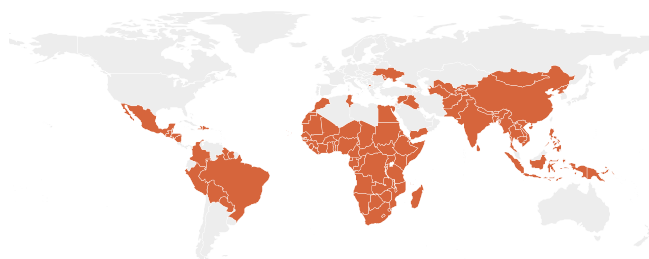
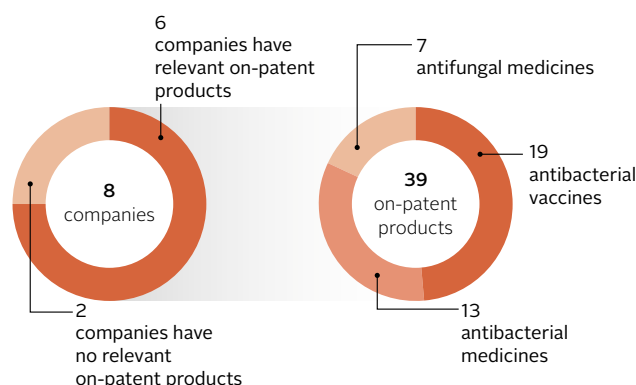


FIGURE 32

Companies have 39 on-patent* products on the market

The figure shows how many on-patent products are in the portfolios of the companies in scope. In total, there are 39 on-patent* antibacterial and antifungal products, with vaccines making up 50% of these products.

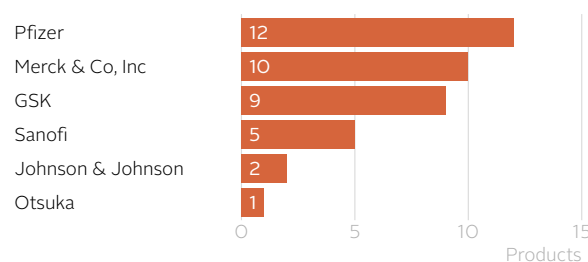


* All on-patent antibacterial and antifungal medicines and vaccines marketed by the companies in scope.

FIGURE 33

Companies have from 1 to 12 on-patent antibacterials and antifungals each

This chart shows the six large research-based pharmaceutical companies that have relevant on-patent products.*



* Novartis and Shionogi do not have on-patent antibacterial or antifungal medicines or vaccines.

How widely are on-patent products being registered?

The on-patent products in this analysis are generally not registered in many of the 102 access countries. Only three on-patent antibacterial medicines have been filed for registration in ten or more access countries. For four on-patent antibacterials, the Benchmark found no reports of registration filings in any of the target countries.

Of all 39 on-patent products, 24 (62%) are reported to have been filed for registration in at least one access country; only nine of these have filings in more than 20 access countries (figure 34).

Two on-patent products have not yet been filed for registration in any access country (where Pfizer has licensing rights): the antifungals tavaborole (Kerydin®), approved by the US FDA in 2014, and isavuconazonium sulfate (Cresemba®), authorised in 2015, both produced by Pfizer.

Which companies have completed the most registration filings for on-patent products?

In this analysis, GSK has completed the most filings for registration in access countries for on-patent products (in total 149 filings) and has filed its products in an average of 16.6 countries per product. Pfizer has filed one of its on-patent products, the vaccine Prevnar 13®, in more access countries (62 countries) than any other product in this analysis. Sanofi has the most widely filed products on average: with filings in an average of 20.4 access countries per product.

On-patent products are more likely to be filed in wealthier countries

This analysis indicates that on-patent antibacterial and antifungal medicines and vaccines are more likely to be filed in wealthier access countries (the 102 access countries include 47 lower middle-income countries (LMICs) and 22 upper middle-income countries (UMICs) and 33 low-income countries (LICs). The three access countries with the most registration filings in this analysis are Brazil (a UMIC, with 16 filings), the Philippines (an LMIC, with 16 filings) and Thailand (a UMIC, with 15 filings) (figure 35). Looking only at medicines (20 out of 39 on-patent products), Brazil and India have the most registration filings in this analysis: 6 products filed in each country.

Across sub-Saharan African countries (which account for 45% of access countries), an average of only 3.3 of the 39 products (8%) in this analysis have been filed per country.

Twenty-one access countries – home to 130 million people⁵ – have had none of the 39 products in this analysis filed for registration. Looking only at medicines, 59 access countries have none of the 20 medicines in this analysis filed for registration. This leaves many health systems unable to take even the first steps (such as purchasing products for import) to ensure access.

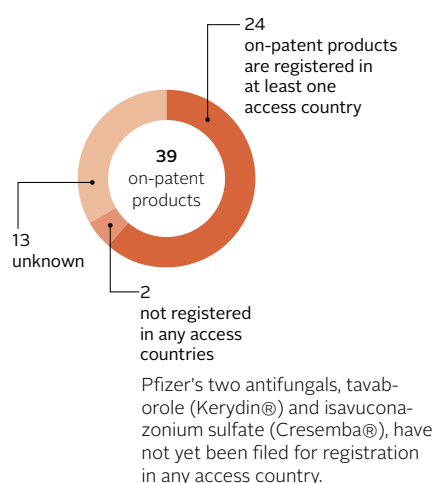
Least registration filings in LICs

Low-income countries (LICs) have had the least registration filings of all the access countries. Out of 33 LICs and 20 medicines in this analysis, 25 LICs (76%) have none of the

FIGURE 34

Only 60% of on-patent products are being registered in any of the countries where access is most needed

This chart shows the proportion of on-patent* antibacterial and antifungal medicines and vaccines that have been filed for registration in at least one access country.

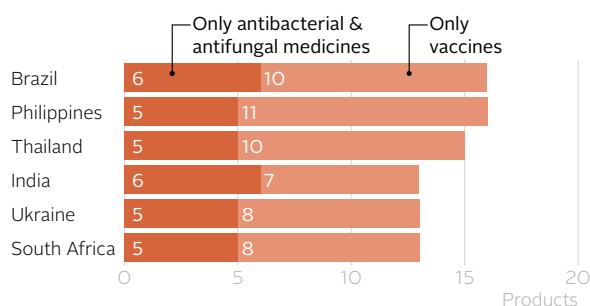


* All on-patent antibacterial and antifungal medicines and vaccines that the company markets.

FIGURE 35

Registrations of on-patent products focus on large middle-income countries

The chart shows the top six access countries (out of 102) that have the most on-patent* antibacterial medicines and vaccines filed for registration. Four countries are upper middle-income and two are lower-middle countries.



* All on-patent antibacterial and antifungal medicines and vaccines that the company markets.

medicines filed for registration. This compares to 49% of LMICs and 45% of UMICs without filings for products in this analysis.

Vaccines are more widely registered than medicines

Vaccines are the product type most widely filed for registration in this analysis. Of the 10 on-patent products most frequently filed in access countries, eight are vaccines (produced by GSK, Pfizer and Sanofi). These are filed in 18 access countries on average, compared to an average of just 7.2 access countries for antibacterial medicines.

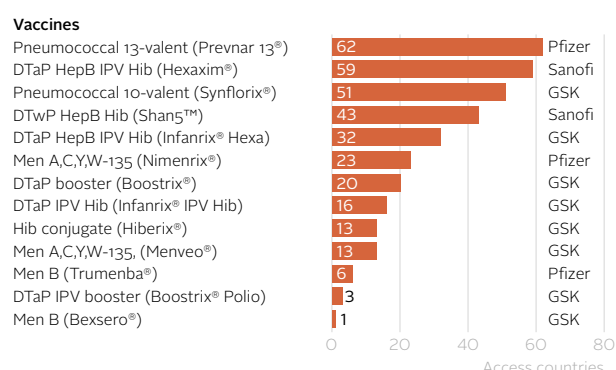
This reflects the high and widespread international demand for vaccines, together with a market that is likely more profitable, as well as the support from pooled-procurement agencies, such as Gavi, the Vaccine Alliance, a public-private global health partnership.⁶

Vaccines can be made widely available through international interventions where companies, governments and multilateral agencies come together. For example, pooled-procurement mechanisms often assure quality through the WHO prequalification process and enable countries to purchase vaccines efficiently and at lower prices. The United Nations' International Children's Emergency Fund (UNICEF) and the Pan American Health Organization (PAHO) also serve as procurement agencies.^{7,8} Fifty-eight access countries are currently eligible for support from Gavi,⁹ which supports these countries via a co-financing policy. Countries qualify for Gavi support based on average gross national income (GNI) per capita and other criteria relevant to the vaccine requested.

FIGURE 36

Pneumococcal vaccines top registration lists

This chart shows the vaccines in scope* that have reportedly been filed for registration in access countries. Pfizer's pneumococcal vaccine has been filed in twice as many access countries as the most widely filed medicine.



* All on-patent antibacterial vaccines that the company markets.

DTaP=Diphtheria, Tetanus, acellular Pertussis
 DTwP=Diphtheria, Tetanus, whole-cell-pertussis
 HepB=Hepatitis B
 IPV=inactivated Poliovirus
 Hib=*Haemophilus influenzae* type b
 Men A,C,Y,W-135=Meningococcal serogroups A, C, Y, W-135
 Men B=Meningococcal serogroup B

Which on-patent medicines are most widely filed?

Merck & Co, Inc has the most widely filed antibacterial medicine: ceftolozane/tazobactam (Zerbaxa®), for complicated urinary tract and intra-abdominal infections. This medicine has been filed for registration in at least 30 access countries.

The second most widely filed antibacterial medicine is Johnson & Johnson's bedaquiline (Sirturo®), which is used to treat multidrug-resistant tuberculosis (MDR-TB) and is on the WHO Model Lists of Essential Medicines. Since 2012, when it was awarded fast-track accelerated approval by the FDA, bedaquiline has been filed for registration in 28 access countries: seven LICs, 14 LMICs and seven UMICs.

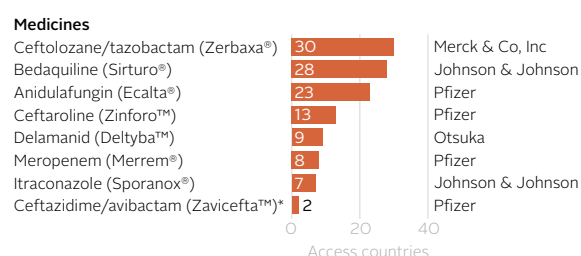
Pfizer's anidulafungin (Ecalta®), for treatment of invasive candidiasis, is the most widely filed antifungal medication: in 23 access countries, comprising one LIC (Nepal), 14 LMICs, and eight UMICs.

This is followed by Johnson & Johnson's antifungal oral liquid itraconazole (Sporanox®), filed for registration in seven access countries: two LMICs and five UMICs.

FIGURE 37

Medicine for complicated urinary tract infection is filed most widely

This chart shows the most widely filed on-patent* antibacterial and antifungal medicines in access countries. Merck & Co, Inc's antibacterial medicine for complicated urinary tract infections has been filed in the highest number of access countries.



* All on-patent antibacterial and antifungal medicines and vaccines that the company markets.

OFF-PATENT/GENERIC REGISTRATION

Registration of off-patent/generic products

The WHO Model Lists of Essential Medicines (EML), identifies medicines considered essential for all modern healthcare systems.¹⁰ The EML lists antibacterial medicines in three groups: Access, Watch and Reserve. Medicines in the Access category are generally first and second-line antibacterials for common infections, which should be widely accessible. Watch group antibacterials are those at risk of increased resistance, and are only to be used for certain diseases as a first or second-line treatment. Reserve group antibacterials need to be conserved most carefully, and are only to be given as a last resort where other treatments fail.

The Benchmark uses the EML groupings as it examines registration filings for off-patent/generic products. It looks at registration filings for: (1) companies' top off-patent/generic antibacterial medicines by global sales volume, as well as (2) companies' top two antifungal and anti-tuberculosis medicines with highest volumes of sales. The analysis includes products from both the large research-based pharmaceutical companies and generic medicine manufacturers in the scope of the Benchmark.

Reserve group antibacterials are registered much less widely than other types

Seventeen off-patent/generic antibacterial medicines, most in the Access and/or Watch categories, are registered in more than five access countries. Antibacterials in the Reserve category are registered much less widely (figure 39); only two are registered in more than ten access countries (tigecycline, produced by Pfizer; and cefepime, produced by Pfizer, Aurobindo and Fresenius Kabi).

Many off-patent antibacterials are unlikely to be widely available

For over 40% of off-patent/generic products, there is no evidence of having been registered in any access country. The barriers to registering products are considerably challenging, and include regulatory and infrastructure issues, such as systems that lack significant capacity, poor healthcare infrastructure, and local regulatory requirements for clinical trials, and/or originator product dossiers, as well as supply constraints, low-volume markets, ability to pay/financing, the availability of equivalents, political instability, conflict and/or economic sanctions.^{11,12}

It is concerning that in many countries where people urgently need better access to medicine, many on-patent products and off-patent/generic antibacterial and antifungal medicines have not been registered. If appropriate treatment is not available, doctors and patients often resort to less optimal treatments.

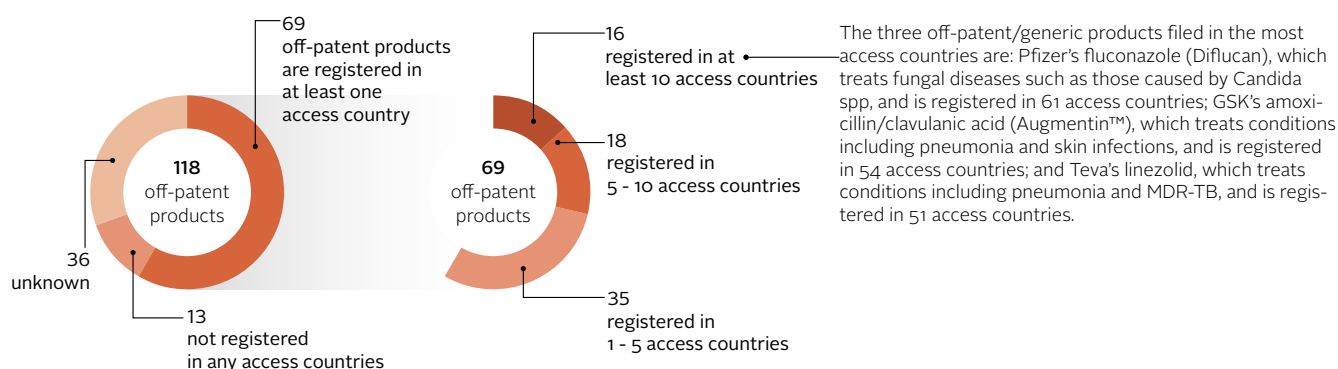
WHAT OFF-PATENT/GENERIC PRODUCTS ARE ANALYSED TO EVALUATE ACCESS ACTIVITIES?

The Benchmark evaluates each company's top three antibacterial medicines with highest volume sales medicines in the Access, Watch, and Reserve categories of the 2017 WHO Model Lists of Essential Medicines (EML).¹⁰ It also evaluates each company's top three antifungal and anti-tuberculosis medicines, per highest volume sales, also from the WHO EML. All eight of the large research-based pharmaceutical companies, and all nine of the generic medicine manufacturers, have such products.

FIGURE 38

How widely are off-patent/generic medicines being registered where needed?

This chart shows the proportion of off-patent* antibacterial and antifungal medicines that have been filed for registration in access countries.



* Top-selling off-patent antibacterial and/or antifungal medicines and vaccines, max. 10 per company.

PRICING

Companies address pricing in different ways

In low- and middle-income countries, up to 75% of health spending is paid by people from their own pockets. In Cambodia, for example, where more than 16 million people live, 64.4% of health spending is out of pocket. In Sudan, home to more than 40 million, this reaches 74.5%.¹³ Globally, medicine is the largest household expenditure after food.¹⁴ People living in low- and middle-income countries face higher rates of infectious diseases yet struggle to access appropriate treatments when they need them.¹⁵

New antimicrobials are still unaffordable to many, while older products are generally priced sufficiently low as to be available to many people (although still not to everyone).

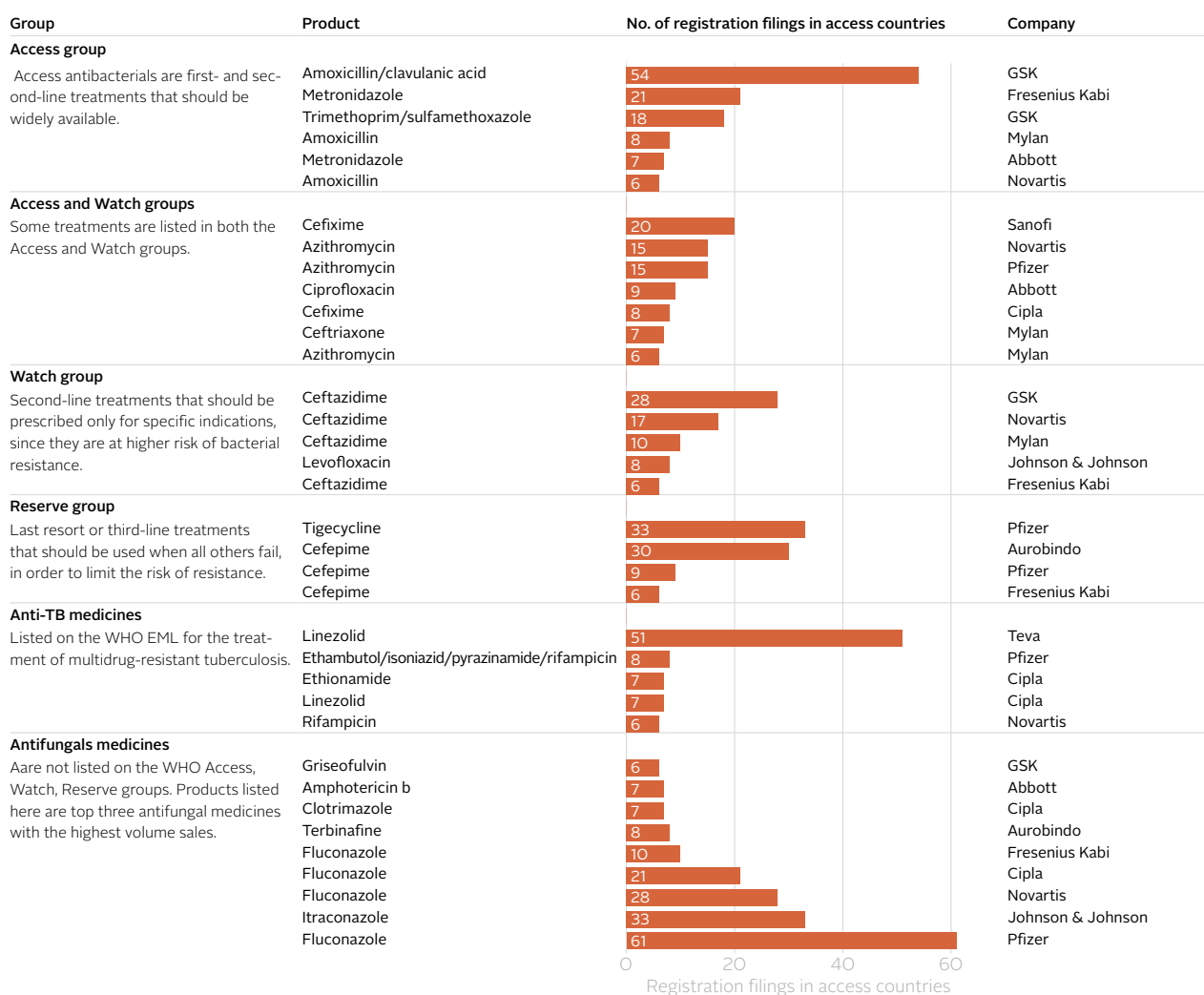
However, the low prices mean that keeping production lines going has become economically unattractive.

There are multiple factors that determine the prices set by pharmaceutical companies for their products. These include supply factors, such as product development costs, the cost of purchasing and sourcing active pharmaceutical ingredients (APIs), patent status and the level of competition. These also include demand factors, including ability to pay and disease burden, and regulatory systems where governments have greater control over prices.¹⁶ This year, as part of the Sustainable Development Goals, UN Member States have committed to achieving universal health coverage (UHC) by 2030.¹⁷ To achieve UHC, and fewer out-of-pocket payments, pharmaceutical companies will need to play an important role

FIGURE 39

Which off-patent/generic antibacterial and antifungals are filed in more than five access countries?

This chart shows the off-patent/generic products* that have been filed for registration in more than five access countries. These products are divided into the Access, Reserve and Watch groups, as well as into anti-tuberculosis and antifungal medicines. The anti-TB medicine linezolid is also listed in the Reserve group.



by setting affordable prices for medicines that consider the ability of people to pay, whether either at an individual level or through a reimbursement authority.

In this section, the 2020 AMR Benchmark reports on the pricing strategies that pharmaceutical companies are applying to their antibacterial and antifungal medicines and vaccines. In particular, it looks for evidence of pricing strategies that take account of payers' ability to pay (here termed 'equitable pricing') in low- and middle-income countries. Companies' pricing strategies can take into account a payer's ability to pay by considering socioeconomic factors, such as gross national income (GNI) and Human Development Index (HDI).

The Benchmark examines 16 companies in this area: seven* large research-based pharmaceutical companies and nine generic medicine manufacturers. Of these, 13 companies report that they apply a diverse range of pricing strategies to relevant on-patent and off-patent products (figure 40). The remaining three companies (Alkem, Hainan Hailing and Sun Pharma) do not provide information about pricing strategies.

Pricing strategies based on socioeconomic factors: Eight companies (seven large research-based pharmaceutical companies and one generic medicine manufacturer (Mylan)) report that their strategies take account of socioeconomic factors, most frequently GNI per capita and HDI.

Tiered pricing as a means of addressing different populations' needs: Six companies report that they use tiered pricing, which can mean countries with greater financial constraints pay less. This mechanism is no guarantee, however, of affordability as inter-country tiered pricing does not address the large income differentials within countries. Tiered pricing

is being used by two large research-based pharmaceutical companies in scope: Johnson & Johnson and Otsuka, both for multidrug-resistant tuberculosis. Johnson & Johnson's lowest tier for bedaquiline (Sirturo®) is available at USD 400 for a six-month course of treatment. Otsuka uses tiered pricing for delamanid (Deltysba™), and prices the lowest tier at USD 1,700 for a six-month course. These 'lowest-tier' prices may achieve some coverage of poorer populations, but this coverage is not complete. The degree of coverage the lowest tier achieves is a function of the ability of public or private payers to both prioritise and pay for the product. By applying pricing strategies that carefully consider payer constraints, companies can work to expand coverage further.

Procurement partnerships that pool demand: Eight companies report having procurement partnerships with organisations that pool the demand and costs of essential products globally. Companies such as GSK, Merck & Co, Inc, Pfizer and Sanofi partner with Gavi, the Vaccines Alliance, for example, to make their vaccines available to the world's poorest countries. Johnson & Johnson and Otsuka have global supply agreements with the Global Drug Facility for their MDR-TB products bedaquiline (Sirturo®) and delamanid (Deltysba™), respectively.

Out-licensing for availability at scale: Two large research-based pharmaceutical companies (GSK and Otsuka) report entering into licensing agreements for some products in scope, which enables other manufacturers to make generic versions of their products available in specific territories. However, in the absence of competition, or of price controls in the licensing agreement, there is no reason to assume that these licences result in lower prices. Expanding the number

FIGURE 40

Most companies apply a diverse range of pricing strategies

This chart shows the proportion of companies that apply pricing strategies to relevant on-patent and off-patent products.

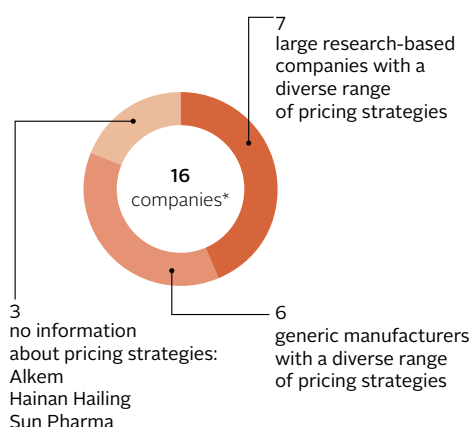
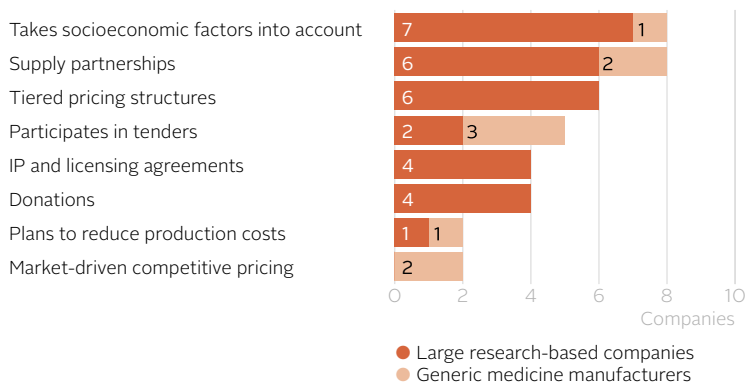


FIGURE 41

Which pricing strategies are reported most frequently?

This chart depicts pricing strategies reported by large research-based companies and generic medicine manufacturers, showing how many companies report these strategies. Four companies do not report any information about pricing strategies.



* One large research-based company, Shionogi, was not included in this assessment, as it only sells its products in Japan and Taiwan, and therefore could not report the pricing strategies it applies in access countries.

of licences to more manufacturers, and ensuring they are not exclusive within a given territory, will increase access and affordability.¹⁸ Three companies do not file on-patent products in LDCs.

Lowering production cost as a means of offering lower prices:

Two companies (Cipla and Novartis) report working to reduce production costs in order to lower prices. Pursuing lower production costs may increase efficiency and profitability for a company. Nevertheless, as these companies do not report how this will translate into lower prices, it is not yet clear whether patients will benefit.

Donations for poorest population segments: Four companies (GSK, Pfizer, Johnson & Johnson and Teva) report making

donations of antibacterial and antifungal medicines and vaccines. Donations of medicines and other products can be an important tool for improving access to medicine in certain circumstances: for the control, elimination or eradication of diseases impacting the poorest populations in the world; or for supporting governments with severely constrained budgets. While they offer clear short-term advantages — particularly for poorer populations, and in the case of bedaquiline fast access to new antibacterials — the benefits of donation and discount strategies are generally not sustainable.¹⁹ They can, however, bridge the gap until a sustainable route of equitable pricing or licensing is established. Pharmaceutical companies can integrate donation programmes within their overall pricing strategies, and/or work with governments on transition plans for when a donation programme reaches its end.

CASE STUDY: HOW FIVE COMPANIES ARE ADDRESSING ACCESS TO TUBERCULOSIS TREATMENTS

- Tuberculosis (TB) is a bacterial infection that affects the lungs and kills more than a million people each year.²⁰ The two most effective treatments for TB are the antibacterials isoniazid and rifampicin. When the disease does not respond to these treatments, it becomes known as multidrug-resistant tuberculosis (MDR-TB), and requires treatment with new drugs, such as bedaquiline and delamanid.
- Johnson & Johnson addresses access to bedaquiline (Sirturo®), for MDR-TB, via multiple routes: traditional pricing and reimbursement by national authorities; via the Global Drug Facility; institutional purchasing by international NGOs; and through a donation programme managed by USAID. The lowest reported price offered is USD 400 for a six-month course. It also reports transferring the manufacturing of its APIs and drug products to manufacturing sites in India, where MDR-TB is endemic, and burden of the disease is high. This may result in reduced manufacturing costs and improved supply of the product for India.
- Otsuka addresses access to delamanid (Deltyba™), for MDR-TB, through two routes. The first is via the Global Drug Facility for the lowest global price of USD 1,700 per six-month course. Otsuka is also in the process of a technology transfer to Mylan to make delamanid more widely available globally.
- Mylan, in collaboration with the TB Alliance, is about to launch its new antibacterial pretomanid, only the third anti-TB medicine to be approved by the FDA in more than 40 years. The aim is to treat pulmonary tuberculosis in India, although pricing is as yet unknown.
- Teva, a major supplier of linezolid, reports having won a tender to supply linezolid to the Stop TB/IDA Foundation and makes linezolid available in 51 access countries.
- Cipla has registered its products linezolid and ethionamide in seven access countries each.

TABLE 9

14 companies produce TB medicines

The table shows which TB medicines companies are producing and how widely they report registering their different versions. Teva's linezolid stands out for 51 registration filings in access countries. None of the companies that produce isoniazid report registering it in access countries.

| Company* | Product name | No. of access countries where product is being registered |
|-------------------|--|---|
| Johnson & Johnson | Bedaquiline | 28 |
| GSK | Dapsone | 1 |
| Otsuka | Delamanid | 9 |
| Mylan | Delamanid | 4 |
| Pfizer | Ethambutol/isoniazid/pyrazinamide/rifampicin | 8 |
| Cipla | Ethionamide | 7 |
| Teva | Isoniazid | 0 |
| Sanofi | Isoniazid | No data |
| Sun Pharma | Isoniazid | No data |
| Teva | Linezolid | 51 |
| Cipla | Linezolid | 7 |
| Pfizer | Linezolid | 0 |
| Mylan | Linezolid | 0 |
| Alkem | Linezolid | No data |
| Aurobindo | Linezolid | No data |
| Novartis | Rifampicin | 6 |
| Mylan | Rifampicin | 0 |
| Sanofi | Rifampicin | No data |

* Two further companies also produce TB medicines, registered in only a few access countries, more information is provided under confidentiality.

TABLE 10

Which pricing strategies do companies report using for antimicrobials?

This table gives an overview of pricing strategies that companies report applying to relevant products, as well as a definition of each strategy and examples of how companies are applying them. In some cases, demand from buyers or governments determine which strategy is used.

| What | How | Example of company practice |
|--|---|---|
| PRICING STRATEGIES DETERMINED BY PHARMACEUTICAL COMPANIES | | |
| Has supply partnerships with NGOs and health organisations | Companies partner with organisations that facilitate and pool product demand/costs globally, enabling the former to continue to manufacture relevant products. These partnerships can lead to lower prices while maintaining incentives for companies to continue to make needed products. | Johnson & Johnson works with the Global Drug Facility and USAID to make bedaquiline (Sirturo®) available in more than 130 low- and middle-income countries. Since its 2016 agreement with Global Drug Facility, Otsuka has supplied delamanid (Delyba™) to 89 countries, including 30 with a high burden of multidrug-resistant TB (MDR-TB). |
| Takes socioeconomic factors into account | Companies take account of factors such as gross national income (GNI) and Human Development Index (HDI) ranking when determining prices. While companies apply price differentials, this does not guarantee that the lowest prices will be affordable. | Johnson & Johnson's equitable tiered pricing strategy uses socioeconomic factors such as a country's economic conditions, patients' ability to pay and disease burden to set the price of bedaquiline (Sirturo®) for the treatment of multidrug-resistant TB. Its lowest tier is set at USD 400 for a six-month course of the antibacterial medicine. |
| Tiered pricing structures²¹ | Companies sell products to different buyers at different prices, charging less in LMICs than in higher-income countries. In general, tiered pricing is a strategy used by companies selling on-patent products, with relative monopolies over those products. | GSK uses tiered pricing strategies for its vaccines Synflorix® and Infanrix®-hexabased on the Human Development Index (HDI) ranking. It sets a ceiling price for vaccines in LDCs. |
| IP and licensing agreements | Companies allow other manufacturers to make generic versions of patented products, which can support affordability but only where the agreements facilitate competition, or where licences make explicit stipulation on price-setting. | GSK, Novartis and Merck & Co, Inc do not file patents in Least Developed Countries (LDCs). GSK has voluntary licensing for some of its vaccines, and Otsuka has a voluntary licence agreement with Mylan to enable generic manufacturing of delamanid for the treatment of TB. |
| Plans to reduce production costs | To increase profit for companies and enable cheaper prices for consumers, companies search for ways to decrease their production costs. | Cipla selects vendors based on quality and the lowest cost APIs, improves batch yields in manufacturing and pursues overhead cost reductions. |
| Donations/discounts | Governments sometimes require companies to make donations and give discounts, and companies may offer discounts in negotiation with buyers. Donations can be beneficial in the short term (for example where there are shortages, and for the poorest populations), but are not sustainable. | Teva provides its products, for example, under US donations programme via NGO partnerships with Americares, Brother's Brother Foundation, Direct Relief International, Operation Blessings and Universal Heart. |
| PRICING STRATEGIES MORE DETERMINED BY BUYERS AND REGULATORY SYSTEMS | | |
| Participates in tenders²² | Method used by governments or other agencies to procure large amounts of medicines or vaccines from particular companies. Bidding by all interested suppliers is facilitated, helping to produce lower prices. However, tenders do not always promote affordability, particularly when negotiating conditions are limited. | GSK has intra-country tenders for sub-populations of specific countries. |
| Market-driven competitive pricing¹⁴ | Generic medicine manufacturers usually engage in competitive pricing to maintain their business models. This allows them to make sufficient income to cover production costs and continue operating while charging the lowest standard prices for products. Increased returns to companies raise competition, thereby lowering prices. Decreased returns to companies cause companies to drop out, raising product prices back to 'the lowest standard'. Patented medicines are also subject to market-driven competitive pricing in therapeutic areas where there are effective substitutes. | Aurobindo and Mylan report market-driven competitive pricing — a very common pricing approach. |

Tenders for off-patent/generic products: Five companies (GSK, Fresenius Kabi, Aurobindo, Novartis and Mylan) report that they participate in tenders for their off-patent/generic products in scope. Tenders can help governments and other procurers achieve significant price discounts. However, tendering does not always promote affordability, particularly when negotiating conditions are limited.

Needs-based pricing needs momentum

For on-patent products, the Benchmark considers good practice for setting prices to be: (1) taking account of socioeconomic factors, with the goal of increasing affordability; (2) entering into supply contracts with health organisations to pool product demand globally; and (3) allowing other companies to manufacture generic versions of patented products through non-exclusive licensing agreements.

For large research-based pharmaceutical companies that sell off-patent/generic products, participating in tenders and competitive marketing may yield the lowest prices for patients. However, where there are few competitors, companies should take payers' ability to pay into consideration when setting prices.

Generic medicine manufacturers that already tend to operate in competitive environments with slim margins, should also take into account the payer's ability to pay, when there are few competitors.

Pharmaceutical companies may need to deploy multiple, integrated pricing strategies per product and market to ensure that prices are sufficiently low to achieve affordability while ensuring sufficient margins to continue investing in the manufacture and supply of these medicines.

CONTINUOUS SUPPLY

Companies focus on stopping falsified medicines entering supply chain, followed by preventing shortages.

Antibacterial supply chains are complex and highly fragmented, at some stages consisting of many players, while at vital stages consisting of fewer players.²³ Batches of medicines and vaccines are passed through multiple distributors before reaching the patient, at times with little alignment to ensure that supply matches demand. These inefficiencies can lead to stockouts, while the fragmentation of the supply chain is a factor driving shortages and poor-quality medicines reaching pharmacy shelves.

To reduce the threat of AMR, doctors must ensure that sufficient amounts of the right treatment is always used against the right type of infection. There is little information available about the exact consequences of antibacterial shortages on patients' outcomes, but the mortality rates due to treatable infectious diseases give some indication. According to a 2015 Europe-based survey, half of the hospital pharmacists respondents reported that patients were given inferior drugs during shortages, while more than a third said stockouts led to medication errors.²⁴ National agencies have also reported that some patients experienced negative outcomes because

of a less effective or more toxic alternative.

To create an uninterrupted supply of quality products, companies can employ various strategies. The Benchmark evaluates 17 companies in this area: eight large research-based pharmaceutical companies and nine generic medicine manufacturers. It reports on their participation in seven areas of activity that can contribute toward a continuous supply of such products (table 11). Of the 17 companies in scope, more than half report undertaking at least four of these activities, with more companies active in the prevention of falsified medicines than other areas, followed by shortage mitigation and demand forecasting. Five companies (Alkem, Aurobindo, Hainan Hailing, Shionogi and Sun Pharma) report limited or no data about activities in the seven areas.

Preventing falsified medicines: 12 companies report various strategies to prevent falsified medicines entering the supply chain: e.g., auditing warehouses, track-and-trace coding, using tamper-proof seals on products, increasing public awareness, conducting undercover online test purchases, and deploying laboratories to test for falsified medicines.

Shortage mitigation: 11 companies report strategies to mitigate shortages: e.g., maintaining buffer stocks of finished products and critical ingredients; reporting stockouts to the US Food and Drug Administration (FDA) Office of Drug Shortage; increasing production in response to stockouts or prioritising essential medicines.

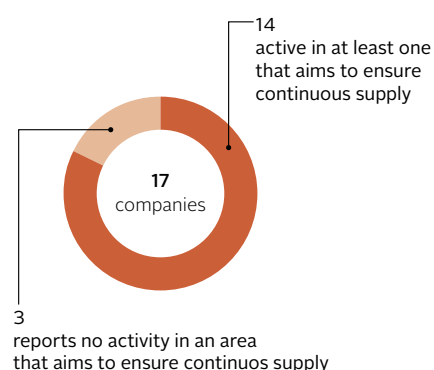
Demand forecasting: Ten companies report forecasting processes for demand planning. Several forecast between 12 and 36 months ahead. Cipla and Pfizer report additional long-term planning (five years ahead), as does GSK (10 years ahead).

GSK, followed by Novartis, undertakes more of the activities analysed than other companies in scope. Specifically, it uses three-year forecasts and long-term projections for demand

FIGURE 42

Most companies report some activity in areas that aim to ensure continuous supply

This figure shows the number of companies that are active in at least one area that aims to ensure continuous supply of their antibacterial and antifungal products.



forecasting, with a focus on those countries expected to demand the highest volumes. GSK also uses dual sourcing for active pharmaceutical ingredients (APIs) for its critical products — in order to prevent over-dependence on a single manufacturer — and it maintains and monitors safety stocks. In its mVaccination programme to improve immunisation coverage, GSK works with the Tanzania and Nigeria Ministries of Health, among other partners. It is a member of the International Federation of Pharmaceutical Manufacturers and Associations' (IFPMA) 'Fight the Fakes' campaign which aims to prevent falsified medicine reaching the supply chain. GSK also uses security features, tamper evident packaging, track-and-trace coding, auditing of warehouses and reviews areas of potential fraudulent activity.

Among generic companies, Mylan leads in activities to ensure continuous supply. Its Rapid Response Advanced

Planning system looks 24 months ahead for demand planning, and it holds regular meetings with external stakeholders to discuss forecasting. To help ensure a secure supply of APIs, it has a global supply network of more than 40 sites. It also uses dual sourcing and maintains safety and strategic stocks. To prevent falsified medicines reaching the supply chain, Mylan employs strategies such as track-and-trace serialisation for products, and ensures its contract manufacturers include its 2D data matrix on products.

FORGOTTEN ANTIBIOTICS

Older, still clinically useful antibacterials are not yet completely unavailable in LMICs – but supply is endangered

'Forgotten antibiotics' are older but still clinically effective off-patent antibacterials that are not always marketed or

TABLE 11 **How can companies help ensure the continuous supply of their antibacterial and antifungal products?**

This table lists the priority activities for companies to help ensure the uninterrupted supply of their products, along with examples of company activity in each area.

| What | Number of companies who report activity in this area | | Example of company activity |
|---------------------------------|--|---|--|
| | How | | |
| Forecasting | 10 | To maintain a continuous supply of products, companies make use of short- and long-term forecasting mechanisms to ensure there are sufficient APIs and finished products to meet future demand of products. | GSK reports three-year forecasts that feed into monthly supply/demand reviews, where escalations and decisions can be managed. It also has a ten-year (long-term) forecasting process, and focuses on countries it expects will demand the highest volumes. |
| Sharing data | 9 | Companies exchange information with external stakeholders (such as government ministries of health) to align supply with demand. | Johnson & Johnson reports that its supply-chain team visits priority countries and researches product distribution and challenges for demand. Its team set up week-long visits to sub-Saharan countries to follow products from point of entry to point of access by patients and visited ministries of health, distribution centres and hospitals. |
| Procuring | 9 | Companies set up contracts with multiple suppliers to help reduce over-reliance on a few manufacturers and have mechanisms in place that evaluate ingredient quality. | Abbott and GSK report promoting local procurement to help improve regional supply chains. |
| Mitigating shortage | 11 | To mitigate shortages and prevent stock-outs, companies have communication processes in aim to ensure uninterrupted supply. When issues arise, companies responses and processes should be agile and quick. | GSK reports that to cope with variability in supply and demand, it maintains safety stocks (finished products and APIs) and monitors these monthly. For example, when it grows low on stocks of ceftazidime (Fortum®), an antibacterial medicine that treats conditions including pneumonia and skin infections, GSK prioritises supply to emerging markets. |
| Building capacity | 6 | To strengthen supply chains, companies increase the capacity of local staff or other stakeholders through training, for example, or by obtaining equipment and/or other resources | GSK works with ministries of health in Tanzania and Nigeria for its mVaccination programme; and works with Katholieke Universiteit Leuven (KUL) to establish an academic research group to provide technical assistance to LICs and LMICs in Africa. |
| Preventing falsified medicines | 12 | Companies prevent or mitigate the production or supply of medicines that appear to be authentic, but are of low quality or contain replacement and/or non-working ingredients. | Novartis has several mobile laboratories which use authentication spectrometric toolkits to identify falsified medicines rapidly. |
| Supplying forgotten antibiotics | 12 | Companies supply older off-patent antibacterial medicines that (for reasons of economics and demand) are not produced frequently, but still considered effective. | Mylan reports supplying access countries with six antibacterials: chloramphenicol, flucloxacillin, nitrofurantoin, sulfamethoxazole/trimethoprim, teicoplanin and tobramycin. |

produced, due to economic reasons, lack of awareness of their importance or a lack of demand.²⁵ With antimicrobial resistance on the rise, such medicines can still have a role to play in public health – medicines such as colistin, clofazime and amoxicillin-clavulanate, which were first produced in the 1950s and remain effective against a number of conditions, including pneumonia (colistin, as a last resort), tuberculosis (clofazime) and multidrug-resistant tuberculosis.²⁶

In this section, the Benchmark compares 118 off-patent products* against a list of 30 forgotten antibiotics identified by Pulcini et al in 2017, which are unavailable in any quantity in several select countries.²⁵ The Benchmark examines whether low- and middle-income countries are also missing out on these 'forgotten' products, using data on registration filings and whether they are being supplied to access countries by the companies that can still produce them.

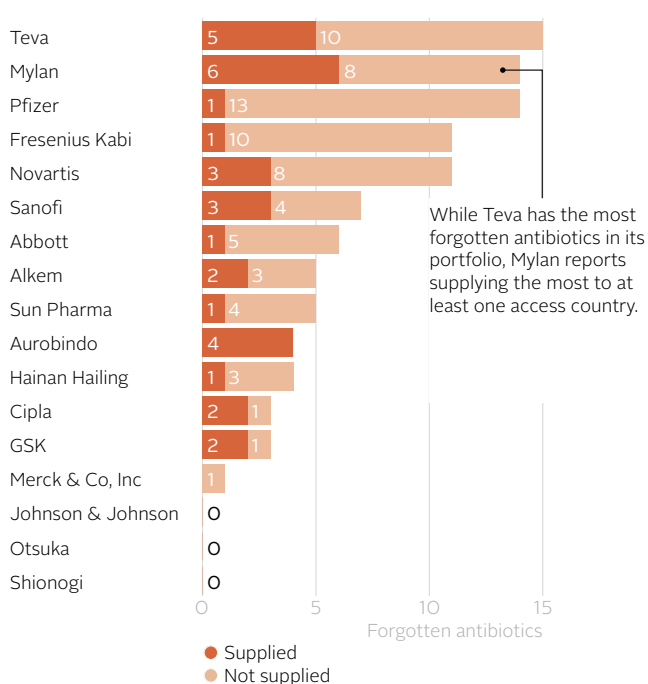
Out of 17 companies in scope, 14 manufacture one or more forgotten antibiotics (figure 43). Together, they are manufacturing at least 24 of the 30 forgotten antibiotics in the list (most are manufactured by multiple companies).

Teva and Mylan produce more of the forgotten antibiotics than other companies, and report supplying more to access countries. Nevertheless, they supply less than half of the forgotten antibiotics they could be supplying to access countries

FIGURE 43

Only 30% of forgotten antibiotics are supplied to access countries

This chart shows the number of forgotten antibiotics that each of the companies in scope have in their portfolios, as well as how many they supply to at least one access country.



Data for this figure is based on two sources: (a) reports by companies in scope and (b) highest volume sales data in at least one access country (provided by IQVIA).

(5/15, 6/14, respectively). Aurobindo reports that it supplies all four of the forgotten antibiotics in its portfolio to access countries.

Cefepime is the forgotten antibiotic that can be produced by the most companies (figure 44). It is reportedly being supplied to access countries by seven companies. It can be used to treat various conditions including pneumonia and urinary tract infections and is a relatively cheap and safe antibacterial for treating multidrug-resistant pathogens.²⁷

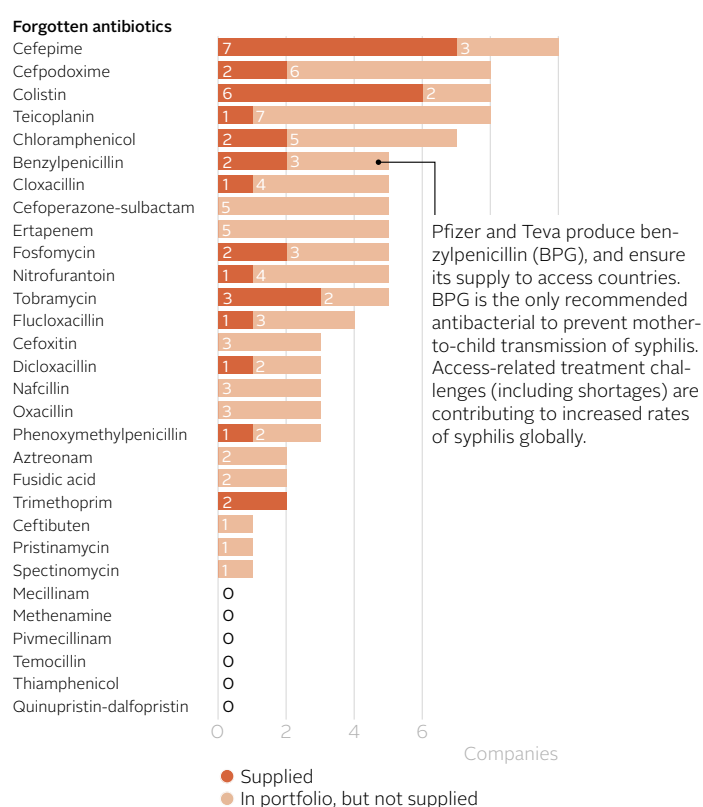
Cefepime is followed by teicoplanin, colistin and cefpodoxime, which are produced by eight companies each and supplied to at least one access country by one, six and two companies respectively.

The Benchmark encourages companies to expand registration and supply of forgotten antibiotics to more access countries, as these antibiotics may be cheap, safe and effective treatments to help reduce the morbidity and mortality caused by infections, and to halt the increasing antibiotic resistance to current antibacterial treatments.

FIGURE 44

Cefepime is the most widely produced and supplied forgotten antibiotic

This chart shows how many companies produce and supply each of the forgotten antibiotics to at least one access country. Cefepime, used to treat many kinds of bacterial infections, is the forgotten antibiotic produced and supplied to access countries by the most companies



STEWARDSHIP

Pharmaceutical companies take more measures to safeguard their products by monitoring their resistance and ensuring responsible promotion

AMR SURVEILLANCE

More programmes than in 2018; the majority share results publicly

Surveillance systems are critical for monitoring the spread of diseases and the rise of resistance.¹ As pharmaceutical companies have the means, expertise, and experience, they therefore have the responsibility to assist with these systems and share their results, as confirmed by the global health community.

The 2020 AMR Benchmark has compared all eight large research-based pharmaceutical companies on their activities in this area, considering whether they are active in the surveillance of bacterial or fungal pathogens and/or infections anywhere in the world and whether these results are shared publicly. Although it does not compare generic medicine manufacturers or small- and medium-sized enterprises (SMEs) in this area, it does report on their activities where data is available. This results in a total of 22 companies being reported on all with antibacterial and/or antifungal medicines on the market.

In 2018, the Benchmark stated that nearly half of companies reported in this area (9 of 19) were involved in AMR surveillance. In 2020, 22 companies in scope have antibacterial and/or antifungal medicines on the market, and of these 13 are active in AMR surveillance (figure 45). This includes eight of the nine companies previously involved in AMR surveillance. The exception is Roche, which is no longer in scope for the Benchmark. The increase in the number of companies involved in AMR surveillance is attributed to Abbott, Achaogen (filed for bankruptcy in April 2019), Melinta (filed for bankruptcy in December 2019), Mylan and Tetrphase; with only Abbott newly in scope in 2020.

In 2020, companies reported a total of 20 active surveillance programmes - with some programmes being supported by multiple companies - compared with 19 surveillance programmes in 2018. In 2020, the Benchmark evaluates a maximum of five programmes per company. The Benchmark identified 17 surveillance programmes that six large research-based pharmaceutical companies are active in (GSK, Johnson & Johnson, Merck & Co, Inc, Pfizer, Sanofi and Shionogi; all also active in surveillance in 2018). In addition, three generic medicine manufacturers (Abbott, Cipla and Mylan) and four small- and medium-sized enterprises (Achaogen, Melinta, Tetrphase and Wockhardt) are active in at least nine surveillance programmes. Three companies are active in two-thirds of the programmes between them (14 out of 20; by Pfizer, Merck & Co, Inc and Shionogi; with five, five and four programmes respectively).

What do surveillance programmes look like?

The 20 (total) programmes identified collect data relating to 37 bacteria and fungi, including 13 priority pathogens (figure 46).^{*} *Streptococcus pneumoniae* and *Enterobacteriaceae* are the pathogens most commonly under surveillance, most likely because these two pathogens are causes of community-acquired pneumonia, urinary tract infections (UTIs) and complicated intra-abdominal infections, for which many companies have recent medicines on the market.

All companies active in AMR surveillance are involved in at least one long-term programme. Only one programme, run by Mylan, is short-term. Most programmes have been operational for more than ten years (figure 48). The value of running a long-term programme is the ability to measure the spread of diseases by monitoring whether resistance is rising or is stable. The longest running programme was started in 1992 by Shionogi. Active only in Japan, it monitors resistance to marketed products, including cefiderocol, an antibacterial used to treat complicated UTIs.

Ten programmes evaluated operate in more than one country (figure 49). These ten programmes are active in an average of 34 countries. Pfizer's ATLAS programme has the largest geographical reach, running in 73 countries including countries with less specialised health networks. By covering countries with less specialised health networks, companies can contribute to building surveillance networks where health systems cannot do this alone. WHO's new Global Antimicrobial Resistance Surveillance System (GLASS) is being developed to analyse and report global surveillance data and research regularly. This data will then feed into the global action plan on AMR to help inform decision making. It currently has data from 87 countries, while the companies reported in the Benchmark have programmes in 38 countries that are not covered by GLASS. Companies have an opportunity to share AMR surveillance results for these countries with data going back for more than ten years for at least 11 programmes.

Making surveillance results (most importantly raw data) publicly available is key to helping governments, public health authorities and healthcare professionals measure and respond to the spread of resistant infections, analyse local trends and prioritise objectives in stewardship policies. The Benchmark looks for companies to share raw data so that WHO, third-party researchers and other experts can explore the potential for further research, beyond the specific questions asked by the companies themselves. The Benchmark finds that results

^{*} Priority pathogens: bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

FIGURE 45

The majority of companies are involved in AMR surveillance

The chart shows the proportion of pharmaceutical companies with antibacterial and/or antifungal medicines on the market that are active in surveillance.

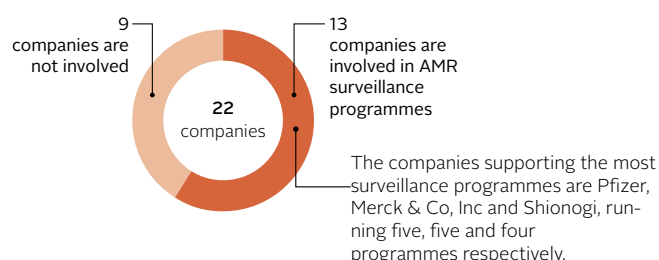


FIGURE 46

AMR surveillance programmes track majority of priority pathogens*

The chart shows which of the biggest bacterial and fungal threats from AMR are covered by surveillance programmes that pharmaceutical companies in scope are active in. The Benchmark looks at 18 such pathogens, identified by the WHO and CDC.

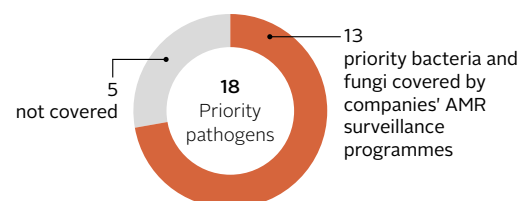


TABLE 12

Which surveillance programmes are companies active in?

The chart shows which of the priority bacterial and fungal pathogens* are covered by surveillance programmes that pharmaceutical companies in scope are active in. *Streptococcus pneumoniae* and *Enterobacteriaceae* are the priority pathogens most commonly under surveillance.

| AMR surveillance programme | Companies Active | Priority pathogens covered | <i>Streptococcus pneumoniae</i> | <i>Enterobacteriaceae</i> | <i>Pseudomonas aeruginosa</i> | <i>Staphylococcus aureus</i> | <i>Haemophilus influenzae</i> | <i>Enterococcus spp.</i> | <i>Acinetobacter spp.</i> | <i>Streptococcus (group A & B)</i> | <i>Neisseria gonorrhoeae</i> | <i>Salmonella spp.</i> | <i>Mycobacterium tuberculosis</i> | <i>Candida spp.</i> |
|--|---|----------------------------|---------------------------------|---------------------------|-------------------------------|------------------------------|-------------------------------|--------------------------|---------------------------|--|------------------------------|------------------------|-----------------------------------|---------------------|
| CANWARD | Abbott; Achaogen; Merck & Co, Inc; Pfizer | 11 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ○ | ● |
| ASPIRE | Wockhardt | 10 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ○ | ○ |
| ATLAS | Pfizer | 9 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ○ | ○ | ○ |
| SENTRY | Cipla; Melinta; Pfizer | 9 | ● | ● | ● | ● | ● | ● | ● | ● | ○ | ○ | ○ | ● |
| Study of Bacterial Resistance Kinki Region of Japan | Shionogi | 8 | ● | ● | ● | ● | ● | ● | ● | ○ | ○ | ○ | ○ | ● |
| Study for Monitoring Antimicrobial Resistance Trends (SMART) | Merck & Co, Inc | 7 | ● | ● | ● | ● | ● | ● | ● | ○ | ○ | ○ | ○ | ○ |
| BSAC Bacteraemia Resistance Surveillance Programme | Merck & Co, Inc; Pfizer | 6 | ● | ● | ● | ● | ○ | ● | ○ | ● | ○ | ○ | ○ | ○ |
| Global <i>in vitro</i> Surveillance of Eravacycline | Tetraphase | 4 | ○ | ● | ○ | ● | ○ | ● | ● | ○ | ○ | ○ | ○ | ○ |
| SIDERO-WT Programme | Shionogi | 3 | ○ | ● | ● | ○ | ○ | ○ | ● | ○ | ○ | ○ | ○ | ○ |
| Surveillance of Tedizolid Activity and Resistance (STAR) | Merck & Co, Inc | 3 | ○ | ○ | ○ | ● | ○ | ● | ○ | ● | ○ | ○ | ○ | ○ |
| Program to Assess Ceftolozane/Tazobactam Susceptibility (PACTS) | Merck & Co, Inc | 2 | ○ | ● | ● | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Shionogi Japanese Surveillance Studies Programme | Shionogi | 2 | ○ | ○ | ○ | ● | ○ | ○ | ○ | ● | ○ | ○ | ○ | ○ |
| Survey of Antibiotic Resistance (SOAR) | GSK | 2 | ● | ○ | ○ | ○ | ● | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| Drug Resistance Emergence Assessment in MDR-TB (DREAM) | Johnson & Johnson | 1 | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ● | ○ |
| Observatoires Régionaux du Pneumocoque (ORP) | Sanofi | 1 | ● | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ |
| TB Active Case Finding Campaign | Mylan | 1 | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ○ | ● | ○ |
| China-based antibiotic resistance surveillance progr. (CHINET) / CHIFNET | Pfizer | 0 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Data Development | Mylan | 0 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |
| Three Academic Societies Joint Antimicrobial Susceptibility Surveillance Program | Shionogi | 0 | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● |

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the US Centers for Disease Control and Prevention (CDC). See Appendix V.
Priority bacteria and fungi that are not covered by surveillance programmes are not listed in this table. These are: *Campylobacter* spp, *Clostridioides difficile*, *Helicobacter pylori*, *Shigella* spp. and *Candida auris*.
One surveillance programme is not shown in this table as the information was provided on the basis of confidentiality.

● Pathogen covered by programme
○ Pathogen not covered by programme
● Unknown

are shared publicly from at least 15 (of 20) programmes run by companies in scope. Nine of the 13 companies involved in AMR surveillance share their results (Abbott, Achaogen, Cipla, GSK, Melinta, Merck & Co, Inc, Shionogi, Tetrphase and Pfizer). Three companies (Johnson & Johnson, Mylan and Wockhardt) commit to sharing their results after data collection is completed, however it is unclear whether results will be made publicly available. Pfizer demonstrates best practice by sharing the raw data from its ATLAS programme on the AMR Register, an open-access data platform that collects raw data from surveillance programmes run by pharmaceutical companies (figure 50 and 51). All companies involved in AMR surveillance should contribute to monitoring AMR by making their raw data publicly available. Initiatives and platforms that could benefit from companies' raw data include the Global Burden of Disease study, published by the Institute of Health Metrics and Evaluation (IHME) and Wellcome Trust's Data Reuse Prize. In 2018, the IHME announced that it will begin to incorporate AMR morbidity and mortality rates in its

study. The Data Reuse Prize launched in 2018, aims to reward researchers who develop new insights, tools or health applications based on available data in its AMR Register.

What type of data are companies collecting?

In India, Mylan supports two programmes: the Revised National TB Control Programme, and a multi-centre retrospective study of AMR in intensive care unit (ICU) patients. Wockhardt runs the ASPIRE programme in 16 medical centres across the country, focusing on clinical nosocomial (hospital-acquired) infections caused by pathogens such as *Staphylococcus* spp. and *Haemophilus* spp.

Abbott, Achaogen, Merck & Co, Inc and Pfizer, among others support the CANWARD programme, which is managed by the Canadian Antimicrobial Resistance Alliance and focuses on pathogens isolated in Canadian hospitals. Cipla, Melinta and Pfizer (among others) support the SENTRY programme, which is managed by JMI laboratories and is active in 30 countries. Merck & Co, Inc and Pfizer, among others support

FIGURE 47

India - a key country for tracking resistance

Tracking antimicrobial resistance in India

In 2010, India was the largest consumer of antibacterials. Today, it has one of the highest AMR rates in the world with more than 50% resistance against 14 out of 16 bacteria measured.* If resistant strains are detected early and changes in microbial populations are tracked, stewardship policies could be more easily developed to address AMR. Nine of the 20 surveillance programmes in scope are aiming to achieve this.

How can data support India's burden of AMR?

By gathering and sharing data on the spread of infections and resistance, pharmaceutical companies are directly supporting the Indian government identifying where stewardship efforts are working and where greater efforts are needed. This data also highlights where informed and appropriate access to antibacterials and antifungals are in high demand to curb the spread of infections.

What next?

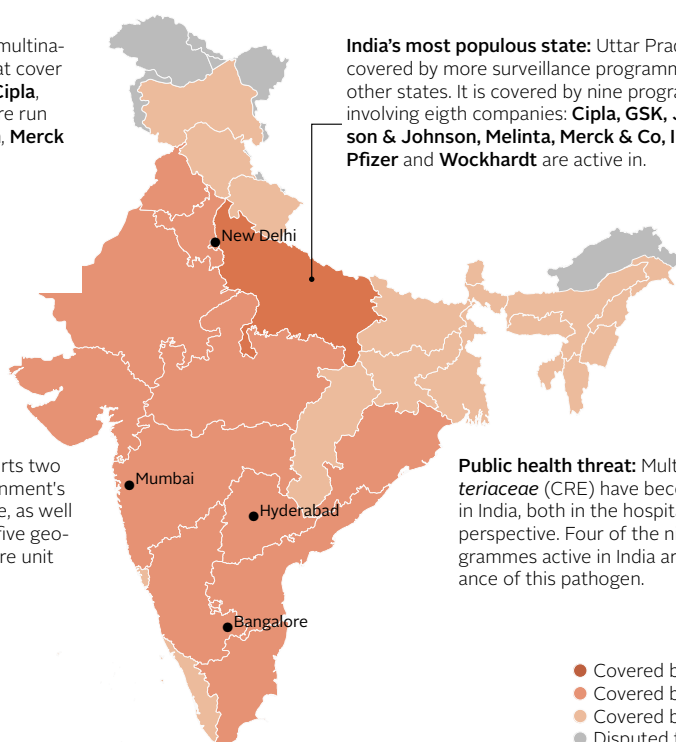
The resistance rates of pathogens varies considerably in different states across India. It is therefore crucial that pharmaceutical companies continue to support surveillance programmes at the regional level in order to strengthen AMR evidence at the country level. This will help make informed-decisions and drive both national and global actions.

Multinational coverage: There are five multinational AMR surveillance programmes that cover India. One programme is supported by **Cipla, Melinta and Pfizer**. Four programmes are run separately by **GSK, Johnson & Johnson, Merck & Co, Inc and Pfizer**.

One company stands out: Mylan supports two programmes in India — the Indian government's Revised National TB Control Programme, as well as a retrospective study of AMR across five geographical areas, focusing on intensive care unit patients.

India's most populous state: Uttar Pradesh is covered by more surveillance programmes than other states. It is covered by nine programmes involving eight companies: **Cipla, GSK, Johnson & Johnson, Melinta, Merck & Co, Inc, Mylan, Pfizer and Wockhardt** are active in.

Public health threat: Multi-resistant *Enterobacteriaceae* (CRE) have become very common in India, both in the hospital and public health perspective. Four of the nine surveillance programmes active in India are evaluating the resistance of this pathogen.



- Covered by nine surveillance programmes
- Covered by eight surveillance programmes
- Covered by seven surveillance programmes
- Disputed territory

* Source: the Center for Disease Dynamics, Economics & Policy (CDDEP)^{2,3}

FIGURE 48

The majority of AMR surveillance programmes have been running for more than ten years

The chart shows the proportion of surveillance programmes that pharmaceutical companies have been running for more than ten years to measure long-term AMR trends. Together, these programmes represent a wealth of data on AMR.

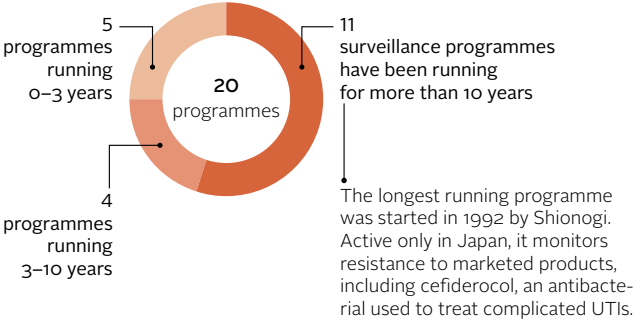


FIGURE 49

Half of AMR surveillance programmes are multinational

The chart shows the proportion of AMR surveillance programmes supported by the pharmaceutical companies in scope that are multinational or national. Half run in more than one country, covering between two and 73 countries. Given this geographic reach, these datasets are likely to be extensive.

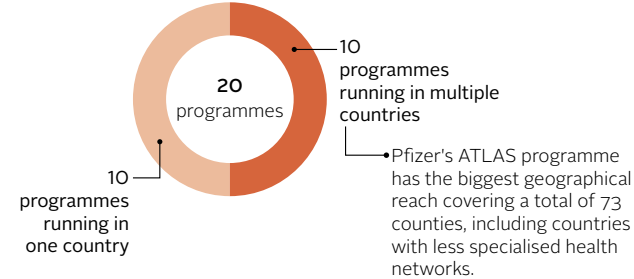


FIGURE 50

Only one company shares the raw data from AMR surveillance programmes

The chart shows the proportion of surveillance programmes where results or raw data are made publicly available. Sharing surveillance data enables governments and others to measure the spread of AMR and design stewardship policies. For most programmes, the companies involved share their results.

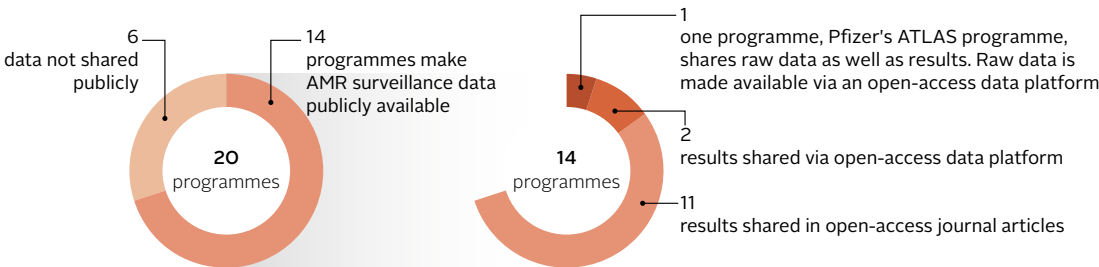
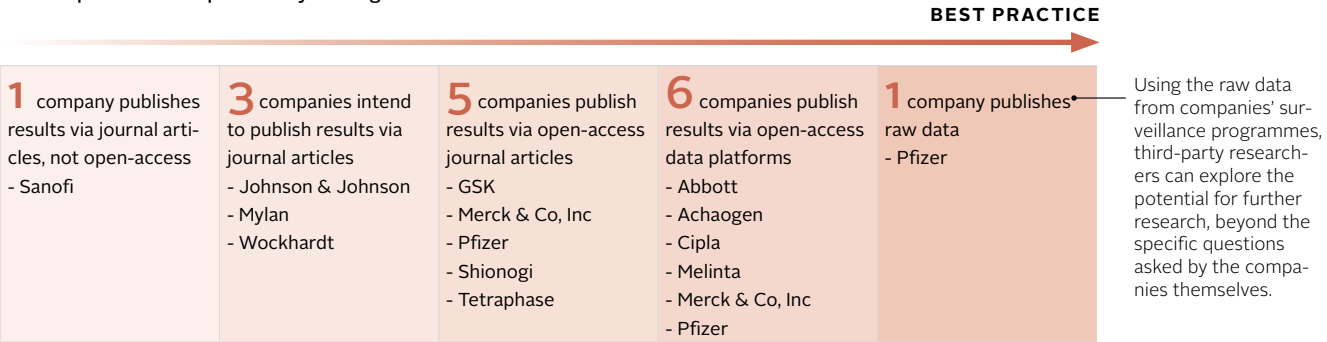


FIGURE 51

Pfizer represents best practice by sharing raw surveillance data



the BSAC Bacteraemia Resistance Surveillance Programme, which is managed by the British Society for Antimicrobial Chemotherapy (BSAC) and is active in the Ireland and the UK. Finally, Tetrphase supports a programme managed by IHMA that focuses on surveillance of eravacycline (Xerava™) against Gram-negative and Gram-positive bacterial pathogens globally.

Five companies (GSK, Johnson & Johnson, Merck & Co, Inc, Pfizer and Shionogi) have company-owned multinational surveillance programmes, active in between 11 and 73 countries. These demonstrate aspects of good practice.

GSK's SOAR programme (Survey of Antibiotic Resistance) is a multinational programme active in more than 30 countries and focusing on community-acquired infections of the respiratory tract. It runs periodically and shares its results through peer-reviewed open-access journal articles.

Johnson & Johnson's DREAM programme (Drug Resistance Emergence Assessment in Multidrug-resistant tuberculosis), repeated every year since 2015, is active in 11 countries and focuses on resistance to bedaquiline (Sirturo®), testing 12 antibacterials. The study is an FDA post-marketing requirement: Johnson & Johnson currently restricts access to the database, but it does share methodological aspects through peer-reviewed open-access journal articles.

Merck & Co, Inc's SMART programme (Study for Monitoring Antimicrobial Resistance Trends) is active in 63 countries and covers complicated intra-abdominal infections, complicated urinary tract infections and respiratory infections. Merck & Co, Inc shares its results through peer-reviewed, open-access journal articles.

Pfizer's ATLAS programme (Antimicrobial Testing Leadership and Surveillance) runs in 73 countries and focuses on resistance against its antibacterials on the market and also those in development. Pfizer expanded ATLAS by focusing on more priority pathogens* and it plans to incorporate antifungal data collected from the SENTRY surveillance programme. It runs periodically and publicly shares its raw data on a data platform, as well as its results through peer-reviewed open-access journal articles.

Shionogi's SIDERO-WT programme, which collects data annually, is active in 13 countries and focuses on resistance in Gram-negative bacteria. Shionogi shares its results through peer-reviewed, open-access journal articles.

RESPONSIBLE PROMOTIONAL PRACTICES

More companies decouple sales incentives from sales volume

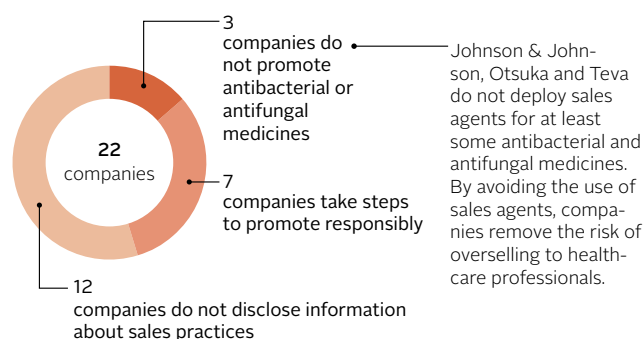
One of the main drivers for the emergence of AMR is the inappropriate use of antibacterial and antifungal medicines – for example, by using them when they are not needed, or by not using these medicines at the right dose. Inappropriate use has been shown to cause antibacterial and antifungal medicines to become ineffective more rapidly.⁴

Pharmaceutical companies should ensure that their antibacterial and antifungal medicines are used appropriately and only when needed in order to prolong their effectiveness. For

FIGURE 52

How many companies are engaging in responsible promotion?

The chart shows whether and how 22 pharmaceutical companies promote their antibacterial and antifungal medicines. Ten companies take steps to promote their medicines responsibly.



SALES INCENTIVES AND PRESCRIBING PRACTICES

If a company incentivises its sales agents to sell a high volume of products to increase total pay, it increases the risk that it will promote inappropriate use of its products.

example, companies can halt the promotion of antibacterial and antifungal medicines to healthcare professionals (HCPs), or, where companies do actively promote, they can decouple sales agents' incentives from sales volumes, so that bonuses are not dependent on how much product agents sell.

The Benchmark evaluates the practices employed by eight large research-based pharmaceutical companies and nine generic medicine manufacturers to ensure their antibacterial and antifungal medicines are promoted responsibly. Although it does not compare small- and medium-sized enterprises in this area, it does report on their activities where data is available. This results in a total of 22 companies being reported on all with antibacterial and antifungal medicines on the market.

Two companies stand out for no promotion

Overall, ten out of 22 companies in scope with antibacterial and antifungal medicines on the market report that they implement responsible promotional practices that aim to prevent the inappropriate use of their antibacterial and antifungal medicines. These companies either do not promote antibacterial and antifungal medicines at all, or they take steps to promote them responsibly by weakening the link between sales agents' remuneration and sales volume (figure 52). This shows progress from the 2018 Benchmark, which found that only five companies were taking steps to decouple sales incentives from sales volumes (GSK, Johnson & Johnson, Novartis, Pfizer and Shionogi). GSK's performance in this area is lower than in the 2018 Benchmark as it now evaluates the variable pay component of sales agents' remuneration using sales targets that are closer to

* Priority pathogens: bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

TABLE 13

How far does responsible promotion go when it comes to deploying sales staff and linking bonuses to sales volumes?

The sales practices of ten companies are shown below. Cipla, Shionogi and Wockhardt fully decouple incentives for sales agents from sales volumes. GSK, Novartis and Pfizer partly decouple these incentives.

| | Company | Sales practices | Incentives for sales agents | Percentage of variable pay and level of incentives | |
|------------------|-------------------|--|--|---|--|
| No promotion | Teva | None (no active promotion) | N/A | N/A | Teva demonstrates best practice by not promoting any of its antibacterial and/or anti-fungal medicines, while Otsuka and Johnson & Johnson each apply this practice to one product. Promotion of products could lead to bias in prescribers' practices by encouraging inappropriate use. This risk is removed when companies decide not to promote. |
| | Otsuka | None (no active promotion). Treatment with delamanid (Delyba™) is only available in specialised centres under tightly controlled conditions. | N/A | N/A | |
| | Johnson & Johnson | None (no active promotion of bedaquiline (Sirturo®)) | N/A | N/A | |
| | | No data on sales practices of other antibacterial and anti-fungal medicines | No data on sales practices of other antibacterial and antifungal medicines | No data on level of incentives | |
| Fully decoupled | Cipla | Retail | Fully decoupled from volumes | 100% | As in 2018, Shionogi demonstrates best practice by fully decoupling its sales incentives from sales volumes, and is joined in 2020 by Cipla and Wockhardt. Decoupling mitigates the risk that sales agents promote irresponsibly. |
| | Shionogi | Retail | Fully decoupled from volumes | 100% | |
| | Wockhardt | Retail | Fully decoupled from volumes | 100% | |
| Partly decoupled | Pfizer | Retail | Fully decouples sales incentives from volumes in UK pilot | 100% | Pfizer and GSK partly decouple their sales incentives from sales volumes. Pfizer's incentives are at a national (less direct) level, with a lower risk of incentivising sales agents to increase sales. GSK's performance is lower than in 2018 as its incentives are aimed at a smaller group of sales agents within a country, which is closer to the individual effort. |
| | | | Partly decouples sales incentives from volumes in other countries | Of variable pay, 50% linked to volumes and incentives at national level | |
| | GSK | Retail | Partly decoupled from volumes | Of total pay, 25% variable, linked to volumes and incentives at smaller group level | |
| | Novartis | Retail | Partly decoupled from volumes | Of total pay, 35% variable, and 80% of variable pay linked to volumes | |
| | Merck & Co, Inc | Retail | (In UK pilot) Fully decoupled from volumes | No data on sales incentives outside of the UK | |

12 companies do not appear in this table. They provide no information regarding sales practices that aim to address the appropriate use of antibacterial and/or antifungal medicines.

KEY TERMS IN PHARMACEUTICAL SALES PRACTICES

- **Retail:** The sale of medicines for consumption (in clinics and pharmacies, for example).
- **Tender:** A procedure to procure medicines using competitive bidding.
- **Decoupling incentives from sales:** Full decoupling means that no component of a sales agents' incentives is linked to that agent's volume of sales. Partial decoupling means that a proportion of the agent's pay is variable and depends on incentives linked to sales volumes.
- **Level of incentives:** Incentives for sales agents can be awarded at individual, smaller group or national level. When incentives are awarded at national and smaller group (rather than individual) level, they are linked less directly to total pay, so that when an individual agent sells a higher volume of products, this does not directly increase that person's total pay.

the individual effort, which raises the incentive, and risk, of increasing sales volumes. In 2020, Otsuka and Teva are two of the five companies in this area to demonstrate best practice: they do not promote any of their antibacterial or antifungal medicines (Otsuka has only one medicine in scope). Because they do not deploy sales agents to promote products, they remove the risk that promotional activities will increase inappropriate use.

Tuberculosis medicines, such as Otsuka's delamanid (Delyba™), are generally not promoted as a stewardship measure, given the comparatively wide spread of extensively drug-resistant and multidrug-resistant strains of tuberculosis. The 2018 Benchmark reported that Johnson & Johnson did not promote its TB medicine, bedaquiline (Sirturo®), and this continues in 2020 and also results in a best practice. Johnson & Johnson reports that for its other antibacterial and antifungal medicines, sales agents may be deployed.

Two new companies fully decouple pay and sales volume

As in 2018, Shionogi demonstrates best practice by fully decoupling its sales incentives from sales volumes to help prevent the inappropriate use of antibacterial and antifungal medicines. Newly reported in 2020, Cipla and Wockhardt also show best practice by fully decoupling. Cipla is the first generic medicine manufacturer identified by the Benchmark to do so.

GSK, Novartis and Pfizer partially decouple incentives for sales agents from sales volumes (table 13). At GSK, 25% of sales agents' total pay is variable (based on performance incentives). Incentives are linked to smaller groups of sales agents (within a country), rather than at a national level. This represents a shift in performance compared to 2018, as the smaller the group of sales agents' incentives, the stronger the incentive for sales agents to increase their own volumes of sales. While Pfizer does not clearly indicate what proportion of sales agents' remuneration is variable, it links only 50% of its sales agents' variable pay to sales volumes. Its assessment of sales volumes is conducted at the national level. Through pilots established in 2019, both Pfizer and Merck & Co, Inc have fully decoupled incentives for sales agents from sales volumes in the UK. The 2018 Benchmark noted that Pfizer was taking steps to begin such a pilot. Looking at Novartis, 35% of sales agents' total pay is variable and 80% of its variable pay is linked to sales volumes.

Novartis and Fresenius Kabi report that they sell most of their products through government and/or hospital tenders. As sales agents are not involved in tendering processes, there are no direct incentives linked to sales volumes of these products.

As promotion of antibacterial and/or antifungal medicines can lead to inappropriate use, all companies should be looking to avoid such promotion. To help prevent inappropriate use, companies that do promote their products need to fully decouple sales agents' incentives from sales volumes; and ensure these remain decoupled.

CONFLICT OF INTEREST MITIGATION (COI)

The majority of companies mitigate COI comprehensively

Pharmaceutical companies often engage in educational activities for healthcare professionals (HCPs) to raise awareness and build knowledge about AMR and how to prevent it.⁵ However, it is paramount that when companies aim to play a role in educational HCPs, they should proactively mitigate conflicts of interest (COI) that may arise from providing information about how their products should be used. The Benchmark assesses companies in this area (eight large research-based pharmaceutical companies and nine generic medicine manufacturers), considering whether and how they engage in educational activities aimed at HCPs, and whether they mitigate COI when they do so. The Benchmark looks at a maximum of five programmes for each company. Although it does not compare small- and medium-sized enterprises, it does report on their activities where data is available. This results in a total of 22 companies being reported on all with antibacterial and antifungal medicines on the market.

Of 22 companies with antimicrobial products on the market, 14 are involved in at least 50 AMR-related educational programmes aimed at healthcare professionals (figure 53). Aurobindo, Otsuka and Teva are not involved in any programmes. After the period of analysis, Aurobindo stated that it is involved in several educational programmes. For six companies it is unknown whether they are involved in educational programmes. On average, companies reported four programmes, with seven companies reporting the maximum of five programmes. Of the 50 programmes, the Benchmark finds that 40 mitigate conflicts of interest (COI) in a comprehensive way (figure 54). Of the remaining 10 programmes, at least some COI strategies are in place for seven of them.

In the Benchmark, companies can mitigate COI comprehensively either by: (1) receiving accreditation from an independent body that evaluates potential COI; or (2) providing an unrestricted grant to an independent third party to develop a programme; or (3) implementing all three of the Benchmark's defined COI mitigation strategies. These are: (a) developing content independently from the marketing department, (b) pledging not to provide financial or material incentives to participants, and (c) not using branded materials. This definition was reached through detailed stakeholder consultations held during the Benchmark's methodology development process.

As in 2018, the Benchmark finds that all three COI strategies are used most commonly: not using branded materials; pledging not to provide financial or material incentives to participants; and independence of content development (figure 55). Four companies (Abbott, Johnson & Johnson, Merck & Co, Inc and Pfizer) provide unrestricted grants to independent third parties to develop their programmes. These parties, such as the British Society for Antimicrobial Chemotherapy (BSAC), ensure programme content is scientifically accurate and has no marketing components. GSK and Melinta are the only companies to receive accreditation for COI mitigation (from the Health Authority of Abu Dhabi and the American Society of Hospital Pharmacists, respectively) for four programmes in

FIGURE 53

The majority of companies are involved in AMR-related educational programmes

The chart shows the proportion of pharmaceutical companies that are involved in AMR-related educational programmes aimed at healthcare professionals (HCPs). Out of 22 companies, two companies avoid conflict of interest by not engaging in educational activities aimed at HCPs.

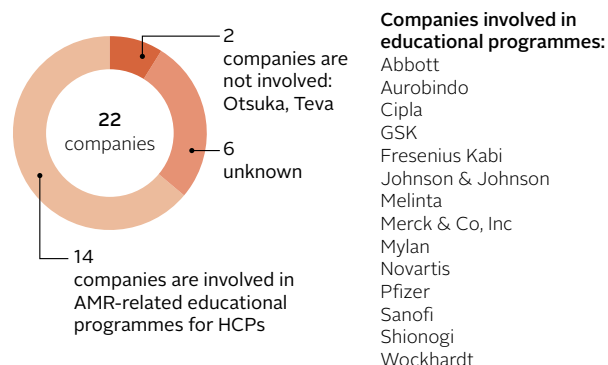
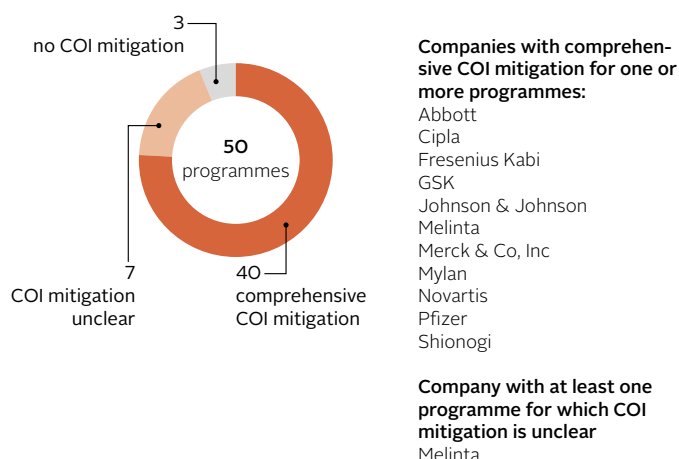


FIGURE 54

Comprehensive COI mitigation in place for majority of AMR-related educational programmes

The chart shows the proportion of AMR-related educational programmes for healthcare professionals (HCPs) that are covered by comprehensive mitigation of conflict of interest (COI). The Benchmark analysed 50 such programmes from 14 pharmaceutical companies. For 40 of these programmes, companies comprehensively mitigate the risk of COI.



HOW CAN COMPANIES MITIGATE CONFLICT OF INTEREST (COI) IN HCP EDUCATIONAL PROGRAMMES?

- **No branded materials:** A COI mitigation strategy can consider whether the content of an educational programme includes branded products or materials.
- **No incentives to participants:** A COI mitigation strategy can consider whether a company pledges that it will not provide financial and material incentives to those who participate in educational programmes.
- **Independence of content development:** A COI mitigation strategy can stipulate the exclusion of a company's marketing department in content development and speaker selection.
- **Unrestricted grant:** Companies can provide unrestricted grants to independent third parties. These can be used for AMR-related educational activities, without any involvement of the company and without any obligation to include marketing aspects in the programme.
- **Accreditation COI mitigation:** Accreditation is one of the most comprehensive ways for companies to show they mitigate COI within programmes. An independent body such as the Accreditation Council for Continuing Medical Education (ACCME) can evaluate how COI is mitigated if the provider is a company, and accredit educational programmes;

FIGURE 55

What do COI mitigation strategies look like?

The chart shows the proportion of AMR-related educational programmes for healthcare professionals (HCPs) that are covered by COI mitigation strategies. From the pharmaceutical companies assessed, only four out of 50 programmes received accreditation from an independent body, which is the most comprehensive way to mitigate COI.

Type of COI mitigation

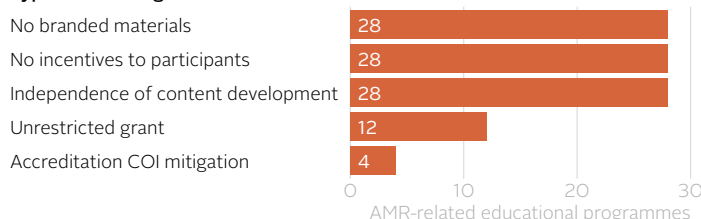
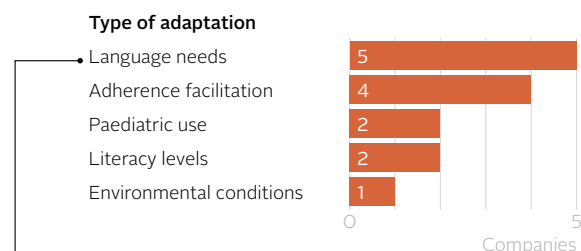


FIGURE 56 Companies take language needs into account most frequently in their brochures and packaging

The chart shows how many pharmaceutical companies are making the different types of brochure and/or packaging adaptations assessed by the Benchmark.



Companies mostly take language needs into account. When people are prescribed medicines or buy them over the counter, the information that pharmaceutical companies provide in their brochures and packaging can improve the likelihood that medicines will be used appropriately, which in turn limits AMR.

total (out of ten for both companies in total). Abbott and Melinta are involved in educational programmes for which it is unclear whether COI is mitigated. After the period of analysis, Abbott reported that it has policies in place to mitigate COI for all its educational events. In addition to receiving accreditation for two of Melinta's programmes, it also has three programmes with no company-specific COI mitigation strategies. Wockhardt reports one programme, which develops its content independently from the company's marketing department.

Because of the risks of COI, companies should have strong COI mitigation strategies in place. If these strategies are not robust, companies should not be involved in educational programmes aimed at HCPs. Some programmes (run by Cipla, Johnson & Johnson, Melinta, Merck & Co, Inc, Novartis, Sanofi and Wockhardt) have only some or no COI mitigation. After the period of analysis, Cipla stated that it creates the content for its programmes by the medical affairs team that aim to ensure independence of content development, indicating that all of its programmes are comprehensively mitigated for COI. Companies need to work towards ensuring comprehensive COI mitigation; for example, by seeking to be accredited by an independent body that evaluates COI.

BROCHURE AND PACKAGING ADAPTATIONS

Companies most commonly consider language needs

EXAMPLES OF HOW COMPANIES ADAPT THEIR PRODUCT PACKAGING TO HELP IMPROVE APPROPRIATE USE

- **Five companies have made language adaptations.** Cipla, for example, has adapted its patient education leaflets for itraconazole, amorolfine and oxiconazole in India, giving information in both English and Hindi. These leaflets contain QR codes that direct patients to information in eight other regional languages: Kannada, Telugu, Tamil, Malayalam, Marathi, Gujarati, Bengali and Oriya.
- **Four companies have adapted their packaging to improve adherence.** One is Johnson & Johnson, which packaged a six-month treatment regimen (188 tablets) in a single bottle. This was designed to enable patients to follow a full course of treatment without needing to make multiple visits to a pharmacy or clinic.
- **Two companies have made literacy-related adaptations.** GSK has developed a graphics-based smartphone application to educate patients about the appropriate use of antibacterials. A bar code on the packaging of its amoxicillin/clavulanic acid (Augmentin™) provides access to the app, which is being piloted in the Gulf Cooperation Council (GCC) region.
- **Two companies have made adaptations for paediatric use.** For Japan, Shionogi created a brochure for cefcapene pivoxil (Flomox®) which has simple illustrations that appeal to children. The brochure also contains information on how to dissolve and administer the granules.
- **One company has an environmental adaptation.** GSK created blister packaging with a specific foil lid to protect its product – amoxicillin/clavulanic acid (Augmentin™) – from moisture in high-humidity environments in Pakistan.

When people are prescribed medicines or buy them over the counter, the quality of information that pharmaceutical companies provide in their brochures and packaging can improve the likelihood that medicines will be used appropriately, which in turn mitigates the risk of emergence and spread of AMR. For example, companies can adapt their brochures and product packaging by translating into languages for local populations; addressing low levels of literacy through the use of pictograms; giving guidelines to improve the likelihood that patients will adhere to treatment; and offering child-specific information so that medicines can be used appropriately. Moreover, companies can preserve the quality of medicines by considering the environmental conditions in a country. The Benchmark assesses how 17 companies in scope – eight large research-based pharmaceutical companies and nine generic medicine manufacturers – adapt brochures and packaging of antibacterial and antifungal medicines to improve the likelihood of their appropriate use, and so limit the emergence of AMR.

Of the companies evaluated, only seven provide information about the ways they adapt their brochures and/or packaging to improve likelihood of appropriate use and limit AMR. The Benchmark evaluates adaptations (except those relating to language) that go beyond regulatory requirements.

Language is the most common adaptation companies

make with regard to brochures and packaging (figure 56). Four companies (GSK, Johnson & Johnson, Otsuka and Teva) translate their brochures into common global languages such as French, Spanish and Portuguese. In addition, Cipla, the only company in scope to include adaptations for antifungal medicines, has created leaflets that contain QR codes directing users to information about antifungal resistance in Indian regional languages.

Five companies (Cipla, GSK, Johnson & Johnson, Novartis and Shionogi) adapt their brochures and/or packaging to take account of needs other than language. Notably, GSK has adapted the brochure and packaging for its antibacterial amoxicillin/clavulanic acid (Augmentin™) to facilitate adherence to treatment, literacy levels and environmental conditions. To facilitate adherence to treatment, it uses a Patient Knowledge Card to highlight important information. In the Gulf Cooperation Council (GCC) countries, it addresses literacy levels by providing a graphics-based chatbot that patients can use to access information on the appropriate use of its antibacterial medicines. GSK also takes account of high-humidity environments in Pakistan by using a blister packaging with a specific foil lid to protect tablets from moisture. This curbs AMR by ensuring the quality of these tablets to contain

effective doses of the active ingredient when patients take them. Novartis has adapted its brochures to take account of literacy levels and paediatric use. In collaboration with the Pan-African Society of Cardiology, it created a patient brochure for benzathine benzylpenicillin using pictograms. It also created paediatric guidance for amoxicillin/clavulanic acid, explaining the correct dosing for children. After the period of analysis, Pfizer stated that it has adapted the packaging of azithromycin (Zithromax®), named the Z-Pak, which aims to facilitate patient adherence.

REFERENCES

Appropriate Access

- World Bank list of economies (June 2018). <https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups>.
- Committee for Development Policy of ECOSOC Least Developed Country (LDC) list (as of March 2018) <https://www.un.org/development/desa/dpad/least-developed-country-category.html>
- Human Development Indices and Indicators: 2018 Statistical Update. http://hdr.undp.org/sites/default/files/2018_statistical_annex_all.xlsx.
- Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2017 (GBD 2017) Results. 2018. <http://ghdx.healthdata.org/gbd-results-tool>.
- Worldometers. <https://www.worldometers.info/world-population/>. Accessed November 29, 2019.
- Zerhouni E. GAVI, the Vaccine Alliance. *Cell*. 2019;179(1):13-17. Doi:10.1016/j.cell.2019.08.026
- UNICEF <https://www.unicef.org/> (accessed Nov 2019)
- PAHO Pan American Health Organization. <https://www.paho.org/hq/index.php?lang=en>. Accessed November 29, 2019.
- Gavi The Vaccine Alliance. <https://www.gavi.org/types-support/sustainability/eligibility>. Accessed November 29, 2019.
- WHO Model List of Essential Medicines (20th List, March 2017, Amended August 2017). <https://www.who.int/medicines/publications/essentialmedicines/en/>

- Narsai K, Williams A, Mantel-Teeuwisse AK. Impact of regulatory requirements on medicine registration in African countries - perceptions and experiences of pharmaceutical companies in South Africa. *South Med Rev*. 2012;5(1):31-37.
- Ahonkhail V, Martins SF, Portet A, Lumpkin M, Hartman D. Speeding Access to Vaccines and Medicines in Low- and Middle-Income Countries: A Case for Change and a Framework for Optimized Product Market Authorization. *PLoS One*. 2016;11(11):e0166515. doi:10.1371/journal.pone.0166515
- Spending on health and HIV/AIDS: domestic health spending and development assistance in 188 countries, 1995-2015. *Lancet* (London, England). 2018;391(10132):1799-1829. doi:10.1016/S0140-6736(18)30698-6
- WHO. WHO Guideline On Country Pharmaceutical Pricing Policies; World Health Organization, 2015
- Stevens H, Huys I. Innovative Approaches to Increase Access to Medicines in Developing Countries. *Front Med*. 2017;4:218. doi:10.3389/fmed.2017.00218
- Borges Dos Santos MA, Dos Santos Dias LL, Santos Pinto CDB, da Silva RM, Osorio-de-Castro CGS. Factors influencing pharmaceutical pricing - a scoping review of academic literature in health science. *J Pharm policy Pract*. 2019;12:24. doi:10.1186/s40545-019-0183-0
- Universal Health Coverage for Sustainable Development - Issue

Brief; United Nations Development Programme, 2019.

- Simmons B, Cooke GS, Miraldo M. Effect of voluntary licences for hepatitis C medicines on access to treatment: a difference-in-differences analysis. *Lancet Glob Heal*. 2019;7(9):e1189-e1196. doi:10.1016/S2214-109X(19)30266-9
- Perez-Casas C, Herranz E, Ford N. Pricing of drugs and donations: options for sustainable equity pricing. *Trop Med Int Health*. 2001;6(11):960-964. doi:10.1046/j.1365-3156.2001.00801
- Global Tuberculosis Report.; World Health Organization, 2019. <https://apps.who.int/iris/bitstream/handle/10665/329368/9789241565714-eng.pdf?ua=1>
- Danzon PM. Differential Pricing of Pharmaceuticals: Theory, Evidence and Emerging Issues. *Pharmacoeconomics*. 2018;36(12):1395-1405. doi:10.1007/s40273-018-0696-4
- Maniadakis N, Holtorf A-P, Otavio Correa J, Gialama F, Wijaya K. Shaping Pharmaceutical Tenders for Effectiveness and Sustainability in Countries with Expanding Healthcare Coverage. *Appl Health Econ Health Policy*. 2018;16(5):591-607. doi:10.1007/s40258-018-0405-7
- Cogan D, Karrar K, Iyer JK. Shortages, stockouts and scarcity. Access to Medicine Foundation. 2018.
- Pauwels K, Simoens S, Casteels M, Huys I. Insights into European drug shortages: a survey of hospital pharmacists. *PLoS One*. 2015;10(3):e0119322. doi:10.1371/journal.pone.0119322
- Pulcini C, Beovic B, Béraud G, et al. Ensuring universal access to old anti-biotics: a critical but neglected priority. *Clin Microbiol Infect*. 2017;23(9):590-592. doi:10.1016/j.cmi.2017.04.026
- Cassir N, Rolain J-M, Brouqui P. A new strategy to fight antimicrobial resistance: the revival of old antibiotics. *Front Microbiol*. 2014;5:551. doi:10.3389/fmicb.2014.00551
- Shahid SK. Cefepime and its role in pediatric infections. *Recent Pat Antiinfect Drug Discov*. 2008;3(2):145-148. doi:10.2174/157489108784746614

Stewardship

- WHO. Global Action Plan on Antimicrobial Resistance. World Health Organization; 2017.
- Ganesh Kumar S, Adithan C, Harish BN, Sujatha S, Roy G, Malini A. Antimicrobial resistance in India: A review. *J Nat Sci Biol Med*. 2013;4(2):286-291. doi:10.4103/0976-9668.116970
- The Center for Disease Dynamics Economics & Policy. ResistanceMap: Antibiotic Resistance. <https://resistancemap.cddep.org/AntibioticResistance.php>. Published 2019. Accessed November 5, 2019.
- Laxminarayan R, Matsoso P, Pant S, et al. Access to effective antimicrobials: A worldwide challenge. *Lancet*. 2016;387(10014):168-175. doi:10.1016/S0140-6736(15)00474-2
- Parsonage B, Hagglund PK, Keogh L, Wheelhouse N, Brown RE, Dancer SJ. Control of antimicrobial resistance requires an ethical approach. *Front Microbiol*. 2017;8(NOV):1-14. doi:10.3389/fmicb.2017.02124

Company Report Cards

The 2020 Antimicrobial Resistance Benchmark includes a set of 30 company report cards, that provide the most detailed overviews of each company's performance. Companies are all different in the way they operate, where they operate, and in their portfolio of investigational and marketed products.

Each Report Card includes a summary of the company's strengths and weaknesses, and drivers behind its performance. The report cards are divided into six sections:

Performance

Explains the company's 2020 performance, including the drivers behind any movement, and the main areas where it scores well or poorly compared to peers.

Opportunities

Sets out tailored opportunities for the company to do more to ensure access and address AMR, taking account of its R&D pipeline, product portfolio, and other factors.

Changes since 2018

Highlights the most notable changes in the company's performance since 2018, including a selection of new or expanded activities and programmes.

Sales and operations

Summarises the company's global operations, revenue per product and region, including mergers and acquisitions relevant to antibacterial and anti-fungal products.

Pipeline and portfolio

General description of the company's operations, recent mergers & acquisitions, revenue per region and geographical reach.

Performance by Research Area

Details the company's performance in each of the three areas measured by the Benchmark: R&D, Responsible Manufacturing and Appropriate Access & Stewardship.

.

Abbott Laboratories

Generic medicine manufacturer

Stock exchange: NYSE • Ticker: ABT • HQ: Illinois, USA • Employees: 103,000

PERFORMANCE

Abbott performs above average overall in its evaluated Research Areas compared to other generic medicine manufacturers in scope.

Responsible Manufacturing: Performs strongly. Reports comprehensive environmental risk management strategy, including ongoing risk assessments using discharge limits at own sites; suppliers are covered but degree of implementation is lower.

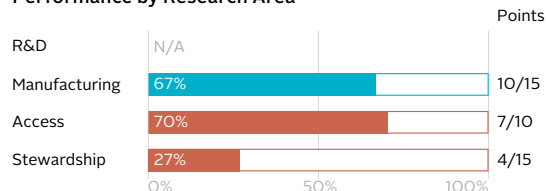
Appropriate Access: Performs well. Files for registration for all relevant off-patent products in access countries. Reports some information on the basis of confidentiality on its strategies for pricing and ensuring continuous supply.

Stewardship: Performs less well. It has educational programmes with broad conflict of interest (COI) mitigation. It has no marketing or sales practices that aim to address appropriate use and it does not adapt its brochures or packaging.

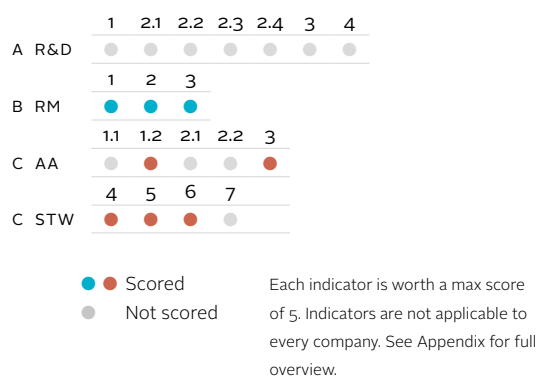
Performance in the Benchmark



Performance by Research Area



How Abbott was evaluated



SALES AND OPERATIONS

Therapeutic areas: Cardiovascular diseases; Gastroenterology; Metabolic disorders; Women's health; Pain and movement disorders

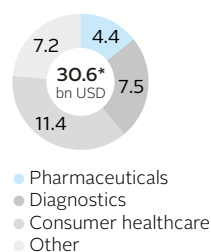
Business segments: Pharmaceutical Products; Diagnostic Products; Nutritional Products; Cardiovascular; Neuromodulation Products

Product categories: Diagnostics; Generic medicines; Medical devices; Nutritional; Vaccines

Manufacturing & supply: No information available

M&A since 2018: None in the antibacterial and/or antifungal sectors

Revenues by product (2018)



Revenues by region (2018)



* Segments do not add up to 30.6 bn USD due to rounding.

PORTFOLIO for diseases in scope

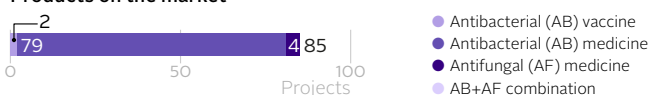
Mid-sized portfolio: At least 85 products (51 unique INNs): 79 antibacterial medicines; 2 antibacterial vaccines; 4 antifungal medicines

Essential medicines: 41% (35) of products are on the 2019 WHO EML

AWaRe medicines*: 12 Access group; 10 Watch group; 1 Reserve Group

Anti-TB medicines*: 7 (incl. 2 Watch group, 2 Reserve group)

Products on the market



The number of products is based on data from public sources, IQVIA, and data submitted by the company. It may not account for Abbott's entire portfolio.

* Listed on the 2019 WHO EML (Section 6).

OPPORTUNITIES FOR ABBOTT

Expand registration and ensure adequate supply of antibacterial medicines to access countries. Abbott can file for registration and ensure adequate supply of antibacterial medicines on the 2019 WHO EML within its current portfolio (e.g. the forgotten antibiotics sulfamethoxazole/ trimethoprim, chloramphenicol and colistin) in more access countries.

Expand its environmental risk-management strategy to suppliers and waste-treatment plants. Abbott currently has a comprehensive environmental risk-management strategy, including auditing processes and discharge limits for the majority of antibacterials manufactured at its own sites. The company can ensure that such limits cover all antibacterials manufactured at its own sites and, along with the strategy, are implemented at the sites of third-party suppliers and external private waste-treatment plants, including any relevant discharge-monitoring processes.

Decouple sales incentives from sales volumes and/or avoid deploying sales agents. In order to mitigate the risk of inappropriate use of its antibacterial and/or antifungal medicines, Abbott can decouple sales incentives from sales volumes and/or avoid deploying sales agents, as appropriate.

Adapt brochures and packaging. In order to support the appropriate use of its antibacterial and/or antifungal medicines by all patients, Abbott can make brochure and/or packaging adaptations that take account of language, literacy, paediatric use, adherence to treatment and the environment.

CHANGES SINCE 2018

This section lists notable changes in companies' activities since the 2018 Benchmark. Since Abbott was not in scope for evaluation in 2018, no changes are reported.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer (GMM), Abbott is not evaluated in this Research Area.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Comprehensive environmental risk-management; less information on discharge limits for own sites and suppliers

Abbott reports a comprehensive strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites. This includes audits typically every three years. The company reports setting discharge limits for the majority of antibacterials manufactured at its sites based on PNECs to limit AMR (or more stringent PNECs), as published by the AMR Industry Alliance. For the antibacterials for which effluent analytical methods or PNECs are not published, it reports requiring sites to work towards developing them. Abbott reports using a combination of mass balance estimation and analytical testing to assess whether discharge levels meet these limits.

Abbott expects third-party suppliers of antibacterial APIs and drug products to follow the company's supplier guidelines, including minimisation of water and waste impacts. The company has developed audit programmes specifically for suppliers of APIs, including antibacterial APIs, and surveys high-risk suppliers on their waste management practices. It expects external private waste treatment plants to comply with its environmental standards and guidelines. The company reports auditing these plants at least every five years but does not report whether it requires the wastewater plants to set antibacterial discharge limits.

B.2 Publicly discloses some information on environmental risk management

Abbott publishes some components of its environmental risk-management strategy. It does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private waste-treatment plants; (2) a list of these suppliers and waste-treatment plants; or (3) the levels of nor limits for antibacterial discharge from its own sites.

B.3 Has system to maintain production quality for own and suppliers' sites; no requests for official corrective action

Abbott reports having a system to maintain high-quality antibacterial production, consistent with international GMP standards. This includes periodic internal audits and protocols in place for handling corrective and preventive actions. The company reports requiring suppliers to abide by regulatory and company quality standards. This includes submitting suppliers to a qualification process, after which a quality agreement is established and periodic re-evaluations are conducted to assess compliance. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Abbott's own sites or any subsidiaries.**

** Including only wholly-owned direct subsidiaries of the company. More information in Appendix I.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries***

C.1.1 Registering on-patent products

Abbott was not eligible for this indicator, as it does not have on-patent antibacterial or antifungal medicines or vaccines in its portfolio.

C.1.2 Filed to register relevant off-patent products† in 8.6 access countries on average

Abbott is a leading company among generic medicine manufacturers when it comes to filing its relevant off-patent products for registration. It reports filing all of its relevant products (11/11 antibacterial and antifungal medicines) for registration in several access countries. Its most widely filed product in this analysis is the antibacterial medicine clarithromycin, used to treat conditions such as pneumonia, and skin and ear infections. Abbott has filed its version of this product in 60 access countries. Further details were provided on the basis of confidentiality.

C.2.1 Pricing strategies for on-patent products

Abbott was not eligible for this indicator, as it does not have on-patent antibacterial or antifungal medicines or vaccines in its portfolio.

C.2.2 Pricing strategies for off-patent products

Companies were not scored for this indicator as the available data was insufficient for a comparative analysis. Abbott does report some pricing strategies, but further details were provided on the basis of confidentiality.

C.3 Some strategies to ensure the continuous supply of relevant products

Abbott is a middle-performing company, compared to other generic medicine manufacturers evaluated, when it comes to taking steps to ensure the continuous supply of its antibacterial or antifungal medicines or vaccines. It has forecasting processes in place to share API and

and drug supply requirements with suppliers. Shortage mitigation is addressed by targeting at least two sources and by keeping buffer stocks of critical ingredients. To secure the supply of critical ingredients, Abbott states that it is working toward agile relationships with its suppliers, to enable global sourcing and more insight into local opportunities. Abbott keeps a buffer stock of critical ingredients and targets from at least two sources when in need of critical ingredients. To reduce the introduction of falsified medicines into the supply chain, Abbott employs several strategies, such as making use of security features; using an advanced program to detect and delete illicit internet sales; and working with law enforcement to disrupt criminal organisations.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Broad strategy to mitigate COI for most educational programmes

The Benchmark analysed four AMR-related educational programmes for healthcare professionals (HCPs) from Abbott. Abbott reports broad COI mitigation strategies for three of four programmes. Further details were provided on the basis of confidentiality. However, for the remaining programme, it is unclear how the company mitigates COI. After the period of analysis, the company reported that it has policies in place to mitigate COI for all its educational events, which ensure independence of presentations by HCPs and prohibit compensating attendees for time spent at an Abbott-organized educational meeting.

C.5 Reports no marketing or sales practices that aim to address appropriate use

Abbott does not report engaging in practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines, either regarding its marketing materials or its sales practices.

C.6 Does not adapt brochures and/or packaging to facilitate appropriate use

Abbott does not provide evidence of adapting its brochures and/or packaging to facilitate appropriate use of its antibacterial and/or antifungal medicines by patients beyond regulatory requirements.

C.7 Antimicrobial surveillance

As a GMM, Abbott is not eligible for this indicator as GMMs have a limited role in AMR surveillance activities. The Benchmark notes that Abbott is active in CANWARD, a long-term AMR surveillance programme. This is a national programme that is managed by the Canadian Antimicrobial Resistance Alliance with support from Abbott, among others. Its results are shared through an open-access database on its website and in peer-reviewed open-access journal articles.

DIAGNOSTICS, ANIMAL HEALTH & AGRICULTURE

Activities in this area are not scored by the Benchmark. This information is provided given the importance of diagnostics, animal health and agriculture on the topic of AMR.

Abbott has its own diagnostic division and offers products including: (1) Alere™ PBP2a SA Culture Colony Test for the rapid detection of Methicillin-resistant *S. aureus* (MRSA) directly from bacterial isolates in five minutes; (2) Afinion™ CRP test for the quantitative determination of C-reactive protein to differentiate bacterial from viral respiratory tract infections; (3) ID NOW™ Influenza A & B 2 test to diagnose the flu caused by a viral infection. Abbott also provides healthcare professionals with diagnostic information through their Test Target Treat™ website.

*** 102 low- and middle-income countries where better access to medicine is most needed. See Appendix VI.

† See Appendix VII.

Achaogen Inc

Small/medium-sized enterprise

Stock exchange: NASDAQ • Ticker: AKAO • HQ: California, USA • Employees: 42

PERFORMANCE

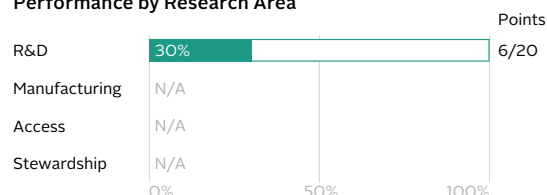
Achaogen performs less than average in Research & Development when compared to other small and medium-sized enterprises in scope.

R&D: Achaogen had four antibacterial projects for priority pathogens in its pipeline. Granted regulatory approval in 2018 for plazomicin, which targets a critical and/or urgent priority pathogen.

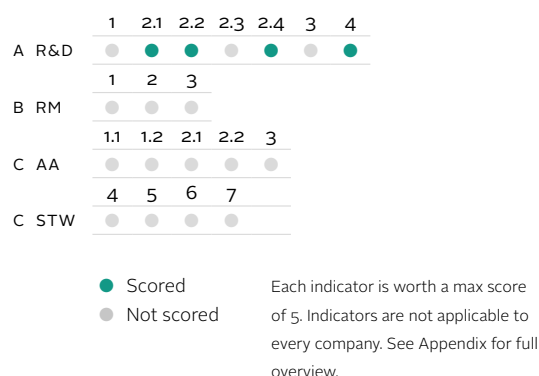
Performance in the Benchmark



Performance by Research Area



How Achaogen was evaluated



SALES AND OPERATIONS *Filed for bankruptcy in April 2019*

Therapeutic areas: Multidrug-resistant (MDR) Gram-negative bacterial infections

Products on the market: 1, plazomicin (Zemdri™) approved in June 2018 for cUTI

R&D grants received since 2016: At least USD 30 million, awarded by four funders (BARDA; Bill & Melinda Gates Foundation; CARB-X; NIAID). Its latest award, from CARB-X, worth USD 4 million with the possibility of a USD 9.6 million extension, was granted in April 2018 to support its early-stage aminoglycoside programme developing antibiotics for difficult to treat infections that are associated with high mortality.

Financing and investment structure: Achaogen was a publicly listed company. It completed its IPO in March 2014, raising USD 72 million, following four funding series raising a total of USD 116.6 million. The company's lead investor was Domain Associates. Its post IPO equity amounted to USD 35.4 million.

M&A since 2018: Achaogen filed for bankruptcy in April 2019 and all assets were sold for USD 16 million.

Revenues

(2018)



PIPELINE *for diseases in scope*

Pipeline size: 4 projects for priority pathogens* (4 antibacterial medicines)

Development stages: 2 clinical projects, before filing for bankruptcy, including plazomicin for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia and complicated intra-abdominal infections, and ceftibuten/clavulanate for the treatment of complicated urinary tract infections, and 1 pre-clinical project

Novelty: No novel clinical-stage medicine projects

Regulatory approvals: 1, for plazomicin (Zemdri™) for the treatment of complicated urinary tract infections including acute pyelonephritis in patients 18 years of age and older.

Access plans: Neither of its 2 late-stage R&D projects have project-specific access plans.

Stewardship plans: Neither of its 2 late-stage R&D medicine projects have project-specific stewardship plans.

Pipeline for priority pathogens



All companies were assessed based on data available in the public domain, including information the companies have made publicly available. This was supplemented by data submitted directly to the Benchmark by the companies. Achaogen declined to submit data to the 2020 AMR Benchmark.

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

OPPORTUNITIES FOR ACHAOGEN

No opportunities are provided for Achaogen because it filed for bankruptcy in April 2019.

CHANGES SINCE 2018

- Filed for bankruptcy in April 2019.
- Publicly shared data on the discontinued LpxC inhibitor antibiotic research programme on the SPARK open-access platform in October 2018.
- Sold by auction the worldwide rights (excl. China) for plazomicin (Zemdri™) to Cipla USA and the rights for China to QiLu Antibiotics Pharmaceutical.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 R&D investments

Achaogen invested USD 198.6 million in the development of antibacterial medicines in 2017 and 2018. Achaogen filed for bankruptcy during the Benchmark's period of analysis. As with all other small and medium-sized enterprises (SMEs) evaluated, Achaogen was not scored in this indicator.

A.2.1 Pipeline size of four projects

Achaogen reports four projects targeting priority pathogens in its pipeline, all of which targeted bacterial pathogens. Two of its four projects were in clinical development, and one project, plazomicin (Zemdri™) received market approval within the period of analysis. The fourth project was in pre-clinical development.

A.2.2 No clinical-stage novel projects

Achaogen's clinical-stage medicine pipeline for priority pathogens consisted of both adapted and new R&D projects. It did not include candidates that were considered novel. Before filing

for bankruptcy, Achaogen was developing one new, non-novel project: a fixed-dose combination of ceftibuten/clavulanate for the treatment of complicated urinary tract infections.

A.2.3 Vaccines in the pipeline

Achaogen is not eligible for this indicator as it is not active in vaccine development.

A.2.4 One candidate targeting critical and/or urgent priorities

Achaogen gained approval for its antibacterial medicine plazomicin (Zemdri™), which targets CRE, in June 2018. The company was also developing an adaptation of this product, in Phase III, which also targeted Carbapenem-resistant *Enterobacteriaceae* (CRE). CRE has been identified as a 'critical' R&D priority for limiting AMR by WHO and as an 'urgent' priority by the US Centers for Disease Control and Prevention (CDC).

A.3 Intellectual capital sharing

Achaogen reported one intellectual capital sharing initiative. It shares data from its discontinued LpxC inhibitor antibiotic research programme on the Pew Charitable Trusts' open-access Shared Platform for Antibiotic Research and Knowledge (SPARK). The data will provide other scientists with valuable information about potential drug targets. As an SME, Achaogen was not scored for this indicator, in line with the external stakeholder consensus defined by the Foundation.

A.4 No access or stewardship plans for late-stage R&D projects targeting priority pathogens

Achaogen had two late-stage R&D projects targeting priority pathogens, for two different indications for plazomicin (Zemdri™). It obtained FDA approval for one, for the treatment of complicated urinary tract infections. The company did not report plans that addressed either the stewardship of or appropriate access to the product.

Pipeline targeting priority pathogens: 4 As at 16 October 2019

| Discovery | Pre-clinical | Phase I | Phase II | Phase III | Approval |
|---|--|---|----------|--|---|
| | Monoclonal antibody programme - GNB (including <i>A. baumannii</i>) | Ceftibuten/clavulanate (C-Scape) - ESBL-producing <i>Enterobacteriaceae</i> - Adaptation (new FDC of an approved beta-lactam and beta-lactamase inhibitor) - cUTI | | Plazomicin (Zemdri™) - <i>Enterobacteriaceae</i> (CRE) - Adaptation (additional indications) - cIAI, HABP and VABP | Plazomicin (Zemdri™) - <i>Enterobacteriaceae</i> (CRE and ESBL-producing <i>Enterobacteriaceae</i>) - cUTI, including acute pyelonephritis - FDA approval 2018 |
| cIAI = Complicated intra-abdominal infection CRE = Carbapenem-resistant <i>Enterobacteriaceae</i> cUTI = Complicated urinary tract infection ESBL = Extended-spectrum beta-lactamase FDC = Fixed-dose combination GNB = Gram-negative bacteria HABP = Hospital-acquired bacterial pneumonia VABP = Ventilator-associated bacterial pneumonia | | | | | |

B RESPONSIBLE MANUFACTURING

As an SME, Achaogen is not evaluated in this Research Area. It has one antibacterial product on the market: plazomicin (Zemdri™).

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

C APPROPRIATE ACCESS & STEWARDSHIP

As an SME, Achaogen is not evaluated in this Research Area. It has one antibacterial and/or antifungal product on the market: the antibacterial plazomicin (Zemdri™). The Benchmark notes that Achaogen is active in two long-term AMR surveillance programmes, and that it openly publishes its results. Achaogen was not scored on these activities.

The two programmes are CANWARD and SENTRY. CANWARD is a national programme that is focused on pathogens isolated in Canadian hospitals. It is managed by the Canadian Antimicrobial Resistance Alliance with support from Achaogen, among other companies. Its results are shared in peer-reviewed open-access journal articles. The SENTRY programme is multinational and is managed by JMI laboratories with support from Achaogen, among other companies. Its results are shared in

an open-access data platform.

DIAGNOSTICS, ANIMAL HEALTH & AGRICULTURE

Activities in this area are not scored by the Benchmark. This information is provided given the importance of diagnostics, animal health and agriculture on the topic of AMR.

Prior to filing for bankruptcy, Achaogen, in partnership with Thermo Fisher Scientific, received FDA clearance for its QMS Plazomicin Immunoassay in late 2018. This diagnostic tool measures the levels of plazomicin in blood, in order to enable safe and effective individual treatment dosing.

Alkem Laboratories Ltd

Generic medicine manufacturer

Stock exchange: NSE • Ticker: ALKEM • HQ: Mumbai, India • Employees: 14,115

PERFORMANCE

Alkem performs less well overall in all its evaluated Research Areas when compared to other generic medicine manufacturers in scope.

Responsible Manufacturing: Performs less well. Reports a general environmental risk-management strategy for own sites without the specific aim to limit AMR.

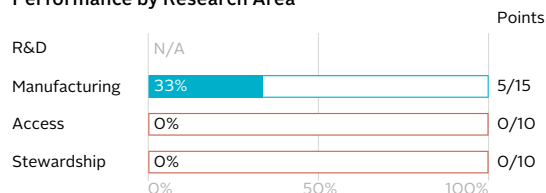
Appropriate Access: Performs low. No information is disclosed on where products are registered. No information is reported on its strategies for pricing and ensuring continuous supply.

Stewardship: Performs low. It has no marketing or sales practices that aim to address appropriate use and it does not adapt its brochures or packaging.

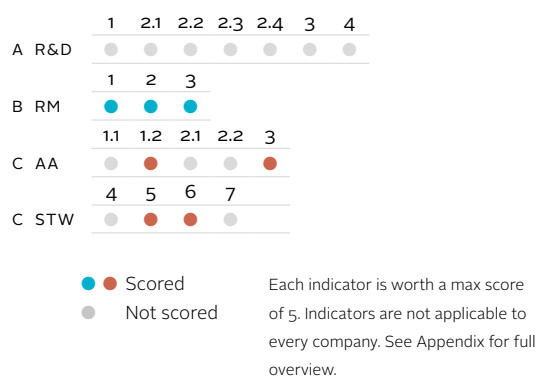
Performance in the Benchmark



Performance by Research Area



How Alkem was evaluated



SALES AND OPERATIONS

Therapeutic areas: Dermatology; Gastroenterology; Infectious diseases; Pain management

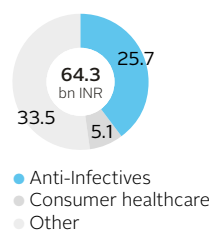
Business segments: Pharmaceuticals

Product categories: Generic medicines

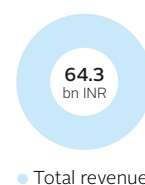
Manufacturing & supply: No information available

M&A since 2018: None in the antibacterial and/or antifungal sectors

Revenues by product (2017-18)



Revenues by region (2017-18)



PORTFOLIO for diseases in scope

Mid-sized portfolio: At least 92 products (51 unique INNs): 89 antibacterial medicines; 3 antifungal medicines

Essential medicines: 28% (26) of products are on the 2019 WHO EML

AWaRe medicines*: 8 Access group; 13 Watch group

Anti-TB medicines*: 4 (incl. 2 Watch group; 2 Reserve group)

Products on the market



All companies were assessed based on data available in the public domain, including information the companies have made publicly available. This was supplemented by data submitted directly to the Benchmark by the companies. Alkem declined to submit data to the 2020 AMR Benchmark.

* Listed on the 2019 WHO EML (Section 6).

OPPORTUNITIES FOR ALKEM

Step up engagement on AMR and increase disclosure of AMR strategies and activities. Alkem is one of the generic medicine manufacturers with the largest portfolio of antibacterial and/or antifungal medicines, including 26 products on the 2019 WHO EML. Alkem can disclose more information (publicly and/or through the Benchmark) about its strategies to improve access and stewardship to the medicines within its portfolio, including their availability in access countries and its steps to mitigate the risk of inappropriate use.

Develop an AMR-specific environmental risk-management strategy. Alkem reports a commitment to manufacture its products in an environmentally responsible manner and a management system to ensure environmental regulations are met. Yet, it is unclear whether AMR is specifically taken into account. The company can develop a strategy that takes AMR into account, including discharge limits based on PNECs to limit AMR (or more stringent) at the company's own manufacturing sites, the sites of third-party suppliers and external private waste-treatment plants. The AMR Industry Alliance has developed a Common Antibiotic Manufacturing Framework and list of discharge limits that could serve as a starting point for such endeavour.

Decouple sales incentives from sales volumes and/or avoid deploying sales agents. In order to mitigate the risk of inappropriate use of its antibacterial and/or antifungal medicines, Alkem can decouple sales incentives from sales volumes and/or avoid deploying sales agents, as appropriate.

CHANGES SINCE 2018

This section lists notable changes in companies' activities since the 2018 Benchmark. Since Alkem was not in scope for evaluation in 2018, no changes are reported.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer (GMM), Alkem is not evaluated in this Research Area.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 General environmental risk-management strategy for own sites

Alkem reports a commitment to manufacture its products in an environmentally responsible manner, supported by a management system that includes periodic impact assessments. It is unclear how the strategy takes AMR into account or aims to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its own sites, third-party suppliers of antibacterial APIs and/or drug products or external private waste-treatment plants.

B.2 Limited publicly available information on environmental risk management

Alkem publishes limited information on its approach to environmental risk management, without specific references to antimicrobial resistance. It does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private waste-treatment plants; (2) a list of these suppliers and waste-treatment plants; or (3) the levels of nor limits for antibacterial discharge from its own sites.

B.3 Has system to maintain production quality for own and suppliers' sites; regulator requested official corrective action

Alkem reports having a system to maintain

high-quality antibacterial production, consistent with international GMP standards, including periodic internal audits. In February 2019, an FDA drug quality inspection identified non-conformities with cGMP at an S&B Pharma site (an Alkem subsidiary), resulting in an official request for corrective action. It is unclear whether the site produces antibacterials. This suggests potential risks regarding how the system is being implemented at sites producing antibacterials. The company reports requiring suppliers to abide by regulatory and company quality standards. This includes submitting suppliers to a qualification process and periodic audits for re-qualification. It reports engaging with suppliers to implement corrective and preventive actions.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries**

C.1.1 Registering on-patent products

Alkem was not eligible for this indicator as it does not have on-patent antibacterial or antifungal medicines or vaccines in its portfolio.

C.2.1 Pricing strategies for on-patent products

Alkem was not eligible for this indicator, as it does not have on-patent antibacterial or antifungal medicines or vaccines in its portfolio.

C.3 No information on measures to ensure continuous supply of relevant products

Alkem discloses no information on how it takes steps to ensure the continuous supply of antibacterial or antifungal medicines or vaccines to access countries.

C.1.2 No information on registration filings for relevant off-patent products***

Alkem reports no evidence of filing relevant off-patent products for registration in access countries. However, there is evidence of sales in at least one access country.

C.2.2 Pricing strategies for off-patent products

Companies were not scored for this indicator as the available data was insufficient for a comparative analysis. There is no available evidence that Alkem considers affordability or socioeconomic factors when setting prices for off-patent antibacterial or antifungal medicines or vaccines.

** 102 low- and middle-income countries where better access to medicine is most needed. See Appendix VI.

*** See Appendix VII.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Educational stewardship activities

Alkem is not eligible for this indicator as there is no information regarding its involvement in AMR-related educational programmes aimed at healthcare professionals (HCPs).

C.5 No information on marketing or sales practices that aim to address appropriate use

There is no information regarding Alkem's engagement in practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines, either regarding its marketing materials or its sales practices.

C.6 No information on brochure and/or packaging adaptations to facilitate appropriate use

There is no information regarding Alkem's adaptations in its brochures and/or packaging to facilitate the appropriate use of its antibacterial and/or antifungal medicines by patients beyond regulatory requirements.

C.7 Antimicrobial surveillance

As a GMM, Alkem is not eligible for this indicator as GMMs have a limited role in AMR surveillance activities.

Amplix Pharmaceuticals Inc

Small/medium-sized enterprise

Stock exchange: Privately held • Ticker: N/A • HQ: California, USA • Employees: 27

PERFORMANCE

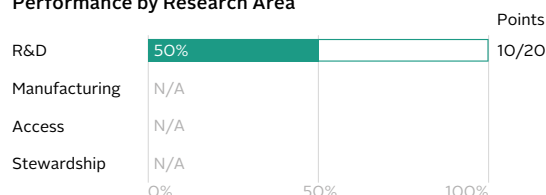
Amplix performs on average in Research & Development when compared to other small and medium-sized enterprises in scope.

R&D: Amplix has one novel project in its clinical pipeline for treatment of invasive antifungal infections, fosmanogepix. Reports a project-specific access plan for an Expanded Access Program for this late-stage project.

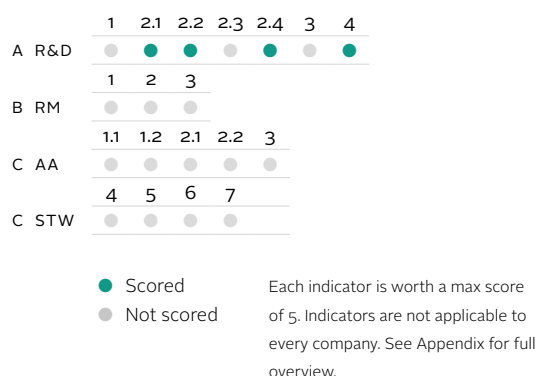
Performance in the Benchmark



Performance by Research Area



How Amplix was evaluated



SALES AND OPERATIONS

Therapeutic areas: Invasive fungal infections

Products on the market: None

R&D grants received since 2016: At least USD 4.4 million, awarded from one funder (NIH) to support its drug discovery and development efforts.

Financing and investment structure: Amplix is a privately held company. Following three funding series, it has raised a total of USD 118.5 million. Its lead investors were RiverVest and New Enterprise Associates.

M&A since 2018: None in the antibacterial and/or antifungal sectors

Revenues

(2018)



PIPELINE for diseases in scope

Pipeline size: 1 project for priority pathogens* (1 antifungal medicine)

Development stages: 1 clinical project, fosmanogepix (APX001), a Phase II clinical candidate for the treatment of invasive fungal infections including invasive candidiasis and invasive aspergillosis

Novelty: 1 novel project, fosmanogepix (APX001), a Phase II clinical candidate for the treatment of invasive fungal infections including invasive candidiasis and invasive aspergillosis, that belongs to a new chemical class of antifungals and has a new drug target, mode of action and no known cross-resistance to other antifungal classes

Regulatory approvals: 0 approvals for priority pathogens

Access plans: Its 1 late-stage R&D project has a project-specific access plan

Stewardship plans: Its 1 late-stage R&D medicine project lacks a project-specific stewardship plan.

Pipeline for priority pathogens



- Antibacterial (AB) vaccine
- Antibacterial (AB) medicine
- Antifungal (AF) medicine
- AB+AF combination

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

OPPORTUNITIES FOR AMPLYX

Operationalise access and stewardship plans for fosmanogepix. Amplyx is developing one antifungal candidate (fosmanogepix) in late-stage clinical development. Amplyx can develop more detailed plans to ensure that fosmanogepix will be available and affordable in low- and middle-income countries and appropriately used globally after market approval. As examples of access plans, the company can commit to an equitable pricing strategy and/or look for out-licensing opportunities with multiple manufacturers in low- and middle-income countries. As examples of stewardship plans, the company can commit to developing companion diagnostics and susceptibility testing devices and/or become involved in antifungal surveillance activities.

CHANGES SINCE 2018

This section lists notable changes in companies' activities since the 2018 Benchmark. Since Amplyx was not in scope for evaluation in 2018, no changes are reported.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 R&D investments

As with all other small and medium-sized enterprises (SMEs) evaluated, Amplyx was not scored in this indicator.

A.2.1 Pipeline size of one project

Amplyx reports one project targeting a priority pathogen. The company is focused on antifungal medicine development, and its project fosmanogepix (APX001) is currently in Phase II of clinical development.

A.2.2 One clinical-stage novel project

Amplyx's clinical-stage medicine pipeline for priority pathogens consists of one new R&D project. Amplyx has one clinical-stage antifungal medicine project that is considered novel: fosmanogepix (APX001), for the treatment of invasive candidiasis, invasive aspergillosis and invasive rare mould infections, which belongs to a new chemical class and has a new target and mode of action and no known cross-resistance to existing classes of antifungals.

A.2.3 Vaccines in the pipeline

Amplyx is not eligible for this indicator as it is not active in vaccine development.

A.2.4 One candidate targeting critical and/or urgent priorities

Amplyx's clinical pipeline includes one new, novel candidate (APX001) in Phase II that targets multi-drug resistant *C. auris*, which is listed since November 2019 as an urgent pathogen by the US Centers for Disease Control and Prevention (CDC).

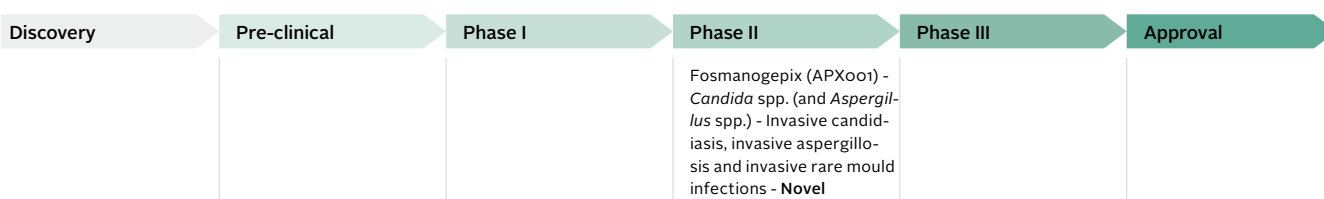
A.3 Intellectual capital sharing

Amplyx reports one intellectual capital sharing initiative: it has shared some of its projects for in-vitro testing with different researchers and institutions such as the CDC. As an SME, Amplyx was not scored for this indicator, in line with the external stakeholder consensus defined by the Foundation.

A.4 Specific access plan for one project

Amplyx has one late-stage R&D project targeting a priority pathogen: fosmanogepix (APX001) for *Candida* spp. and *Aspergillus* spp. Amplyx is developing its Expanded Access Program as a mechanism to provide access to investigational therapies for clinical trial participants. It intends to follow the 2016 Davos Declaration, and has made a general commitment to help ensure the appropriate access and stewardship of this project.

Pipeline targeting priority pathogens: 1 As at 16 October 2019



B RESPONSIBLE MANUFACTURING

As an SME, Amplyx is not evaluated in this Research Area. It has no antibacterial products on the market.

C APPROPRIATE ACCESS & STEWARDSHIP

As an SME, Amplyx is not evaluated in this Research Area. It has no antibacterial and/or antifungal products on the market.

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

Aurobindo Pharma Ltd

Generic medicine manufacturer

Stock exchange: NSE • Ticker: AUOPHARMA • HQ: Hyderabad, India • Employees: 17,855

PERFORMANCE

Aurobindo performs average overall in its evaluated Research Areas compared to other generic medicine manufacturers in scope.

Responsible Manufacturing: Middle-performing. Reports an environmental risk-management strategy for own sites, including initiation of risk assessments based on discharge limits. Limited information available on how the strategy applies for suppliers.

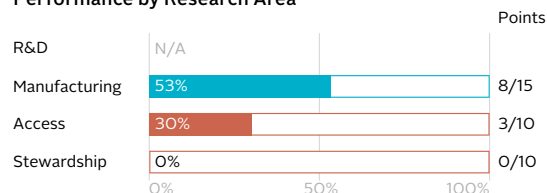
Appropriate Access: Middle-performing. Files for registration for over half of relevant off-patent products in access countries. Supplies forgotten antibiotics to several access countries.

Stewardship: Performs low. It has no marketing or sales practices that aim to address appropriate use and it does not adapt its brochures or packaging.

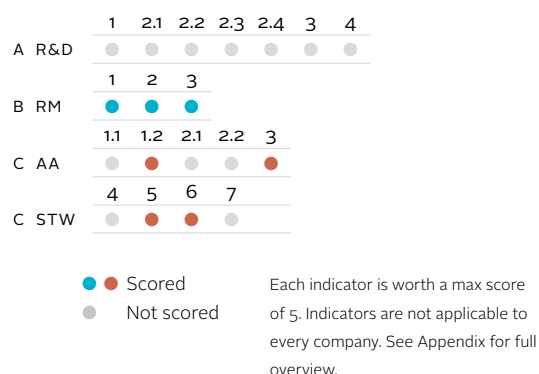
Performance in the Benchmark



Performance by Research Area



How Aurobindo was evaluated



SALES AND OPERATIONS

Therapeutic areas: Gastroenterology; Infectious diseases; Neurology

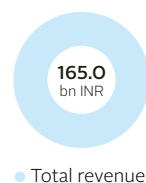
Business segments: Pharmaceuticals (including APIs and formulations)

Product categories: Generic medicines; Vaccines

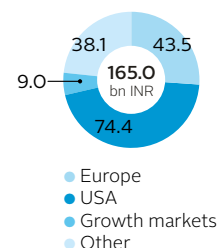
Manufacturing & supply: Aurobindo reports having 18 manufacturing sites that produce antibacterial APIs and/or drug products. It supplies its antibacterial medicines, antibacterial vaccines and antifungal medicines across more than 150 countries.

M&A since 2018: In September 2018, Aurobindo announced that it would acquire the dermatology and oral-solids businesses from Novartis' generic division, Sandoz, for USD 900 million. Earlier that year, Aurobindo signed a definitive agreement in July to acquire Apotex's businesses in Belgium, Czech Republic, the Netherlands, Poland and Spain for more than USD 80 million.

Revenues by product (2017-18)



Revenues by region (2017-18)



PORTFOLIO for diseases in scope

Mid-sized portfolio: At least 43 products (30 unique INNs): 37 antibacterial medicines; 1 antibacterial vaccine; 5 antifungal medicines

Essential medicines: 68% (29) of products are on the 2019 WHO EML

AWaRe medicines*: 12 Access group; 5 Watch group; 1 Reserve group

Anti-TB medicines*: 5 (incl. 1 Watch group, 2 Reserve group)

Products on the market



The number of products is based on data from public sources, IQVIA, and data submitted by the company. It may not account for Aurobindo's entire portfolio.

* Listed on the 2019 WHO EML (Section 6).

OPPORTUNITIES FOR AUROBINDO

Expand registration and ensure adequate supply of antibacterial medicines in more access countries. Aurobindo can file for registration and ensure adequate supply of antibacterial medicines on the 2019 WHO EML within its current portfolio (e.g. the forgotten antibiotics colistin, phenoxymethylpenicillin and sulfamethoxazole/trimethoprim) in more access countries.

Implement and monitor its environmental risk-management strategy, including discharge limits, at its own manufacturing sites, at third-party suppliers and at external private waste-treatment plants. Aurobindo currently has an environmental risk-management strategy and auditing processes for its own manufacturing sites and has started implementing discharge limits. The company can ensure such limits cover all antibacterials manufactured at its own sites and, along with the strategy, extend fully to the sites of third-party suppliers and external private waste-treatment plants. It can also ensure any relevant auditing and discharge-monitoring processes are in place.

Decouple sales incentives from sales volumes and/or avoid deploying sales agents. In order to mitigate the risk of inappropriate use of its antibacterial and/or antifungal medicines, Aurobindo can decouple sales incentives from sales volumes and/or avoid deploying sales agents, as appropriate.

CHANGES SINCE 2018

- Joined the AMR Industry Alliance and began data collection on antibacterial discharge from its sites for comparison with the predicted no-effect concentrations (PNECs) published by the Alliance.
- Received market authorization for its antifungal product terbinafine in March 2019 in Tanzania.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer (GMM), Aurobindo is not evaluated in this Research Area.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Environmental risk-management strategy for own sites

Aurobindo reports a strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, which includes audits. It reports being in the process of implementing adaptations to this strategy that take AMR into account. This includes setting antibacterial discharge limits based on PNECs to limit AMR (or more stringent PNECs), as published by the AMR Industry Alliance. It will use these limits in a future risk assessment of its sites with respect to AMR. For a subset of its antibacterials (beta-lactams and cephalosporins), Aurobindo already employs a deactivation procedure to ensure that antibacterial levels in wastewaters are below these limits.

There is limited information on the requirements that Aurobindo makes of third-party suppliers of antibacterial APIs and/or drug products in terms of environmental strategy, audits and antibacterial discharge limits. The company reports that suppliers' environmental performance is assessed but it is unclear whether this currently takes AMR into account. After the period of analysis, the company reported having conveyed the expectations of the AMR Industry Alliance manufacturing framework to its suppliers. Aurobindo reports procuring around 25% of its antibacterial API volume from third-party suppliers, and no antibacterial drug product. There is limited information on the requirements the company makes of external private waste-treatment plants in terms of environmental strategy, audits and antibacterial discharge limits.

B.2 Publicly discloses some information on environmental risk management

Aurobindo publishes some components of its environmental risk-management strategy. Further, it is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. Aurobindo does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private waste-treatment plants; (2) a list of these suppliers and waste-treatment plants; or (3) the levels of antibacterial discharge from its own sites.

B.3 Has system to maintain production quality for own and suppliers' sites; regulator requested official corrective action

Aurobindo reports having a system to maintain high-quality antibacterial production, consistent with international GMP standards, including protocols to track corrective and preventive actions. In February 2019, an FDA drug quality inspection identified non-conformities with cGMP at three of the company's antibacterial API sites, resulting in an official request for corrective action. The company reports requiring suppliers to abide by regulatory and company quality standards. This includes submitting suppliers to a qualification process and periodic audits.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries**

C.1.1 Registering on-patent products

Aurobindo was not eligible for this indicator as it does not have on-patent antibacterial or antifungal medicines or vaccines in its portfolio.

C.1.2 Filed to register relevant off-patent products*** in 5.3 access countries on average

Aurobindo is a middle-performing company when it comes to filing relevant off-patent products for registration. It has filed 67% of its relevant products (6/9 antibacterial and antifungal medicines) for registration in access countries. Its most widely filed product in this analysis is the antibacterial cefepime, used for conditions including pneumonia and urinary tract infections. Aurobindo has filed its version of this product in

30 access countries. Cefepime is followed by the antifungal terbinafine and antibacterial clarithromycin, filed by Aurobindo for registration in eight and five access countries, respectively.

C.2.1 Pricing strategies for on-patent products Aurobindo was not eligible for this indicator, as it does not have on-patent antibacterial or antifungal medicines or vaccines in its portfolio.

C.2.2 Pricing strategies for off-patent products Companies were not scored for this indicator as the available data was insufficient for a comparative analysis. Aurobindo does report that it participates in tendering in the EU and that its product prices are based on market-driven competitive prices.

C.3 Limited information on measures to ensure continuous supply of relevant products

Aurobindo discloses limited information on how it takes steps to ensure the continuous supply of antibacterial or antifungal medicines or vaccines to access countries. It does report supplying the forgotten antibiotics† cefepime, cefpodoxime, phenoxymethylpenicillin and sulfamethoxazole/trimethoprim to several access countries.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Educational stewardship activities

Aurobindo is not eligible for this indicator as it reports no involvement in AMR-related educational programmes aimed at healthcare professionals (HCPs). After the period of analysis, the company stated that it has been involved in several educational programmes for HCPs.

C.5 Reports no marketing or sales practices that aim to address appropriate use

Aurobindo does not report engaging in practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines, either regarding its marketing materials or its sales practices.

C.6 Does not adapt brochures and/or packaging to facilitate appropriate use

Aurobindo does not provide evidence of adapting its brochures and/or packaging to facilitate appropriate use of its antibacterial and/or antifungal medicines by patients beyond regulatory requirements.

C.7 Antimicrobial surveillance

As a GMM, Aurobindo is not eligible for this indicator as GMMs have a limited role in AMR surveillance activities.

** 102 low- and middle-income countries where better access to medicine is most needed. See Appendix VI.

*** See Appendix VII.

† A set of older off-patent antibacterials that are not always marketed or available, due to economic reasons, lack of

awareness and lack of demand but are still considered effective as a treatment for bacterial infections. See Appendix VII for citation.

Cidara Therapeutics

Small/medium-sized enterprise

Stock exchange: NASDAQ • Ticker: CDTX • HQ: California, USA • Employees: 68

PERFORMANCE

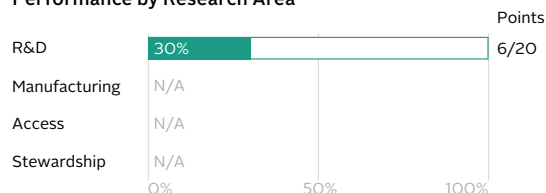
Cidara performs less than average in Research & Development when compared to other small and medium-sized enterprises in scope.

R&D: Cidara has three antibacterial and antifungal projects for priority pathogens in its pipeline. One candidate (rezafungin) in Phase III that is active against fluconazole-resistant *C. auris*, which is listed since November 2019 as an urgent pathogen by the US Centers for Disease Control and Prevention (CDC).

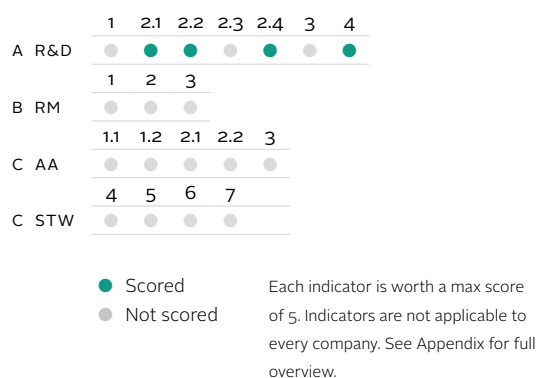
Performance in the Benchmark



Performance by Research Area



How Cidara was evaluated



SALES AND OPERATIONS

Therapeutic areas: Anti-infectives

Products on the market: None

R&D grants received since 2016: At least USD 12.4 million, awarded by two funders (CARB-X; NIH). Its latest award, from NIH, worth USD 5.5 million occurred in May 2018. The award was granted to enable the continued research of novel immunotherapy agents for the treatment and prevention of multidrug-resistant (MDR) Gram-negative bacterial infections in high-risk patient populations, through Cidara's Cloudbreak anti-infective immunotherapy platform.

Financing and investment structure: Cidara is a publicly listed company. It completed its IPO in April 2015, raising USD 76.8 million, following two funding series, raising USD 74 million. Lead investors were 5AM Ventures, RA Capital Management, and Square 1 Bank.

M&A since 2018: None in the antibacterial and/or antifungal sectors

Revenues

(2018)



PIPELINE for diseases in scope

Pipeline size: 3 projects for priority pathogens* (1 antibacterial medicine; 2 antifungal medicines)

Development stages: 2 clinical projects, including a subcutaneous formulation of its antifungal medicine rezafungin, in Phase I of clinical development, to allow for administration of this medicine outside of hospitals, and 1 discovery project

Novelty: No novel clinical-stage medicine projects

Regulatory approvals: 0 approvals for priority pathogens

Access plans: Its 1 late-stage R&D project has no project-specific access plans

Stewardship plans: Its 1 late-stage R&D medicine project has no project-specific stewardship plans

Pipeline for priority pathogens



- Antibacterial (AB) vaccine
- Antibacterial (AB) medicine
- Antifungal (AF) medicine
- AB+AF combination

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and

Prevention (CDC). See Appendix V.

OPPORTUNITIES FOR CIDARA

Work to develop access and to expand stewardship plans for rezafungin. Cidara is developing one antifungal candidate (rezafungin) in late-stage clinical development. In September 2019, Cidara entered into a strategic partnership with Mundipharma, granting Mundipharma exclusive commercialization rights to rezafungin outside the U.S. and Japan. Cidara can work with Mundipharma to ensure that rezafungin will be available and affordable in low- and middle-income countries and appropriately used globally after first market approval. An example of an access plan for Cidara and Mundipharma would be to develop an equitable pricing strategy. In stewardship, Cidara should continue their involvement in surveillance activities, including the SENTRY surveillance program. An example for expanded stewardship will be to decouple sales incentives from sales volumes.

CHANGES SINCE 2018

This section lists notable changes in companies' activities since the 2018 Benchmark. Since Cidara was not in scope for evaluation in 2018, no changes are reported.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 R&D investments

Cidara invested USD 91.9 million in the development of antibacterial and antifungal medicines in 2017 and 2018. As with all other SMEs evaluated, Cidara was not scored in this indicator.

A.2.1 Pipeline size of three projects

Cidara reports three projects targeting priority pathogens in its pipeline. The company focuses mainly on antifungal medicine development, with two projects in clinical development (one in Phase III and one in Phase I) and one antibacterial project in discovery stage.

A.2.2. No clinical-stage novel projects

Cidara's clinical-stage medicine pipeline for priority pathogens consists of both new and adapted R&D projects. Cidara is not currently developing clinical-stage medicine projects that are considered novel. However, it is developing rezafungin, a new clinical-stage R&D candidate

for the treatment of fungal infections including invasive candidiasis.

A.2.3 No vaccines in the pipeline

Cidara is not eligible for this indicator as it is not active in vaccine development.

A.2.4 Two candidates targeting critical and/or urgent priorities

Cidara's pipeline includes one discovery candidate (its Cloudbreak antibacterial programme) that targets multi-drug resistant Gram-negative bacteria, including *Enterobacteriaceae*, *A. baumannii* and *P. aeruginosa*. These pathogens are among those that are considered critical and/or urgent R&D priorities for limiting AMR, as identified by WHO and/or US Centers for Disease Control and Prevention (CDC). Furthermore, it has one candidate (rezafungin) in Phase III that is active against fluconazole-resistant *C. auris*, which is listed since November 2019 as an

urgent pathogen by the CDC.

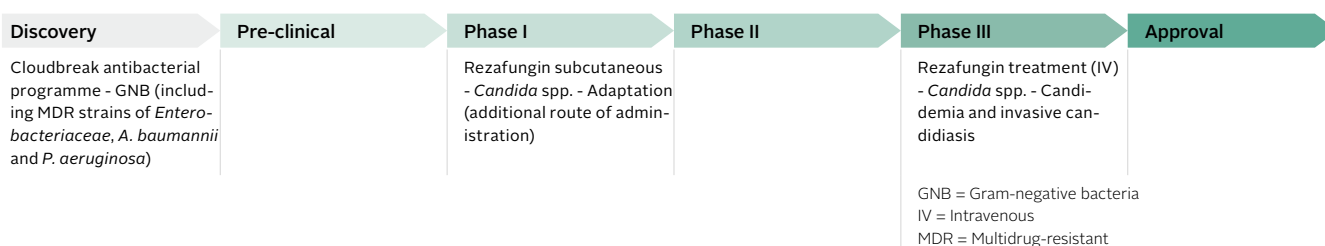
A.3 Intellectual capital sharing

As a small and medium-sized enterprise (SME), Cidara was not scored for this indicator, in line with the external stakeholder consensus defined by the Foundation initiatives.

A.4 No access or stewardship plans in place for late-stage R&D projects targeting priority pathogens

Cidara has one such R&D project. It currently reports no plans that address either the stewardship of or appropriate access to the product, upon reaching the market. After the period of analysis, in September 2019, it was announced that Cidara and Mundipharma formed a strategic partnership to develop and commercialise rezafungin.

Pipeline targeting priority pathogens: 3 As at 16 October 2019



B RESPONSIBLE MANUFACTURING

As an SME, Cidara is not evaluated in this Research Area. It has no antibacterial products on the market.

C APPROPRIATE ACCESS & STEWARDSHIP

As an SME, Cidara is not evaluated in this Research Area. It has no antibacterial and/or antifungal products on the market. Cidara actively supports the SENTRY surveillance program to track antifungal activity against clinical fungal species of interest. Cidara makes all publications involving SENTRY surveillance data publicly available.

DIAGNOSTICS, ANIMAL HEALTH & AGRICULTURE

Activities in this area are not scored by the Benchmark. This information is provided given the importance of diagnostics, animal health and agriculture on the topic of AMR.

Cidara is currently developing multiple antimicrobial susceptibility testing (AST) devices for its antifungal medicine rezafungin in Phase III of clinical development for the treatment of candidemia and invasive candidiasis.

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

Cipla Ltd

Generic medicine manufacturer

Stock exchange: NSE • Ticker: CIPLA • HQ: Mumbai, India • Employees: 26,719

PERFORMANCE

Cipla performs well in all its evaluated Research Areas when compared to other generic medicine manufacturers in scope.

Responsible Manufacturing: Performs strongly. Reports environmental risk-management strategy for own sites, including completed risk assessments based on discharge limits, and plans for future supplier assessment.

Appropriate Access: Performs strongly. Files for registration for all relevant off-patent products in access countries. Some reported strategies to ensure continuous supply include forecasting, demand planning, maintains safety stocks, and secures sufficient quantities of APIs in advance of seasonal need.

Stewardship: Performs strongly. Fully decouples incentives for sales agents from sales volumes. Its educational programmes have comprehensive conflict of interest (COI) mitigation. Reports language adaptations to brochures to improve adherence to treatment for antifungals.

SALES AND OPERATIONS

Therapeutic areas: Cardiovascular diseases, infectious diseases, metabolic disorders, oncology, respiratory diseases

Business segments: APIs; Cipla Global Access; Respiratory

Product categories: Generic medicines

Manufacturing & supply: Cipla reports having 11 manufacturing sites that produce anti-bacterial APIs and/or drug products. It supplies approximately 400 million daily defined doses (DDD) of antibacterial and antifungal medicines across at least nine countries to date.

M&A since 2018: In July 2019, Cipla USA announced the acquisition of the antibacterial drug plazomicin (Zemdri™) from Achaogen. In October 2019, Cipla announced the acquisition of the anti-infective product ceftriaxone/sulbactam/disodium EDTA (Elores) from Venus Remedies Limited.

PORTFOLIO for diseases in scope

Mid-sized portfolio: At least 72 products (42 unique INNs): 57 antibacterial medicines; 15 antifungal medicines

Essential medicines: 51% (37) of products are on the 2019 WHO EML

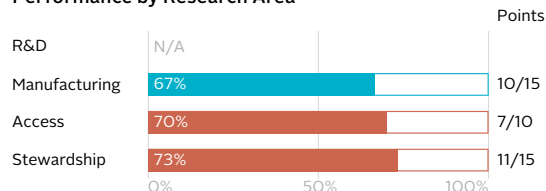
AWaRe medicines*: 12 Access group; 8 Watch group; 2 Reserve group

Anti-TB medicines*: 6 (incl. 1 Watch group, 1 Reserve group)

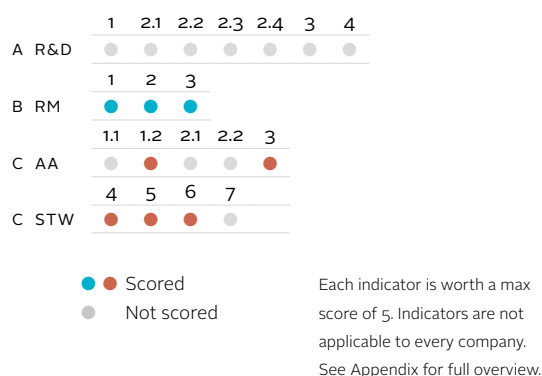
Performance in the Benchmark



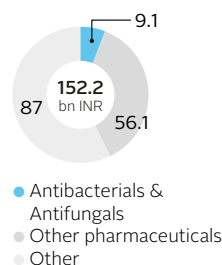
Performance by Research Area



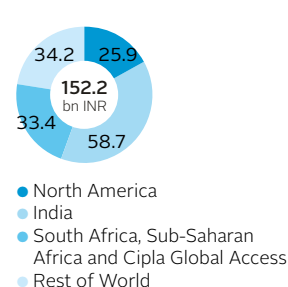
How Cipla was evaluated



Revenues by product (2017-18)



Revenues by region (2017-18)



Products on the market



The number of products is based on data from public sources, IQVIA, and data submitted by the company. It may not account for Cipla's entire portfolio.

* Listed on the 2019 WHO EML (Section 6).

OPPORTUNITIES FOR CIPLA

Ensure availability and affordability of plazomicin (Zemdri™) in access countries. Cipla can file for registration of plazomicin in access countries such as India and countries in Sub-Saharan Africa to ensure the availability of this new antibacterial medicine. Cipla can also apply to plazomicin its public commitment to improve affordability through an equitable pricing strategy among countries based on socioeconomic factors.

Expand registration and ensure adequate supply of antibacterial medicines to more access countries. Cipla can file for registration and ensure adequate supply of antibacterial medicines on the 2019 WHO EML within its current portfolio (e.g. the forgotten antibiotics colistin and fosfomycin) in more access countries.

Implement and monitor its environmental risk-management strategy at third-party suppliers and external private waste-treatment plants. Cipla has an environmental risk-management strategy, including discharge limits, and auditing processes in development for its own manufacturing sites. The company can ensure that this strategy, including the discharge limits, apply also to the sites of third-party suppliers and external private waste-treatment plants. Following up on its commitments as a signatory to the Industry Roadmap for Progress on Combating AMR, Cipla can also work with stakeholders to develop a practical mechanism to publicly disclose (1) a list of its suppliers and waste-treatment plants and (2) the results of environmental audits and the levels of antibacterial discharge from its own sites and the sites of its suppliers.

Build on best practice in sales incentives and develop a comprehensive stewardship approach. Cipla is one of only two companies in the Benchmark fully decoupling sales incentives from sales volumes. Building on this best practice, Cipla can share publicly (e.g. with the AMR Register) the raw data collected for its surveillance programme. It can also expand its brochure and packaging adaptations (taking account of language and adherence to treatment) beyond India.

CHANGES SINCE 2018

- In October 2019, Cipla announced the acquisition of the anti-infective product ceftriaxone/sulbactam/disodium EDTA (Elores) from Venus Remedies Limited.
- In July 2019, Cipla acquired worldwide rights (excluding Greater China) to Achaogen's antibacterial plazomicin (Zemdri™).
- In April 2019, Cipla and Pulmatrix signed an agreement for the co-development and commercialisation of pulmazole, an inhaled iSPERSE™ formulation of the antifungal itraconazole for the treatment of allergic bronchopulmonary aspergillosis (ABPA) in patients with asthma.
- Running an AMR surveillance programme for plazomicin as part of an FDA requirement.
- Newly set up an AMR-targeted environmental strategy for its own sites, including risk assessments based on PNECs to limit AMR.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer (GMM), Cipla is not evaluated in this Research Area.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Environmental risk-management strategy for own sites

Cipla reports a strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, with an AMR-specific audit programme currently in development. The company reports setting discharge limits for all antibacterials manufactured at its sites, based on PNECs to limit AMR (or more stringent PNECs), as published by the AMR Industry Alliance. It has used these limits to conduct an initial risk assessment at its own sites, which identified areas for improvement, for which the company reports having initiated corrective actions.

Cipla has not yet implemented its strategy with third-party suppliers of antibacterial APIs and/or drug products. The company has drawn up supplier assessment plans, prioritised based on the volume of antibacterials supplied, and expects its future audit programme to cover suppliers' and own sites alike. There is limited information on the requirements the company makes of external private waste-treatment plants in terms of environmental strategy and antibacterial discharge limits. The company reports that the plants are currently not audited.

B.2 Publicly discloses some information on environmental risk management

Cipla publishes some components of its environmental risk-management strategy. Further, it is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. Cipla does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private waste-treatment plants; (2) a list of these suppliers and waste-treatment plants; or (3) the levels of antibacterial discharge from its own sites.

B.3 Has system to maintain production quality for own and suppliers' sites; no requests for official corrective action

Cipla reports having a system to maintain high-quality antibacterial production, consistent with international GMP standards. This includes risk-based internal audits and tracking of corrective and preventive actions. The company reports requiring suppliers to abide by regulatory and company quality standards. This includes submitting suppliers to a qualification process, after which a quality technical agreement is established and periodic risk-based re-evaluations are conducted to assess compliance. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Cipla's own sites or any subsidiaries.**

** Including only wholly-owned direct subsidiaries of the company. More information in Appendix I.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries***

C.1.1 Registering on-patent products

Cipla was not eligible for this indicator as it does not have on-patent antibacterial or antifungal medicines or vaccines in its portfolio.

C.1.2 Has filed to register relevant off-patent products† in six access countries on average

Cipla is stronger than other generic medicine manufacturers evaluated when it comes to filing relevant off-patent products for registration in access countries. It reports filing all of its relevant products (10/10 antibacterial and antifungal medicines) for registration in access countries. Its most widely filed product in this analysis is the antifungal fluconazole, used to treat diseases including those caused by *Candida* spp. Cipla has filed its version of this product in 21 access countries. Its antibacterials cefixime, linezolid and ethionamide have been filed in eight,

seven and seven access countries, respectively.

C.2.1 Pricing strategies for on-patent products
Cipla was not eligible for this indicator, as it does not have on-patent antibacterial or antifungal medicines or vaccines in its portfolio.

C.2.2 Pricing strategies for off-patent products
Companies were not scored for this indicator as the available data was insufficient for a comparative analysis. Cipla does report that, to reduce the cost of its medicines, it chooses vendors based on quality and price, improves batch yields at the manufacturing end, and pursues overhead cost reductions.

C.3 Some strategies to ensure the continuous supply of relevant products

Cipla is a middle-performing company, compared to other generic medicine manufacturers eval-

uated, when it comes to taking steps to ensure the continuous supply of its relevant products to access countries. It discloses some strategies for achieving this aim. It has a 12-month rolling forecast process and demand planning that looks five years ahead. It holds monthly sales and operations planning meetings with its sales and supply chain team to review the latest supply and demand updates. To help ensure a secure supply of ingredients, Cipla maintains safety stocks and secures sufficient quantities of APIs in advance of seasonal impact. To mitigate against falsified medicines reaching the supply chain, it uses 2D bar codes with unique identification numbers to improve tracking and tracing.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Some COI mitigation for all educational programmes

The Benchmark analysed the top five AMR-related educational programmes for healthcare professionals (HCPs) from Cipla. Cipla reports some COI mitigation for all five programmes. All programmes include two of three COI mitigation strategies looked for by the Benchmark: (1) a pledge not to provide financial or material incentives to participants (content is delivered online or via webinars); and (2) a policy of not using branded materials. However, it was unclear whether content for the five programmes was developed independently from Cipla's marketing department. After the period of analysis, the company stated that content for these five programmes is developed by its medical affairs team.

C.5 Adapts marketing materials and sales practices to address appropriate use

Cipla engages in practices that aim to address the appropriate use of its antibacterial and/

or antifungal medicines, both via its marketing materials and sales remuneration. At least some of Cipla's marketing materials reflect emerging resistance trends and include guidelines for HCPs to raise awareness of AMR and address appropriate use: namely for the antibacterial colistin and the antifungal itraconazole. Cipla is the only generic medicine manufacturer evaluated to report fully decoupling incentives for sales agents from sales volumes to help prevent the inappropriate use of its antibacterial and/or antifungal medicines.

C.6 Makes several adaptations to brochures and/or packaging to facilitate appropriate use

Cipla adapts brochures and packaging to facilitate appropriate use by patients of relevant products: namely its antifungal medicines itraconazole, amorolfine and oxiconazole. These adaptations take account of language and adherence to treatment. Cipla provides packages and leaflets for these products with QR codes that

direct patients to information about antifungal resistance in six to eight regional languages in India. This information aims to improve adherence to treatment. Cipla is the only company that reports adaptations to its brochures or packaging materials for antifungal medicines.

C.7 Antimicrobial surveillance

As a GMM, Cipla is not eligible for this indicator as GMMs have a limited role in AMR surveillance activities. After the period of analysis, Cipla stated that it runs a surveillance programme for plazomicin (Zemdri™) as part of an FDA requirement.

*** 102 low- and middle-income countries where better access to medicine is most needed. See Appendix VI.

† See Appendix VII.

Debiopharm

Small/medium-sized enterprise

Stock exchange: Privately held • Ticker: N/A • HQ: Lausanne, Switzerland • Employees: 420

PERFORMANCE

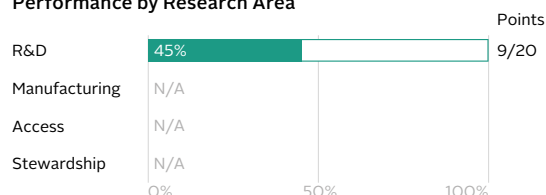
Debiopharm performs on average in Research & Development when compared to other small and medium-sized enterprises in scope.

R&D: Debiopharm has four antibacterial projects for priority pathogens in its pipeline, including one novel clinical-stage candidate, afabacin, for acute bacterial skin and skin structure infections (ABSSSI).

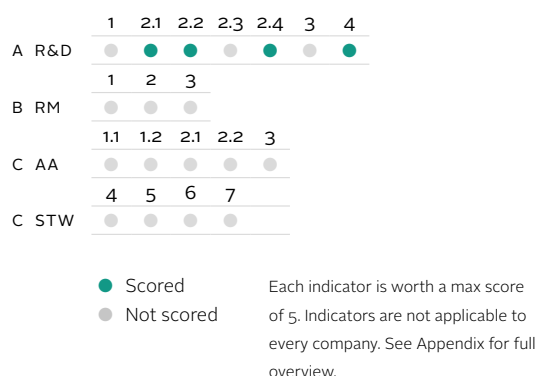
Performance in the Benchmark



Performance by Research Area



How Debiopharm was evaluated



SALES AND OPERATIONS

Therapeutic areas: Oncology; infectious diseases

Products on the market: Two non-antimicrobial medicines: oxaliplatin (Eloxatin®/Elplat®/Dacotin®/Dacplat®) used to treat colorectal cancer, and triptorelin (Decapeptyl®/Trelstar®/Pamorelin®/Triptodur®) a hormonal therapy drug used to treat prostate cancer.

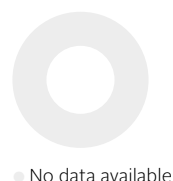
R&D grants received since 2016: At least USD 4.7 million, awarded by one funder (CARB-X). Its latest award, worth USD 2.1 million, was granted by CARB-X in May 2019 to advance the development of its antibiotic programme Debio 1454, targeting multi-drug-resistant (MDR) *A. baumannii*. Debio 1454 compound inhibits bacterial fatty acid biosynthesis, an essential pathway in many bacterial species including Gram-negative, drug-resistant strains.

Financing and investment structure: Family-owned company

M&A since 2018: None in the antibacterial and/or antifungal sectors

Revenues

(2018)



PIPELINE for diseases in scope

Pipeline size: 4 projects for priority pathogens* (4 antibacterial medicines)

Development stages: 2 clinical projects, including afabacin, a Phase II clinical candidate for the treatment of ABSSSI, with an additional indication for bone and joint infections also in development, and 2 pre-clinical projects

Novelty: 1 novel project, afabacin, a Phase II clinical candidate for the treatment of acute bacterial skin and skin structure infections that belongs to a new chemical class of antibacterials and has a new drug target, mode of action and no known cross-resistance to other antibacterial classes

Regulatory approvals: 0 approvals for priority pathogens

Access plans: Neither of its 2 late-stage R&D projects have project-specific access plans.

Stewardship plans: Neither of its 2 late-stage R&D medicine projects have project-specific stewardship plans.

Pipeline for priority pathogens



- Antibacterial (AB) vaccine
- Antibacterial (AB) medicine
- Antifungal (AF) medicine
- AB+AF combination

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

OPPORTUNITIES FOR DEBIOPHARM

Develop access and stewardship plans for afabacin. Debiopharm is developing one antibacterial candidate (afabacin) in late-stage clinical development. Debiopharm can develop plans to ensure that afabacin will be available and affordable in low- and middle-income countries and appropriately used globally after market approval. As examples of access plans, the company can commit to an equitable pricing strategy and/or look for out-licensing opportunities with multiple manufacturers in low- and middle-income countries. As examples of stewardship plans, the company can commit to decouple sales incentives from sales volumes and/or become involved in antibacterial surveillance activities.

CHANGES SINCE 2018

This section lists notable changes in companies' activities since the 2018 Benchmark. Since Debiopharm was not in scope for evaluation in 2018, no changes are reported.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 R&D investments

As with all other small and medium-sized enterprises (SMEs) evaluated, Debiopharm was not scored in this indicator.

A.2.1 Pipeline size of four projects

Debiopharm reports four projects targeting priority pathogens in its pipeline. The company focuses on antibacterial medicine development, and has two projects in clinical development (Phase II) and two in pre-clinical development.

A.2.2 One clinical-stage novel project

Debiopharm's clinical-stage medicine pipeline for priority pathogens consists of both new and adapted R&D projects. Debiopharm has

one clinical-stage antibacterial medicine project that is considered novel: afabacin, for ABSSSI. It meets all criteria set by WHO for innovativeness, including belonging to a new chemical class and having a new target, mode of action and no cross-resistance to other antibacterial classes.

A.2.3 Vaccines in the pipeline

Debiopharm is not eligible for this indicator as it is not active in vaccine development.

A.2.4 One candidate targeting critical and/or urgent priorities

Debiopharm has one pre-clinical candidate that targets *N. gonorrhoeae*, which is considered an urgent R&D priority for limiting AMR, as identified

by the US Centers for Disease Control and Prevention (CDC). Further details were provided on the basis of confidentiality.

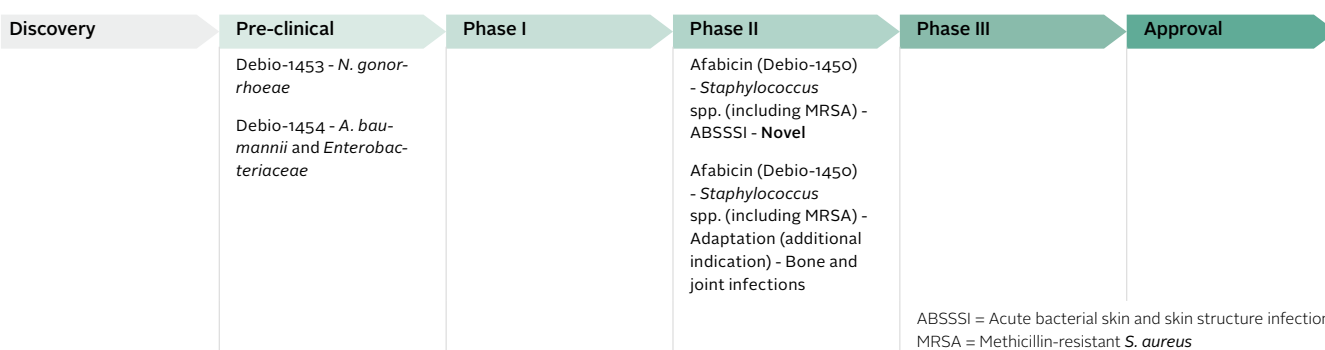
A.3 Intellectual capital sharing

As an SME, Debiopharm was not scored for this indicator, in line with the external stakeholder consensus defined by the Foundation.

A.4 No access or stewardship plans for late-stage R&D projects targeting priority pathogens

Debiopharm has two such R&D projects. It currently reports no plans that address either the stewardship of or appropriate access to the products, upon reaching the market.

Pipeline targeting priority pathogens: 4 As at 16 October 2019



B RESPONSIBLE MANUFACTURING

As an SME, Debiopharm is not evaluated in this Research Area. It has no antibacterial products on the market.

C APPROPRIATE ACCESS & STEWARDSHIP

As an SME, Debiopharm is not evaluated in this Research Area. It has no antibacterial and/or antifungal products on the market.

DIAGNOSTICS, ANIMAL HEALTH & AGRICULTURE

Activities in this area are not scored by the Benchmark. This information is provided given the importance of diagnostics, animal health and agriculture on the topic of AMR.

Debiopharm is developing an antimicrobial susceptibility testing (AST) device for its antibacterial afabacin, which is in Phase II of clinical development. It is also developing a sample preparation technology for direct blood testing, which could shorten the time to identify pathogens and enable appropriate use of antibacterials.

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

Entasis Therapeutics Inc

Small/medium-sized enterprise

Stock exchange: NASDAQ • Ticker: ETTX • HQ: Massachusetts, USA • Employees: 33

PERFORMANCE

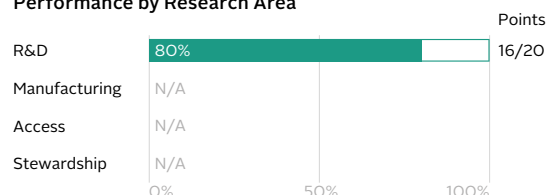
Entasis performs well in Research & Development when compared to other small and medium-sized enterprises in scope.

R&D: Entasis has four antibacterial projects for priority pathogens in its pipeline, including one late-stage candidate that is considered novel: zoliflodacin, for uncomplicated *N. gonorrhoeae*. Reports access and stewardship plans for all of its late-stage projects.

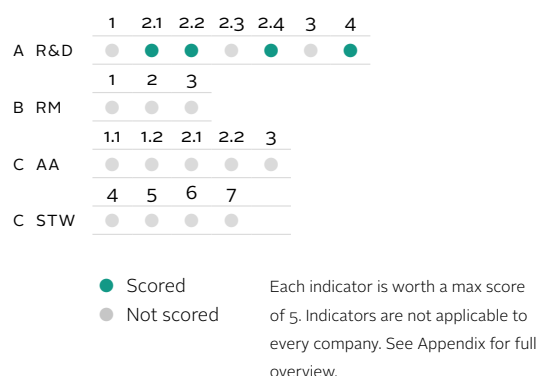
Performance in the Benchmark



Performance by Research Area



How Entasis was evaluated



SALES AND OPERATIONS

Therapeutic areas: Drug-resistant Gram-negative bacteria

Products on the market: None

R&D grants received since 2016: At least USD 4.5 million, awarded by one funder for two projects (CARB-X). These awards were granted in March and October 2017 to support the development of ETX0282 and the company's non-beta-lactam PBP (NBP) inhibitor programme, both targeting Gram-negative infections.

Financing and Investment Structure: Entasis is a publicly listed company. It completed its IPO in September 2018, raising USD 75 million, following three funding series, raising USD 105.4 million. Its lead investor was Clarus Ventures.

M&A since 2018: None in the antibacterial and/or antifungal sectors

Revenues

(2018)



PIPELINE for diseases in scope

Pipeline size: 4 projects for priority pathogens* (4 antibacterial medicines)

Development stages: 3 clinical projects, including sulbactam/durlobactam, a Phase III fixed-dose combination of a beta-lactamase inhibitor (durlobactam) with the PBP inhibitor sulbactam to treat multidrug-resistant *A. baumannii* infections, and 1 pre-clinical project

Novelty: 1 novel project, zoliflodacin, a Phase II clinical candidate for the treatment of uncomplicated gonorrhoea that belongs to a new chemical class of antibacterials and has a new mode of action and no known cross-resistance to other antibacterial classes

Regulatory approvals: 0 approvals for priority pathogens

Access plans: 2 of 2 late-stage R&D projects with project-specific access plans, including equitable pricing strategies through access-oriented licensing agreements and a partnership with GARDP

Stewardship plans: 2 of 2 late-stage R&D projects with a project-specific stewardship plan in place to continue ongoing surveillance studies for zoliflodacin in partnership with GARDP

Pipeline for priority pathogens



* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

OPPORTUNITIES FOR ENTASIS

Expand access and stewardship plans for sulbactam/durlobactam. Entasis' access and stewardship plans for one of its late-stage candidates, zoliflodacin, represent a good practice. For sulbactam/durlobactam, Entasis has already committed to addressing affordability through an equitable pricing strategy and signed an agreement with Zai Lab in China to ensure access to countries in scope in Asia and is actively seeking more partners to license in other regions of the world. In this commitment to find new partners, Entasis has the opportunity to license in other regions of the world. Also in this commitment to find new partners, there is additional opportunity to expand stewardship provisions beyond surveillance.

CHANGES SINCE 2018

- Increased its investment in antibacterial development from USD 10-20 million in 2016 to USD 58.7 million in 2017-2018.
- Completed Phase I trial in June 2019 for its oral beta-lactamase inhibitor ETXo282 in combination with cefpodoxime.
- Initiated Phase III trial in April 2019 for its antibacterial sulbactam/durlobactam (ETX2514SUL), targeting carbapenem-resistant *A. baumannii* infections.
- Initiated Phase III clinical trials for zoliflodacin with GARDP in September 2019 to treat drug-resistant gonorrhoea, including access and stewardship plans.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 R&D investments

Entasis invested USD 58.7 million in the development of antibacterial medicines in 2017 and 2018. As with all other small and medium-sized enterprises (SMEs) evaluated, Entasis was not scored in this indicator.

A.2.1 Pipeline size of four projects

Entasis reports four projects targeting priority pathogens in its pipeline. The company focuses on antibacterial medicine development, and has three projects in clinical development, and one in pre-clinical development.

A.2.2 One clinical-stage novel project

Entasis' clinical-stage medicine pipeline for priority pathogens consists of both new and adapted R&D projects. Entasis has one clinical-stage antibacterial medicine project that is considered novel: zoliflodacin, for uncomplicated *N. gonorrhoeae*, which belongs to a new chemical class and has a new mode of action and no cross-resistance to existing classes of antibacterials.

A.2.3 Vaccines in the pipeline

Entasis is not eligible for this indicator as it is not active in vaccine development.

A.2.4 Four candidates targeting critical and/or urgent priorities

Entasis' clinical pipeline includes a combination medicine candidate in Phase III (sulbactam/durlobactam) that targets Carbapenem-resistant *A. baumannii* (CRAB); a compound in Phase I (ETXo282/cefepodoxime) that targets CRE; and zoliflodacin** in Phase II, being developed with GARDP and that targets *N. gonorrhoeae*. The company's pre-clinical pipeline includes one further candidate that targets Gram-negative pathogens considered critical and/or urgent R&D priorities for limiting AMR, as identified by WHO and/or the US Centers for Disease Control and Prevention (CDC).

A.3 Intellectual capital sharing

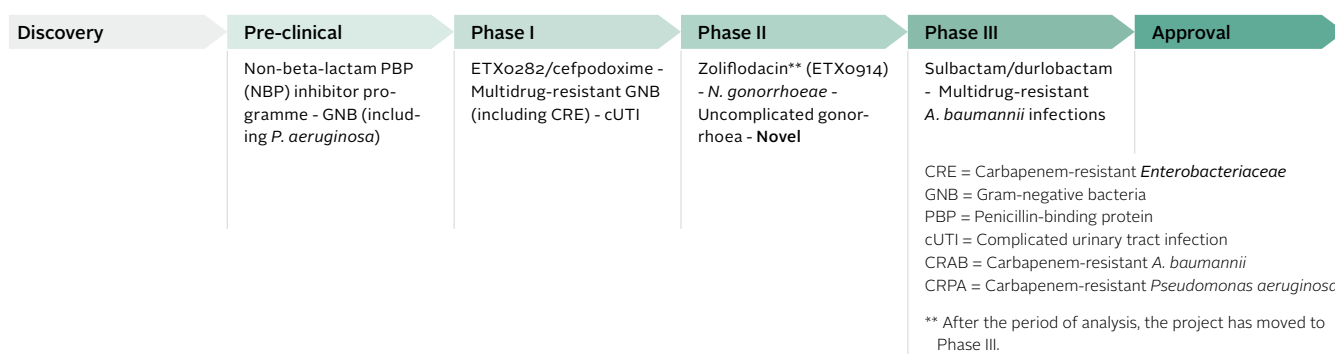
Entasis reports six intellectual capital sharing initiatives. It engages with different universities and research centres to share molecules and drug analogues in order to identify research lead candidates. In addition, it reports that its agreement with Zai Lab and GARDP includes different

examples of intellectual property sharing in terms of manufacturing and commercialisation. As an SME, Entasis was not scored for this indicator, in line with the external stakeholder consensus defined by the Foundation.

A.4 Access and/or stewardship plans for two of two projects

Entasis has two late-stage R&D projects targeting priority pathogens. For zoliflodacin, Entasis has entered a contract with GARDP (a not-for-profit R&D organisation), enabling GARDP to provide access to and promote the responsible use of zoliflodacin in 168 countries. For sulbactam/durlobactam, Entasis is partnering with Zai Lab to conduct clinical trials and obtain regulatory approval in China and other countries belonging to the Association of Southeast Asian Nations (ASEAN), in parallel to the US and Europe. For sulbactam/durlobactam, Entasis is seeking commercial partners to ensure access in low- and middle-income countries. For both projects, Entasis commits to addressing affordability through equitable pricing strategies. Further, Entasis is one of the three SMEs evaluated in the Benchmark that is active in antimicrobial surveillance.

Pipeline targeting priority pathogens: 4 As at 16 October 2019



* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

B RESPONSIBLE MANUFACTURING

As an SME, Entasis is not evaluated in this Research Area. It has no antibacterial products on the market.

C APPROPRIATE ACCESS & STEWARDSHIP

As an SME, Entasis is not evaluated in this Research Area. It has no antibacterial and/or antifungal products on the market.

Fresenius Kabi AG

Generic medicine manufacturer

Stock exchange: FRA • Ticker: FRE (Fresenius SE & Co KGaA) • HQ: Bad Homburg, Germany • Employees: 37,843

PERFORMANCE

Fresenius Kabi performs well overall in its evaluated Research Areas compared to other generic medicine manufacturers in scope.

Responsible Manufacturing: Middle-performing. Reports environmental risk-management strategy for own sites and plans for evaluation of suppliers but limited information on the extent to which AMR and discharge limits are taken into account.

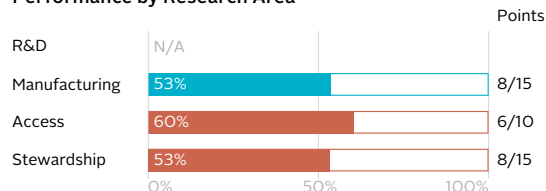
Appropriate Access: Middle-performing. Files for registration for relevant off-patent products in access countries. Reports some information on its strategies for pricing and ensuring continuous supply.

Stewardship: Performs well. It has decoupled incentives for sales agents for most of the volume it sells. Its educational programmes have comprehensive conflict of interest (COI) mitigation.

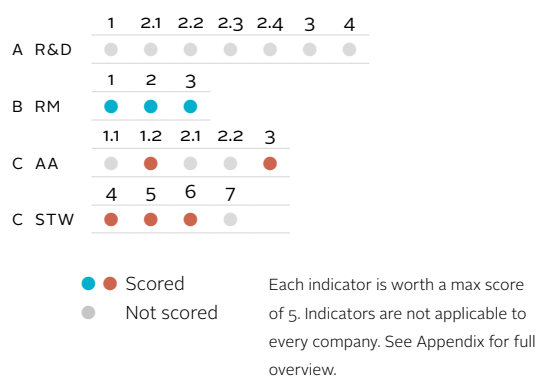
Performance in the Benchmark



Performance by Research Area



How Fresenius Kabi was evaluated



SALES AND OPERATIONS

Therapeutic areas: Anaesthesia; Maldigestion; Oncology

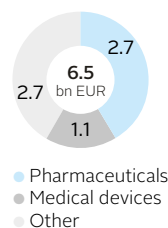
Business segments: Biosimilars; Clinical Nutrition; Devices; Infusion Therapy; Intravenously Administered Drugs; Transfusion Medicine and Cell Therapies

Product categories: Biosimilars; Generic medicines; Medical devices; Nutritionals; Transfusion technology

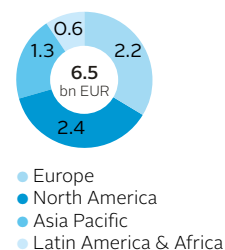
Manufacturing & supply: Fresenius Kabi reports having 17 manufacturing sites that produce antibacterial APIs and/or drug products. It reports selling its antibacterial and antifungal medicines across 44 countries, 10 of which are low- and middle-income countries.

M&A since 2018: None in the antibacterial and/or antifungal sectors

Revenues by product (2018)



Revenues by region (2018)



PORTFOLIO for diseases in scope

Mid-sized portfolio: At least 51 products (46 unique INNs): 47 antibacterial medicines; 4 antifungal medicines

Essential medicines: 53% (27) of products are on the 2019 WHO EML

AWaRe medicines*: 13 Access group; 6 Watch group; 1 Reserve group

Anti-TB medicines*: 5 (incl. 2 Watch group, 1 Reserve group)

Products on the market



The number of products is based on data from public sources, IQVIA, and data submitted by the company. It may not account for Fresenius Kabi's entire portfolio.

* Listed on the 2019 WHO EML (Section 6).

OPPORTUNITIES FOR FRESENIUS KABI

Expand registration and ensure adequate supply of antibacterial medicines to more access countries. Fresenius Kabi can file for registration and ensure adequate supply of antibacterial medicines on the 2019 WHO EML within its current portfolio (e.g. the forgotten antibiotics benzylpenicillin, chloramphenicol and cloxacillin) in more access countries.

Deepen and expand its environmental risk-management strategy. Fresenius Kabi currently has an environmental risk-management strategy that includes auditing processes and is applied to its own manufacturing sites. The company can ensure that its strategy (1) includes specific antibacterial discharge limits and discharge-monitoring processes and (2) extends fully to the sites of third-party suppliers and to external private waste-treatment plants. The AMR Industry Alliance has developed a list of discharge limits that can serve as a starting point for this endeavour.

Adapt brochures and packaging. In order to promote the appropriate use of its antibacterial and/or antifungal medicines by all patients, Fresenius Kabi can make brochure and/or packaging adaptations that take account of language, literacy, paediatric use, adherence to treatment and the environment.

CHANGES SINCE 2018

- Initiated prioritisation of API suppliers for environmental risk assessments.
- Received the Drug Shortage Assistance Award in 2018 by the FDA recognizing its efforts in shortage mitigation.
- Engaged since 2018 in AMR-related educational programmes aimed at healthcare professionals (HCPs) that includes comprehensive conflict of interest (COI) mitigation.
- Sells most of its antibacterial and/or antifungal medicines through tenders and does not have sales incentives linked to the sales volume of these tenders.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer (GMM), Fresenius Kabi is not evaluated in this Research Area.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Environmental risk-management for own sites; no information on discharge limits

Fresenius Kabi reports a general strategy to minimise the environmental impact of wastewater and solid waste from antibacterial manufacturing at its sites. This includes audits every 1-4 years. The company reports that antibacterial-contaminated wastewater is either incinerated, treated or disposed of via an external third parties. It does not report setting antibacterial discharge limits for its own sites with the aim of limiting AMR.

There is limited information on the requirements that Fresenius Kabi makes of third-party suppliers of antibacterial APIs and/or drug products with respect to AMR. It expects suppliers to follow its code of conduct, which includes general provisions on environmental protection. It has also recently established a supplier evaluation programme that prioritises antibacterial API suppliers for environmental impact assessment, but it is not clear how this takes account of the risk of AMR. There is also limited information on the requirements Fresenius Kabi makes of external private waste-treatment plants, in terms of environmental strategy, audits and antibacterial discharge limits. The company reports requiring each site to regularly audit its external waste disposal companies but states that exact audit parameters are defined locally by each site.

B.2 Limited publicly available information on environmental risk management

Fresenius Kabi publishes limited information on its approach to environmental risk management, without specific references to antimicrobial resistance. It does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private waste-treatment plants; (2) a list of these suppliers and waste-treatment plants; or (3) the levels of nor limits for antibacterial discharge from its own sites.

B.3 Has system to maintain production quality for own and suppliers' sites; no requests for official corrective action

Fresenius Kabi reports having a system to maintain high-quality antibacterial production, consistent with international GMP standards. This includes risk-based internal audits and tracking of corrective and preventive actions. The company reports requiring suppliers to abide by regulatory and company quality standards. This includes submitting suppliers to a qualification process, after which a quality agreement is established and periodic risk-based audits are conducted to re-assess compliance. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Fresenius Kabi's own sites or any subsidiaries.**

** Including only wholly-owned direct subsidiaries of the company. More information in Appendix I.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries***

C.1.1 Registering on-patent products

Fresenius Kabi was not eligible for this indicator as it does not have on-patent antibacterial or antifungal medicines or vaccines in its portfolio.

C.1.2 Registering off-patent products

Fresenius Kabi is a middle-performing company when it comes to filing relevant off-patent products† for registration. Further details were provided on the basis of confidentiality.

C.2.1 Pricing strategies for on-patent products

Fresenius Kabi was not eligible for this indicator, as it does not have on-patent antibacterial or antifungal medicines or vaccines in its portfolio.

C.2.2 Pricing strategies for off-patent products

Companies were not scored for this indicator as the available data was insufficient for a comparative analysis. Fresenius Kabi reports that the pricing of its products is controlled by governments through mechanisms such as claw backs, paybacks, rebates and external reference pricing to public procurement/tendering. It reports that it participates in various tender programmes.

C.3 Some strategies to ensure the continuous supply of relevant products

Fresenius Kabi is a middle-performing company, compared to other generic medicine manufacturers evaluated, when it comes to taking steps to ensure the continuous supply of its relevant

products to access countries. It performs forecasting and has a defined safety stock buffer to ensure market supply. To reduce the introduction of falsified medicines in the supply chain, it has implemented a Global Serialization Program which handles the implementation and roll-out to all countries where serialization is required by law. It is one of the co-founders of the European Medicines Verification Organisation (EMVO), that aims to prevent the entry of falsified medicines into the European pharmaceutical supply chain. Fresenius Kabi also takes steps to help ensure its forgotten antibiotics are available in access countries.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Strategy in place to mitigate COI for all of its educational programmes

The Benchmark analysed four AMR-related educational programmes for HCPs from Fresenius Kabi. Fresenius Kabi reports comprehensive COI mitigation for all four programmes. These programmes have all three COI mitigation strategies looked for by the Benchmark: (1) a policy of developing content independently from its marketing department; (2) a pledge not to provide financial or material incentives to participants; and (3) a policy of not using branded materials.

C.5 Adapts sales practices to address appropriate use

Fresenius Kabi engages in practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines via its sales practices. It does not disclose marketing materials

that aim to address appropriate use of its antibacterial and/or antifungal medicines. Fresenius Kabi reports that it sells most of its antibacterial and/or antifungal medicines through hospital tenders, and does not have sales incentives linked to the sales volume of these tenders. After the period of analysis, the company shared marketing materials that include guidelines for HCPs to raise awareness of AMR and address appropriate use for a range of its intravenous antibacterial medicines used in intensive care units.

C.6 Does not adapt brochures and/or packaging to facilitate appropriate use

The majority of Fresenius Kabi's portfolio is composed of IV drugs, which are administered in hospitals by HCPs. The company does not provide evidence of adapting its brochures and/

or packaging to facilitate appropriate use of its self-administered antibacterial and/or antifungal medicines by patients beyond regulatory requirements.

C.7 Antimicrobial surveillance

As a GMM, Fresenius Kabi is not eligible for this indicator as GMMs have a limited role in AMR surveillance activities.

GlaxoSmithKline plc

Large R&D-based pharmaceutical company

Stock exchange: LSE • Ticker: GSK • HQ: Brentford, UK • Employees: 95,490

PERFORMANCE

GSK performs strongly in its evaluated Research Areas, and leads when compared to other large R&D-based pharmaceutical companies in scope. **R&D:** Performs strongly. Pipeline consists of 27 projects for medicines and vaccines for priority pathogens. Its two clinical-stage medicines are both novel. Reports access and/or stewardship planning for most of its late-stage projects and leads in intellectual capital sharing.

Responsible Manufacturing: Performs strongly. Reports comprehensive environmental risk-management strategy for own sites and suppliers; risk assessments based on discharge limits have been completed at own sites and are ongoing at suppliers' sites.

Appropriate Access: Performs strongly. Files its on- and off-patent products for registration in access countries. Leader in strategies for continuous supply to access countries.

Stewardship: Performs well. It has educational programmes with comprehensive conflict of interest (COI) mitigation. Regressed from 2018 to now to only partially decoupling sales incentives from volumes. It shares surveillance results and adapts brochures and packaging for appropriate use.

SALES AND OPERATIONS

Therapeutic areas: Immunology; Infectious diseases; Oncology; Respiratory diseases

Business segments: Pharmaceuticals; Vaccines; Consumer Healthcare;

Product categories: Innovative medicines (including ViiV Healthcare JV with Pfizer and Shionogi); Consumer healthcare (JV with Pfizer); Vaccines

Manufacturing & supply: GSK reports having 24 manufacturing sites that produce antibacterial APIs and/or drug products. It supplies its antibacterial medicines, antibacterial vaccines and antifungal medicines across 121 countries, 71 of which are low- and middle-income countries.

M&A since 2018: None in the antibacterial and/or antifungal sectors

PIPELINE for diseases in scope

Pipeline size: 27 projects for priority pathogens* (12 antibacterial medicines; 15 antibacterial vaccines)

Development stages: 8 clinical projects, including a Phase III project for an expanded indication of its meningococcal B vaccine Bexsero® for the prevention of gonorrhoea and 10 discovery/pre-clinical projects.

Novelty: 2 novel projects, including GSK-3036656, a Phase II clinical candidate for the treatment of tuberculosis (TB) that belongs to a new chemical class of antibacterials and has a new drug target, mode of action and no known cross-resistance to other antibacterial classes

Regulatory approvals: 0 approvals for priority pathogens

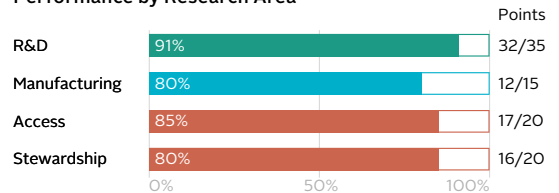
Access plans: 5 of 7 late-stage R&D projects with project-specific access plans, most commonly registration commitments and equitable pricing strategies

Stewardship plans: 2 of 2 late-stage R&D medicine projects with stewardship plans, including commitments to conduct global surveillance studies for all new antibacterials

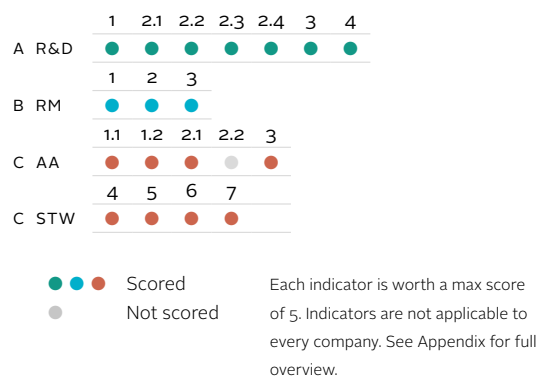
Performance in the Benchmark



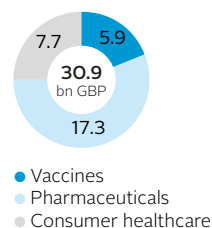
Performance by Research Area



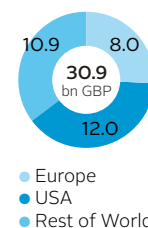
How GSK was evaluated



Revenues by product (2018)



Revenues by region (2018)



PORTFOLIO for diseases in scope

Mid-sized portfolio: At least 95 products (50 unique INNs): 61 antibacterial medicines; 25 antibacterial vaccines; 9 antifungal medicines

Essential medicines: 42% (40) of products are on the 2019 WHO EML

AWaRe medicines:** 17 Access group; 5 Watch group; 1 Reserve group

Anti-TB medicines:** 1

Pipeline for priority pathogens



Products on the market



The number of products is based on data from public sources, IQVIA, and data submitted by the company. It may not account for GSK's entire portfolio.

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

** Listed on the 2019 WHO EML (Section 6).

OPPORTUNITIES FOR GSK

Remain engaged in R&D for antibacterial medicines and vaccines. GSK is one of the few large research-based pharmaceutical companies still active in R&D for antibacterial medicines and vaccines. It is critical for the development and commercialisation of new products that large research-based pharmaceutical companies remain engaged in this space, either through acquisitions and in-licensing or through discovery.

Follow up to public commitments and increase public disclosure on environmental risk management. Following up on its commitments as a signatory to the Industry Roadmap for Progress on Combating AMR, GSK can work with stakeholders to develop a practical mechanism to publicly disclose (1) a list of its suppliers and waste-treatment plants and (2) the results of environmental audits and the levels of antibacterial discharge from its own sites and the sites of its suppliers.

Expand registration and ensure adequate supply of three vaccines and two forgotten antibiotics in access countries. GSK can file for registration and ensure adequate supply of the vaccines Infanrix® Hib, Boostrix® Polio and Bexsero® and two forgotten antibiotics on the 2019 WHO EML within its current portfolio (colistin and cloxacillin) in more access countries.

Publicly share raw data from its surveillance programme SOAR. GSK can share publicly (e.g., with the AMR Register) the raw data collected for its long-term, multinational surveillance programme SOAR.

Fully decouple sales incentives from sales volumes. In order to mitigate the risk of inappropriate use of its antibacterial and antifungal medicines, GSK can change its current incentive programme for its sales agents covering antibacterial and antifungal medicines and ensure that the capped variable pay element of a sales agents' compensation will not be evaluated on the basis of volume targets.

CHANGES SINCE 2018

- Received WHO prequalification in October 2017 for its new Synflorix® 4-dose vial presentation, designed to address cold chain challenges in hot countries.
- Started supply of the Synflorix® 4-dose vial presentation in 2018 to Gavi-supported countries, which is now available in eight countries.
- Donated 150,000 units of essential medicines in 2018, incl. antibacterials via partnerships including, Americares, Direct Relief, and IHP UK, for the humanitarian response in countries such as Guatemala, South Sudan and Syria.
- Partnered with Save the Children to reach over 220,000 children under five in 2018 with interventions including immunisation coverage.
- Changed its policy on engagement with healthcare professionals (HCPs). It now pays HCPs to speak about its innovative products for a limited period after they become available or when new data is released.
- Reverted its incentives for sales agents to partial decoupling from sales volumes at a small group level (within a country).

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 Largest investment in relevant R&D
GSK reports to the Benchmark how much it invested in R&D for antibacterial medicines and vaccines in 2017 and 2018. GSK reports the largest investment in such R&D in 2017 and 2018. As a proportion of its revenues from pharmaceuticals and vaccines, these investments are above

average compared to investments in such R&D made by other large research-based pharmaceutical companies evaluated in the Benchmark. The Benchmark is not able to publish further information, as the details were provided on the basis of confidentiality.

A.2.1 Largest pipeline of all companies evaluated

The company reports 27 projects targeting priority pathogens in its pipeline, all of which target bacterial pathogens, including 15 vaccine and 12 medicine projects. Out of the 27 projects, three are in discovery stage, seven are in pre-clinical

Pipeline targeting priority pathogens: 27*** As at 16 October 2019

| Discovery | Pre-clinical | Phase I | Phase II | Phase III | Approval |
|--|---|---------|---|--|----------|
| Intracellular active series - <i>M. tuberculosis</i> | FimH - <i>E. coli</i> (CRE and ESBL-producing <i>Enterobacteriaceae</i>) | | Gepotidacin† - <i>N. gonorrhoeae</i> , <i>Enterobacteriaceae</i> (CRE and ESBL-producing <i>Enterobacteriaceae</i>) - Bacterial infections (including gonorrhoea) - Novel | ♦ <i>N. gonorrhoeae</i> vaccine - Adaptation (additional indication of meningococcal group B vaccine Bexsero®) | |
| Gram negative antibacterial program (CRE, ESBL, MDR <i>Enterobacteriaceae</i> & <i>P. aeruginosa</i>) | Sanfetrinem cilexetil - <i>M. tuberculosis</i> | | GSK-070 (GSK-3036656) - <i>M. tuberculosis</i> - Novel | ♦ = Vaccine | |
| Whole cell hit-to-lead programme - <i>M. tuberculosis</i> | ♦ <i>C. difficile</i> vaccine† | | ♦ <i>Shigella</i> monovalent GMMA- and biconjugate-based vaccines | COPD = Chronic obstructive pulmonary disease | |
| KasA - <i>M. tuberculosis</i> | ♦ Invasive non-typhoidal <i>Salmonella</i> (iNTS; bivalent GMMA) vaccine - <i>S. enterica</i> Typhimurium & Enteritidis | | ♦ <i>Shigella</i> multivalent biconjugate vaccine (Phase I/II) | CRE = Carbapenem-resistant <i>Enterobacteriaceae</i> | |
| | Tuberculosis Chol-dep-GSK'286 - <i>M. tuberculosis</i> | | ♦ Tuberculosis prophylactic vaccine - <i>M. tuberculosis</i> | ESBL = Extended-spectrum beta-lactamase | |
| | | | ♦ GSK-3277511A - non-typeable <i>H. influenzae</i> (NTHi) and <i>M. catarrhalis</i> (Mcat) multi-antigen vaccine adjuvanted with AS01E - COPD | GMMA = Generalized modules for membrane antigens | |
| | | | | MDR = Multidrug-resistant | |

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

*** Includes 11 projects not shown in the figure: 6 projects provided to the Benchmark on the basis of confidentiality; 3 projects with undisclosed stages of development (2 tuberculosis medicines and 1 other antibacterial medicine); and 2 adapted R&D projects in technical lifecycle (heat-stable and cold-stable formulations of GSK's *S. pneumoniae* (Synflorix®) vaccine)

† After the period of analysis, the project has moved to Phase I.

‡ After the period of analysis, the project has moved to Phase III.

development, eight are in clinical development and two are technical lifecycle projects. The stages of development for seven projects were provided on the basis of confidentiality.

A.2.2 Two late-stage novel projects

GSK's clinical-stage medicine pipeline for priority pathogens consists entirely of new R&D projects. GSK has two late-stage antibacterial medicine projects that are considered novel. The two projects are: GSK-3036656, for TB, which meets all four criteria set by WHO for innovativeness; and gepotidacin, for bacterial infections caused by *Enterobacteriaceae* and *N. gonorrhoeae*, which belongs to a new chemical class, has a new mode of action and no cross resistance to existing antibacterials.

A.2.3 Largest vaccine pipeline

GSK reports 15 vaccine projects in its pipeline. It is by far the largest vaccine pipeline from the five companies evaluated for this indicator. It includes 12 new and 3 adapted projects. One is in discovery; six are in pre-clinical development; and six are in clinical development. It includes vaccines being developed to prevent bacterial infections from Shigella and Salmonella. GSK is also developing, in collaboration with the International Aids Vaccine Initiative (IAVI), a

prophylactic vaccine against TB that is currently in Phase II.

A.2.4 Seven candidates targeting critical and/or urgent priorities

GSK's clinical pipeline includes an antibacterial medicine candidate in Phase II (gepotidacin) that targets *N. gonorrhoeae* and CRE, and a vaccine candidate in Phase III targeting *N. gonorrhoeae*. GSK also has four candidates in its pre-clinical pipeline targeting either a 'critical' pathogen as defined by WHO and/or an 'urgent' pathogen as defined by the US Centers for Disease Control and Prevention (CDC).

A.3 Eight intellectual capital sharing initiatives

Its eight relevant initiatives include its collaboration with WIPO Research consortium, providing UC Berkeley researchers with a library of molecules with activity against *M. tuberculosis*. In addition, GSK is part of the TB Drug Accelerator Programme, a consortium of research institutions and pharmaceutical companies that aims to develop new treatments for TB. A third TB-related initiative includes the GSK TB Compounds Data Set, where the company has published a list of molecule leads with activity against TB. Further, GSK created its Tres Cantos

Open Lab Foundation in 2010, a not-for-profit research centre where external researchers can use the centre's facilities (e.g., animal models) to test its molecules.

A.4 Commits to systematically developing access plans in Phase III

GSK has seven late-stage R&D projects targeting priority pathogens. It reports having project-specific access plans for five of these projects. The company has committed to developing access plans for all of its projects when they reach Phase III. GSK reports that it has developed an equitable pricing strategy framework for LMICs that applies across its portfolio and business units. Its access plans include equitable pricing strategies, registration filings, non-exclusive licensing and supply chain commitments. Furthermore, it commits to registering successful products in those countries where it is running clinical trials. It also commits to not enforce patents in Least Developed Countries (LDCs) or Low Income Countries (LICs) if it is seeking to license that same product in Lower Middle Income Countries. The company reports it is committed to conducting global surveillance studies for all its new antibacterials to enable appropriate use and support stewardship.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Comprehensive environmental risk-management for own sites and suppliers

GSK reports a comprehensive strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, with an aim to limit AMR. This includes audits every three years. The company reports setting discharge limits for all antibacterials manufactured at its sites, based on PNECs to limit AMR (or more stringent PNECs), as published by the AMR Industry Alliance. It reports using a mass balance approach to assess whether discharge levels meet these limits and also reports employing direct sampling and analytical testing to validate or refine this approach. GSK expects third-party suppliers of antibacterial APIs and drug products to follow the same standards, including limits. It reports conducting a questionnaire-based AMR assessment of all suppliers and on-site audits with a risk-based frequency. Suppliers have been requested to provide antibacterial mass balance assessments to GSK and, if these exceed PNEC limits, to

develop appropriate corrective action plans. GSK expects external private waste-treatment plants to comply with its environmental standards and guidelines and reports auditing them on the basis of risk. The company does not report monitoring discharge levels of wastewater plants.

B.2 Publicly discloses some information on environmental risk management

GSK publishes some components of its environmental risk-management strategy. Further, it is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. The underlying methodology was summarised in an open-access journal article co-authored by Alliance members including GSK. GSK does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private waste-treatment plants; (2) a list of these suppliers and waste-treatment plants; or (3) the levels of antibacterial discharge from its own sites.

B.3 Has system to maintain production quality for own and suppliers' sites; no requests for official corrective action

GSK reports having a system to maintain high-quality antibacterial production, consistent with international GMP standards. This includes risk-based internal audits and tracking of corrective and preventive actions. The company reports requiring suppliers to abide by regulatory and company quality standards, as specified, e.g., in quality agreements. It reports auditing its suppliers at its sites and having the same expectations in terms of corrective action implementation. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at GSK's own sites or any subsidiaries.[§]

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries^{||}

C.1.1 Filed to register six of nine relevant on-patent products[¶] in 10+ access countries

GSK is one of the leaders when it comes to filing on-patent products for registration. It files its products in 16.6 access countries on aver-

age. Overall, 67% of its relevant on-patent products (of nine vaccines) are filed in 10+ access countries. Its most widely filed relevant product is the vaccine Synflorix[®], used to prevent diseases such as pneumonia and meningitis, filed in 51 countries.

C.1.2 Filed to register its relevant off-patent products in 12.8 access countries on average

GSK is one of the leaders when it comes to filing relevant off-patent products for registration. It has filed 89% of its relevant products (8/9 anti-

[§] Including only wholly-owned direct subsidiaries of the company. More information in Appendix I.

^{||} 102 low- and middle-income countries

where better access to medicine is most needed. See Appendix VI.

[¶] See Appendix VII.

bacterials) for registration in access countries. Its most widely filed product in this analysis is amoxicillin/clavulanic acid (Augmentin™), used for conditions including pneumonia and skin infections. GSK has filed its version of this product in 54 countries. Amoxicillin/clavulanic acid is followed by ceftazidime and trimethoprim/sulfamethoxazole, filed by GSK for registration in 28 and 18 access countries, respectively.

C.2.1 Takes socioeconomic factors into account when setting prices for on-patent products

When setting prices for on-patent products, GSK takes socioeconomic factors into account. Nine vaccines were included for analysis. For the public sector, GSK uses a seven-tiered pricing strategy based on Gross National Income (GNI). For the private sector, its pricing tiers are based on a country's Human Development Index (HDI). For two vaccines, it applies tiered pricing strategies in 40 and 23 access countries respectively.

In LDCs, GSK has set a ceiling price for the private sector per vaccine.

C.2.2 Pricing strategies for off-patent products

Companies were not scored in this indicator as the available data was insufficient for a comparative analysis. GSK does report several pricing strategies for its off-patent antibacterial or antifungal medicines and vaccines. It states that its prices are driven by a country's relative wealth and the level of affordability. GSK offers discounts and participates in tenders addressing specific populations within a given country. It has a tiered pricing policy for its vaccines, for which it has supply contracts with MSF and UNICEF. These pricing strategies are applied in all access countries.

C.3 Leader in strategies to ensure the continuous supply of relevant products

GSK leads in its approach to ensure the contin-

uous supply of its relevant products to access countries. It discloses multiple strategies to achieve this aim. It uses three-year forecasts and long-term demand projections that look up to ten years ahead. It focuses these initially on those countries expected to demand the highest volumes. GSK uses dual sourcing for APIs for its critical products and maintains and monitors safety stocks. It works with various partners, including the Tanzanian and Nigerian Ministries of Health, in its mVaccination programme to improve immunisation coverage. GSK is a member of International Federation of Pharmaceutical Manufacturers and Associations' (IFPMA) 'Fight the Fakes' campaign, which aims to mitigate against falsified medicine reaching the supply chain, as do its use of security features, tamper evident packaging, track-and-trace coding, auditing of warehouses and reviews of areas of potential fraudulent activity. GSK also supplies one forgotten antibiotic[#] (cloxacillin) to Pakistan and Zambia.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Comprehensive strategy to mitigate COI for all educational programmes

The Benchmark analysed the top five AMR-related educational programmes for HCPs from GSK. GSK reports comprehensive COI mitigation for all five programmes. Three programmes have all three COI mitigation strategies looked for by the Benchmark: (1) content is developed independently from its marketing department (as a company-wide policy); (2) a pledge not to provide financial or material incentives to participants; and (3) a policy of not using branded materials. The remaining two programmes are also accredited by an independent body that evaluates potential COI.

HCPs to raise awareness of AMR and address appropriate use: namely, it includes SOAR surveillance data in marketing materials for antibacterials amoxicillin/clavulanic acid (Augmentin™) and cefuroxime (Zinnat®). GSK reports that it partly decouples incentives for sales agents from sales volumes to help prevent the inappropriate use of its antibacterial and/or antifungal medicines.

C.6 Makes multiple adaptations to brochures and/or packaging to facilitate appropriate use

GSK adapts brochures and packaging to facilitate the appropriate use by patients of relevant products: namely its antibacterial amoxicillin/clavulanic acid (Augmentin™). These adaptations take account of language, adherence to treatment, literacy and the environment. GSK has translated a Patient Knowledge Card into English, French and Portuguese. This card highlights information that aims to improve adherence to treatment. GSK uses an artificial intelligence-enabled chatbot to educate patients on

the appropriate use of antibacterials in a low-literacy format by using graphics. Further, GSK has created blister packaging with a specific lidding foil that is sensitive to moisture for high humidity environments.

C.7 Active in one AMR surveillance programme; openly publishes results; shares consumption data

GSK runs one long-term AMR surveillance programme. The Survey of Antibiotic Resistance (SOAR) is an multinational programme focused on community-acquired respiratory-tract infections in more than 30 countries and runs periodically. It only shares its results through peer-reviewed open-access journal articles. GSK reports that it shares consumption data on colistin periodically with the Pharmaceuticals and Medical Devices Agency in Japan.

DIAGNOSTICS, ANIMAL HEALTH & AGRICULTURE

Activities in this area are not scored by the Benchmark. This information is provided given the importance of diagnostics, animal health and agriculture on the topic of AMR.

While GSK does not have its own diagnostics division, the company reports that it works with third parties to complement AMR product development with diagnostic tests whenever possible, and publicly advocates the need for rapid, accurate diagnostics to further support the appropriate use of all antibacterials.

It has a public policy in place which states that the company will not license its new antibacterials for any agricultural use.

[#] A set of older off-patent antibacterials that are not always marketed or available, due to economic reasons, lack of awareness and lack of demand but are

still considered effective as a treatment for bacterial infections. See Appendix VII for citation.

Hainan Hailing Chemipharma Corporation Ltd

Generic medicine manufacturer

Stock exchange: Privately held • Ticker: N/A • HQ: Haikou, China • Employees: 380

PERFORMANCE

Hainan Hailing performs low overall in its evaluated Research Areas when compared to other generic medicine manufacturers.

Responsible Manufacturing: Performs less well. Reports general environmental risk-management strategy for own sites without the specific aim to limit AMR.

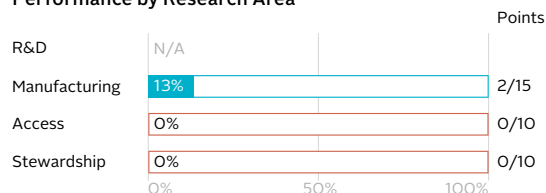
Appropriate Access: Performs low. No information is disclosed on where products are registered. No information is reported on its strategies for pricing and ensuring continuous supply.

Stewardship: Performs low. It has no marketing or sales practices that aim to address appropriate use and it does not adapt its brochures or packaging.

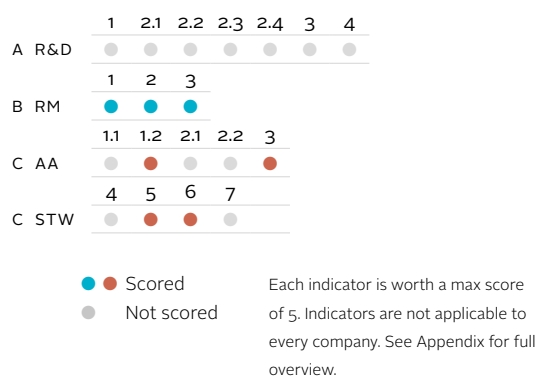
Performance in the Benchmark



Performance by Research Area



How Hainan Hailing was evaluated



SALES AND OPERATIONS

Therapeutic areas: Diabetes; Gastroenterology; Infectious diseases

Business segments: Hailing Pharm

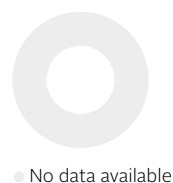
Product categories: Generic medicines

Manufacturing & supply: Hainan Hailing reports having three manufacturing sites of which at least two produce antibacterial APIs and/or drug products.

M&A since 2018: None in the antibacterial and/or antifungal sectors

Revenues

(2018)



PORTFOLIO for diseases in scope

Mid-sized portfolio: At least 47 products (42 unique INNs): 46 antibacterial medicines; 1 antifungal medicine

Essential medicines: 23% (11) of products are on the 2019 WHO EML

AWaRe medicines*: 7 Access group; 4 Watch group

Anti-TB medicines*: None

Products on the market



All companies were assessed based on data available in the public domain, including information the companies have made publicly available. This was supplemented by data submitted directly to the Benchmark by the companies. Hainan Hailing declined to submit data to the 2020 AMR Benchmark.

* Listed on the 2019 WHO EML (Section 6).

OPPORTUNITIES FOR HAINAN HAILING

Develop, implement and monitor an AMR-specific environmental risk-management strategy. Hainan Hailing has stated a commitment to manufacture its medicines in an environmentally responsible manner and a monitoring system to ensure compliance with local regulations. Yet, it is unclear whether AMR is taken into account. The company can develop a strategy that takes AMR into account, including discharge limits based on PNECs to limit AMR (or more stringent) and monitoring of antibacterial levels in discharge, at its own manufacturing sites, to the sites of third-party suppliers and to external private waste-treatment plants. The AMR Industry Alliance has developed a Common Antibiotic Manufacturing Framework and list of discharge limits that could serve as a starting point for such endeavour.

Step up engagement on AMR and increase disclosure of AMR strategies and activities. Hainan Hailing markets 47 antibacterial and/or antifungal medicines within the scope of the Benchmark, including 11 products on the 2019 WHO EML. Hainan Hailing can disclose more information (publicly and/or through the Benchmark) about its strategies to improve access and stewardship to the medicines within its portfolio, including their availability in access countries and its steps to mitigate the risk of inappropriate use.

Decouple sales incentives from sales volumes and/or avoid deploying sales agents. In order to mitigate the risk of inappropriate use of its antibacterial and/or antifungal medicines, Hainan Hailing can decouple sales incentives from sales volumes and/or avoid deploying sales agents, as appropriate.

CHANGES SINCE 2018

This section lists notable changes in companies' activities since the 2018 Benchmark. Since Hainan Hailing was not in scope for evaluation in 2018, no changes are reported.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer (GMM), Hainan Hailing is not evaluated in this Research Area.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 General environmental risk-management strategy for own sites

Hainan Hailing reports a commitment to manufacture its products in an environmentally responsible manner, supported by a discharge monitoring system to ensure compliance with local regulations. It is unclear how the strategy takes AMR into account or aims to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its own sites, third-party suppliers of antibacterial APIs and/or drug products or external private waste-treatment plants.

B.2 Limited publicly available information on environmental risk management

Hainan Hailing publishes limited information on its approach to environmental risk management, without specific references to antimicrobial resistance. It does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private waste-treatment plants; (2) a list of these suppliers and waste-treatment plants; or (3) the levels of nor limits for antibacterial discharge from its own sites.

B.3 Limited evidence of a system to maintain production quality

There is limited information on the systems implemented by Hainan Hailing to maintain high-quality antibacterial production, consistent with international GMP standards. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Hainan Hailing's own sites or any subsidiaries.**

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries***

C.1.1 Registering on-patent products

Hainan Hailing was not eligible for this indicator as it does not have on-patent antibacterial or antifungal medicines or vaccines in its portfolio.

C.2.1 Pricing strategies for on-patent products

Hainan Hailing was not eligible for this indicator, as it does not have on-patent antibacterial or antifungal medicines or vaccines in its portfolio.

C.3 No information on measures to ensure continuous supply of relevant products

Hainan Hailing discloses no information on how it takes steps to ensure the continuous supply of antibacterial or antifungal medicines or vaccines to access countries.

C.1.2 No information on registration filings for relevant off-patent products†

Hainan Hailing reports no evidence of filing its relevant off-patent products for registration in access countries. However, there is evidence of sales in at least one access country.

C.2.2 Pricing strategies for off-patent products

Companies were not scored for this indicator as the available data was insufficient for a comparative analysis. There is no available evidence that Hainan Hailing considers affordability or socioeconomic factors when setting prices for off-patent antibacterial or antifungal medicines or vaccines.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Educational stewardship activities

Hainan Hailing is not eligible for this indicator as there is no information regarding its involvement in AMR-related educational programmes aimed at healthcare professionals (HCPs).

C.5 No information on marketing or sales practices that aim to address appropriate use

There is no information regarding Hainan Hailing's engagement in practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines, either regarding its marketing materials or its sales practices.

C.6 No information on brochure and/or packaging adaptations to facilitate appropriate use

There is no information regarding Hainan Hailing's adaptations in its brochures and/or packaging to facilitate the appropriate use of its antibacterial and/or antifungal medicines by patients beyond regulatory requirements.

C.7 Antimicrobial surveillance

As a GMM, Hainan Hailing is not eligible for this indicator as GMMs have a limited role in AMR surveillance activities.

Johnson & Johnson

Large R&D-based pharmaceutical company

Stock exchange: NYSE • Ticker: JNJ • HQ: New Jersey, USA • Employees: 135,100

BENCHMARK PERFORMANCE

Johnson & Johnson performs well in its evaluated Research Areas, and is one of the leaders when compared to other large R&D-based pharmaceutical companies in scope.

R&D: Middle-performing. Pipeline consists of 11 projects for medicines and vaccines for priority pathogens. Reports the second largest investment in relevant R&D in 2017 and 2018 and is active in intellectual capital sharing.

Responsible Manufacturing: Performs strongly. Reports comprehensive environmental risk-management strategy for own sites and suppliers; risk assessments based on discharge limits have been completed at own sites and are ongoing at suppliers' sites.

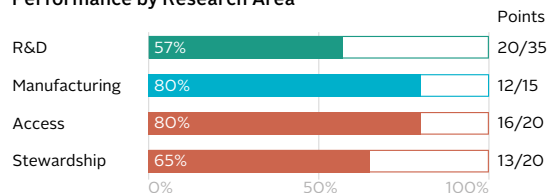
Appropriate Access: Performs well. Files its relevant on- and off-patent products for registration in access countries. Employs strategies including forecasting and capacity building to ensure continuous supply.

Stewardship: Performs well. It has educational programmes with broad conflict of interest (COI) mitigation. It does not deploy sales agents to promote bedaquiline (Sirturo®). It is active in surveillance and adapts brochures and packaging to facilitate appropriate use.

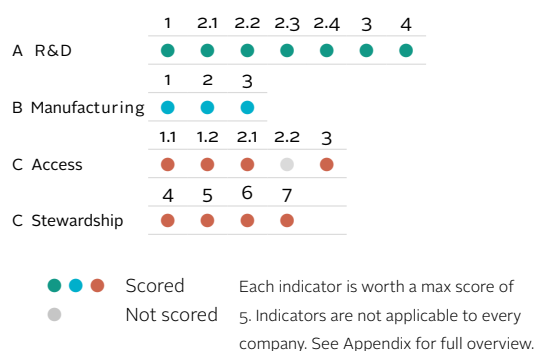
Performance in the Benchmark



Performance by Research Area



How Johnson & Johnson was evaluated



SALES AND OPERATIONS

Therapeutic areas: Cardiovascular diseases; Diabetes; Immunology; Infectious diseases; Neurology; Oncology; Pulmonology

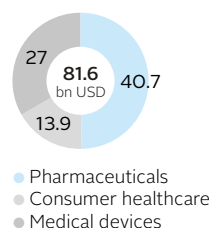
Business segments: Consumer Healthcare; Medical Devices; Pharmaceuticals

Product categories: Consumer health; Medical devices; Innovative medicines; Vaccines

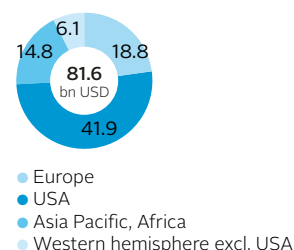
Manufacturing & supply: Johnson & Johnson reports selling its antibacterial and antifungal medicines across 136 countries, 66 of which are low- and middle-income countries.

M&A since 2018: None in the antibacterial and/or antifungal sectors

Revenues by product (2018)



Revenues by region (2018)



PIPELINE for diseases in scope

Pipeline size: 11 projects for priority pathogens* (9 antibacterial medicines; 2 antibacterial vaccines)

Development stages: 3 clinical projects, including a Phase I clinical vaccine candidate for the prevention of infections caused by extraintestinal pathogenic *E. coli* (ExPEC), and seven projects for which the stage of development was provided on the basis of confidentiality

Novelty: No novel clinical-stage medicine projects

Regulatory approvals: 0 approvals for priority pathogens

Access plans: 2 of 2 late-stage R&D projects with project-specific access plans

Stewardship plans: 1 of 2 late-stage R&D medicine projects with project-specific stewardship plans.

PORTFOLIO for diseases in scope

Comparatively small portfolio: At least 25 products (8 unique INNs): 7 antibacterial medicines; 16 antifungal medicines; 2 antibacterial and antifungal medicine combinations

Essential medicines: 28% (7) of products are on the 2019 WHO EML

AWaRe medicines:** None

Anti-TB medicines:** 2 products

Pipeline for priority pathogens



Products on the market



The number of products is based on data from public sources, IQVIA, and data submitted by the company. It may not account for Johnson & Johnson's entire portfolio.

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

** Listed on the 2019 WHO EML (Section 6). Levofloxacin (Levaquin®) is not approved for the treatment of TB but is listed on WHO EML 2019 as an anti-TB medicine (Section 6.2.5).

OPPORTUNITIES FOR JOHNSON & JOHNSON

Target critical/urgent priority pathogens. Johnson & Johnson has one of the largest R&D pipelines targeting antibacterial infections but only very few projects that target critical/urgent priorities. It should ensure that future projects target such pathogens.

Follow up to public commitments and increase public disclosure on environmental risk management. Following up on its commitments as a signatory to the Industry Roadmap for Progress on Combating AMR, Johnson & Johnson can work with stakeholders to develop a practical mechanism to publicly disclose (1) a list of its suppliers and waste-treatment plants and (2) the results of environmental audits and the levels of antibacterial discharge from its own sites and the sites of its suppliers.

Ensure affordability of bedaquiline as part of regimens for treatment of multidrug-resistant tuberculosis (MDR-TB). Bedaquiline (Sirturo®) is recommended as part of MDR-TB regimens by international and national treatment guidelines. Johnson & Johnson can continue ensuring the affordability of its tiered pricing strategy for bedaquiline, when used in combination with other tuberculosis (TB) medicines.

Publicly share raw data from surveillance programme. Johnson & Johnson reports that, because the study is an FDA postmarketing requirement, access to the DREAM database was restricted. Now that data collection has been completed, Johnson & Johnson can share publicly (e.g., with the AMR Register) the raw data collected for this long-term, multinational surveillance programme.

CHANGES SINCE 2018

- Announced its ten-year initiative in September 2018 to help eliminate TB by 2030, and committed in October 2019 more than USD 500 million over the next four years to R&D and access programmes for TB (and HIV).
- Received FDA approval in 2019 for bedaquiline (Sirturo®) tablets for MDR-TB in paediatric patients over the age of 12 years and weighing at least 30 kilograms.
- Expanded the availability of bedaquiline to 130+ countries from 103 in 2018, including all 30 countries with high MDR-TB burden.
- Reduced the price for bedaquiline to USD 400 per six-month course in South Africa and any country purchasing through the GDF; original tiered prices for LMICs range from USD 900 - 3000.
- Joined Gavi's STEP programme in 2018, which aims to solve gaps in supply chain management.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 Second largest investment in relevant R&D

Johnson & Johnson reports to the Benchmark how much it invested in R&D for antibacterial medicines and vaccines in 2017 and 2018. Johnson & Johnson reports the second largest investment in such R&D in 2017 and 2018. As a proportion of its revenues from pharmaceuticals and vaccines, the size of these investments is average compared to investments in such R&D made by other large research-based pharmaceutical companies evaluated in the Benchmark. The Benchmark is not able to publish further information, as the details were provided on the basis of confidentiality.

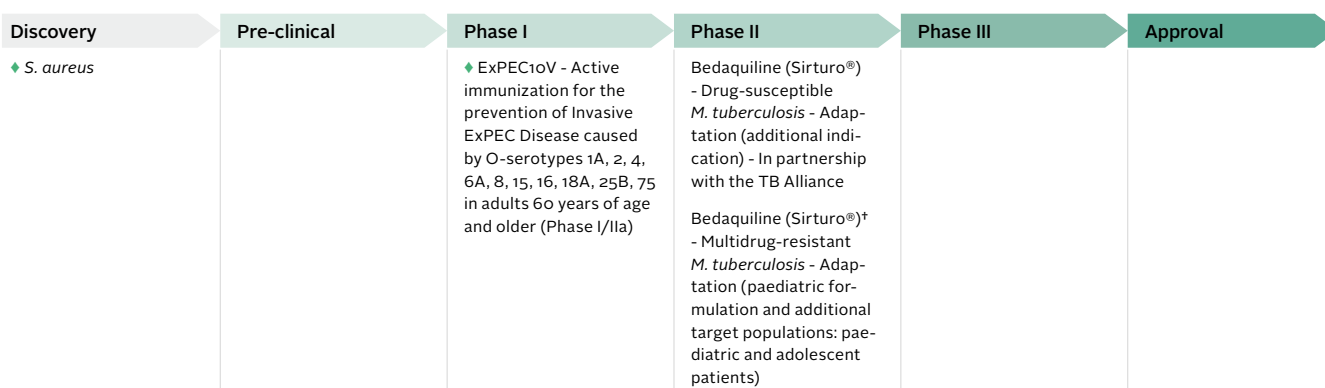
A.2.1 One of the largest pipelines evaluated

Compared to the large research-based pharmaceutical companies evaluated, this pipeline is among the largest. The company reports 11 projects targeting priority pathogen in its pipeline, including two vaccines and nine medicines projects. Of the 11, three are in clinical development and one in discovery stage. The remaining seven projects were provided on the basis of confidentiality.

A.2.2 No clinical-stage novel projects

Johnson & Johnson's clinical-stage medicine pipeline for priority pathogens consists entirely of adapted R&D projects. It does not currently include candidates that are considered novel. However, the company is conducting clinical research to extend the use of bedaquiline (Sirturo®) as a treatment for MDR-TB to younger populations. This includes, after the period of analysis, receiving approval for treatment of pulmonary MDR-TB in adolescents. Johnson & Johnson continues to develop indications and a paediatric formulation of bedaquiline for use in children under 12 years of age.

Pipeline targeting priority pathogens: 11*** As at 16 October 2019



♦ = Vaccine

*** Includes 7 confidential projects not shown in the figure.

* Johnson & Johnson received an approval for bedaquiline from the FDA in August 2019, outside the period of analysis, for an adolescent indication. Phase II studies are ongoing for paediatric patients, with a new paediatric formulation in development.

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

A.2.3 Active in vaccine R&D

Johnson & Johnson has two new vaccine projects, one in clinical development for the prevention of infections due to extra-intestinal pathogenic *E. coli* and one in discovery stage to help prevent *S. aureus* infections.

A.2.4 One candidate targeting critical and/or urgent priorities

Johnson & Johnson has one candidate targeting pathogens considered critical and/or urgent R&D priorities for limiting AMR, as identified by WHO and/or the US Centers for Disease Control and Prevention (CDC). This is its ExPEC vaccine for the prevention of infections due to extra-intestinal pathogenic *E. coli*. Further details were provided on the basis of confidentiality.

A.3 Four intellectual capital sharing initiatives

Its four relevant initiatives include its collaboration with WIPO Research consortium, sharing a library of molecules that might help develop new treatments for TB. In addition, the company reports its collaboration with the Indian Council of Medical Research (ICMR) and its India TB research consortium, providing support to researchers. Further, it is part of the TB Drug Accelerator Programme, a consortium of research institutions and pharmaceutical companies that is developing new treatments for TB.

A.4 Specific access and/or stewardship plans for late-stage projects

Johnson & Johnson has project-specific access plans for its two late-stage antibacterial projects targeting TB, bedaquiline (Sirturo®). In general, once a product is initially approved, Johnson & Johnson commits to submit applications for product registration in countries where the clinical trials for the product have taken place. For its late-stage bedaquiline paediatric project, it conducts clinical trials in access countries where it commits to file for registration (in the Johnson & Johnson territories) upon initial approval. Existing stewardship initiatives and activities for adult use of bedaquiline will be expanded to broaden the audience to those who treat young children. For the use of bedaquiline in DS-TB (TB Alliance), information on access planning was provided on the basis of confidentiality.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)**B.1 Comprehensive environmental risk-management for own sites and suppliers**

Johnson & Johnson reports a comprehensive strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, with an aim to limit AMR. This includes audits every three years. The company reports setting discharge limits for all antibacterials manufactured at its sites, based on PNECs to limit AMR (or more stringent PNECs), as published by the AMR Industry Alliance. It uses these PNECs to conduct risk assessments applying a mass-balance approach, complemented by direct sampling and analytical testing, where needed.

Johnson & Johnson expects third-party suppliers of antibacterial APIs and drug products to follow the same standards, including meeting environmental PNECs. It reports that suppliers are audited typically every three years and are requested to complete a risk assessment as described above for the company's own sites. Johnson & Johnson expects external private waste-treatment plants to comply with its envi-

ronmental standards and reports auditing them on the basis of risk, typically between one and three years. All wastewater sent to these plants is set to be incinerated. Johnson & Johnson does not audit publicly-owned wastewater treatment plants (not in scope of the Benchmark).

B.2 Publicly discloses some information on environmental risk management

Johnson & Johnson publishes some components of its environmental risk-management strategy. Further, it is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. The underlying methodology was summarised in an open-access journal article co-authored by Alliance members including Johnson & Johnson. Johnson & Johnson does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private waste-treatment plants; (2) a list of these suppliers and waste-treatment plants; or (3) the levels of antibacterial discharge from its own sites.

B.3 Has system to maintain production quality for own and suppliers' sites; no requests for official corrective action

Johnson & Johnson reports having a system to maintain high-quality antibacterial production, consistent with international GMP standards. This includes risk-based internal audits and tracking of corrective and preventive actions. The company reports requiring suppliers to abide by regulatory and company quality standards. This includes submitting suppliers to a qualification process, after which a quality agreement is established. It reports auditing its suppliers as its sites and having the same expectations in terms of corrective action implementation. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Johnson & Johnson's own sites or any subsidiaries.||

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries[¶]

C.1.1 Filed to register one of its two relevant on-patent products[#] in 10+ access countries

Johnson & Johnson is one of the leaders with regard to filing patented products for registration. It has filed its antibacterial bedaquiline (Sirturo®), for TB, for registration in 28 access countries and has plans to file bedaquiline for registration in Namibia, Zambia, and Zimbabwe.

C.1.2 Filed to register its relevant off-patent products in 22.5 access countries on average

Johnson & Johnson is one of the leaders when it

comes to filing relevant off-patent products for registration. It has filed all of its relevant products for registration in access countries. It has filed the antifungal itraconazole (Sporanox®) for registration in 33 countries and its antibacterial levofloxacin (Levaquin®) for registration in eight access countries.

C.2.1 Takes socioeconomic factors into account when setting prices for on-patent products

For its two relevant on-patent products bedaquiline (Sirturo®) and itraconazole (Sporanox®), Johnson & Johnson reports considering socio-

economic factors when setting prices. Factors include countries' levels of income and economic development, ability to pay and disease burden, as well as the value the product brings to patients and health system. Johnson & Johnson offers bedaquiline to more than 130 low- and middle-income countries, via the Stop TB Partnership's Global Drug Facility, at the price of USD 400 per six-month course, a reduction from the original tiered prices ranging from USD 900 – USD 3000. Further, the company has committed to donate 105,000 courses of bedaquiline to eligible low- and middle-income countries through a four-year donation

|| Including only wholly-owned direct subsidiaries of the company. More information in Appendix I.

[¶] 102 low- and middle-income countries where better access to medicine is most needed. See Appendix VI.

[#] See Appendix VII.

program, operated in partnership with the U.S. Agency for International Development and JSC Pharmstandard.

C.2.2 Pricing strategies for off-patent products
Companies were not scored for this indicator as the available data was insufficient for a comparative analysis. Johnson & Johnson does report that it applies equity-based tiered pricing to all its products globally, including for off-patent antibacterial or antifungal medicines or vaccines.

C.3 Many strategies to ensure the continuous supply of its relevant products

Johnson & Johnson's performance is one of the strongest when it comes to taking steps to ensure the continuous supply of its relevant products to access countries. It discloses many strategies to achieve this aim. It has various forecasting and data-sharing strategies to predict future demand for its products, as well as country-specific strategies to ensure a rapid response to stockouts. The company also engages with stakeholders on local capacity building initiatives,

including the GAVI Strategic Training for Executive Programme (STEP) to provide non-technical leadership training to supply chain and immunisation managers. To mitigate against falsified medicines reaching the supply chain, Johnson & Johnson uses several strategies, including its Illicit Trade Analytics programme (ITA), which aims to identify illicit trade activity, and its use of serialisation and traceability.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Broad strategy to mitigate COI for all educational programmes

The Benchmark analysed five AMR-related educational programmes for healthcare professionals (HCPs) from Johnson & Johnson. Johnson & Johnson reports broad COI mitigation for all five programmes. To mitigate COI for four programmes, it provides financial resources to independent third parties to carry out the entire programme. For the remaining programme, Johnson & Johnson includes two of three COI mitigation strategies looked for by the Benchmark: (1) content is developed independently from its marketing department; (2) a policy on not using branded materials. However, for this programme, it is unclear whether financial or material incentives are provided to participants. The company may pay for travel, hotel, meals and registration fees to attend third party or company organised events, congresses or symposia for professional or medical education.

C.5 Adapts sales practices to address appropriate use

Johnson & Johnson engages in practices that

aim to address the appropriate use of its antibacterial and/or antifungal medicines via its sales practices. Johnson & Johnson does not disclose marketing practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines. It is, however, one of the three companies evaluated to report that it does not deploy any sales agents to promote a subset of its antibacterial and/or antifungal medicines, namely bedaquiline (Sirturo®). This is not the case for any of its other products.

C.6 Makes several adaptations to brochures and/or packaging to facilitate appropriate use

Johnson & Johnson adapts brochures and packaging to facilitate the appropriate use by patients of relevant products: namely its antibacterial bedaquiline (Sirturo®). These adaptations take account of language and adherence to treatment for bedaquiline. It produces a package insert with information in four languages. Further, it produces a 6-month treatment regimen packaged in a single bottle to improve adherence to treatment.

C.7 Active in one AMR surveillance programme focused on TB

Johnson & Johnson runs one long-term AMR surveillance programme. The Drug Resistance Emergence Assessment in MDR-TB (DREAM) focuses on resistance of bedaquiline (Sirturo®) in 11 countries and has been repeated every year since 2015. The number of antibacterials tested in this programme is 12. Methodological aspects were shared in a peer-reviewed journal article. Data collection is now complete and Johnson & Johnson commits to also sharing raw data via the Yale University Open Data Access (YODA) platform where researchers can request access to raw data from its clinical trials. Johnson & Johnson currently makes some consumption data available about bedaquiline (e.g., from its donation programme) with the Stop TB Partnership.

DIAGNOSTICS, ANIMAL HEALTH & AGRICULTURE

Activities in this area are not scored by the Benchmark. This information is provided given the importance of diagnostics, animal health and agriculture on the topic of AMR.

Johnson & Johnson is supporting development of bedaquiline sensitivity diagnostic tests and panels that are to be deployed on the Becton Dickinson and Thermo Fisher Scientific Inc. lab infrastructure. Next steps are to establish supply agreements to align supply of the tests to the needs of the market. It has also entered into several collaborations including: (1) collaboration with a diagnostic manufacturer to support MDR-TB patient finding in poverty-stricken regions in China through molecular diagnostic testing; and (2) IMI project consisting of an academic and private consortium to identify diagnostic technologies suitable for use in primary care settings. Johnson & Johnson also provides bedaquiline powder for susceptibility testing,

free of charge in 24 countries through its partner, the U.S. National Institutes of Health AIDS Reagent Program.

Melinta Therapeutics Inc

Small/medium-sized enterprise

Stock exchange: NASDAQ • Ticker: MLNT • HQ: New Jersey, USA • Employees: 290

PERFORMANCE

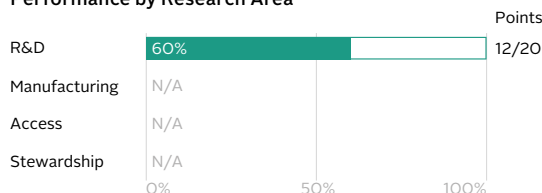
Melinta performs above average in Research & Development when compared to other small and medium-sized enterprises in scope.

R&D: Largest pipeline with 11 antibacterial projects for priority pathogens. Granted approval in 2019 for one antibacterial medicine. Reports access plans to expand availability to access countries.

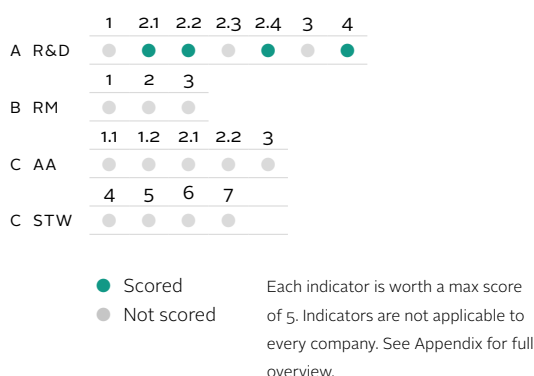
Performance in the Benchmark



Performance by Research Area



How Melinta was evaluated



SALES AND OPERATIONS *Filed for bankruptcy in December 2019*

Therapeutic areas: Antibiotics

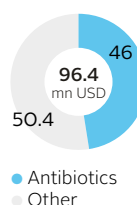
Products on the market: 4 antibacterial medicines: delafloxacin (Baxdela®), meropenem/vaborbactam (Vabomere®), minocycline (Minocin®), and oritavancin (Orbactiv®)

R&D grants received since 2016: At least USD 2.3 million, awarded by one funder (CARB-X). The award, worth USD 2.3 million, was granted in May 2018 to support development of its pyrrolocytosine compounds, part of its ESKAPE Pathogen Programme.

Financing and Investment Structure: Melinta is a publicly listed company. It gained a public listing on NASDAQ on merging with Cembra in November 2017, following five funding series, raising USD 180.5 million. The company's lead investors were EuclidSR Partners, Oxford Bioscience Partners, Sanofi Aventis, SR One, Vatera Healthcare Partners and Warburg Pincus. Its post IPO equity, debt, and other venture funding amounts to USD 360.7 million.

M&A since 2018: On 1 January 2018, Melinta closed the acquisition of the infectious disease business of The Medicines Company, including meropenem/vaborbactam, oritavancin and minocycline. Melinta filed for bankruptcy in December 2019.

Revenues by product (2018)



Revenues by region (2018)



PIPELINE *for diseases in scope*

Pipeline size: 11 projects for priority pathogens* (11 antibacterial medicines)

Development stages: 8 clinical projects, including two Phase I projects for oritavancin (Orbactiv®) and meropenem/vaborbactam (Vabomere®) to expand indications for use in treating bacterial infections in paediatric patients, and 3 pre-clinical projects

Novelty: No novel clinical-stage medicine projects

Regulatory approvals: 0 approvals for priority pathogens

Access plans: 2 of 2 late-stage R&D projects with project-specific access plans, both of which are licensing agreements to expand availability to access countries, though these plans do not address affordability

Stewardship plans: Neither of its 2 late-stage R&D medicine projects have project-specific stewardship plans.

PORTFOLIO *for diseases in scope*

Portfolio size: 5 products (4 unique INNs): 5 antibacterial medicines

Essential medicines: None

AWaRe medicines:** None

Anti-TB medicines:** None

Pipeline for priority pathogens



Products on the market



* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

** Listed on the 2019 WHO EML (Section 6).

OPPORTUNITIES FOR MELINTA

Work with partners to improve availability, affordability and stewardship for meropenem/vaborbactam (Vabomere®) and for delafloxacin (Baxdela®) in more LMICs. Melinta is part of an agreement with Menarini Group which grants Menarini Group the exclusive rights to co-develop and commercialize meropenem/vaborbactam and delafloxacin in 68 countries in Europe, Asia-Pacific and the Commonwealth of Independent States (CIS). Melinta can work with Menarini to ensure that meropenem/vaborbactam will be available and affordable in low- and middle-income countries and appropriately used globally. Melinta is also part of an agreement with Eurofarma Laboratorios, which grants Eurofarma Laboratorios the exclusive rights to co-develop and commercialize delafloxacin in Brazil. Melinta can also look for multiple licensees in other regions of the world. As above, examples of access and stewardship plans for Melinta and its partners, including Menarini Group and Eurofarma Laboratorios, would be developing an equitable pricing strategy and decoupling sales incentives from sales volumes, respectively.

CHANGES SINCE 2018

- Filed for Chapter 11 bankruptcy in December 2019 and reports it will continue to operate in ordinary course throughout the process.
- Received FDA approval for its supplemental New Drug Application for delafloxacin (Baxdela®) in October 2019, expanding the previous indication to community-acquired bacterial pneumonia in adult patients.
- Launched a new antibacterial stewardship programme, including post-marketing susceptibility testing, stewardship-focused promotional standards, and educational programmes with healthcare professionals (HCPs).

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 R&D investments

Melinta invested USD 104.9 million in the development of antibacterial medicines in 2017 and 2018. As with all other small and medium-sized enterprises (SMEs) evaluated, Melinta was not scored in this indicator.

A.2.1 Pipeline size of 11 projects

Melinta reports 11 projects targeting priority pathogens in its pipeline. The company focuses on antibacterial medicine development, and has

eight projects in clinical development, and three in pre-clinical development.

A.2.2 No clinical-stage novel projects

Melinta's clinical-stage medicine pipeline for priority pathogens consists entirely of adapted R&D projects. It does not currently include candidates that are considered novel. However, Melinta is developing eight clinical-stage adapted R&D projects, including studies on the efficacy and safety of meropenem/vaborbactam

(Vabomere®) in children.

A.2.3 Vaccines in the pipeline

Melinta is not eligible for this indicator as it is not active in vaccine development.

Pipeline targeting priority pathogens: 11 As at 16 October 2019

| Discovery | Pre-clinical | Phase I | Phase II | Phase III | Approval |
|-----------|--|--|----------|--|----------|
| | <p>Enhanced macrolide programme, proprietary discovery platform - Drug-resistant <i>Pneumococcus</i> spp. and <i>Staphylococcus</i> spp. (including MRSA)</p> <p>ESKAPE programme: pyrrolocytosine class compound (RX-P2382), proprietary discovery platform - <i>Enterobacteriaceae</i>, <i>P. aeruginosa</i>, <i>A. baumannii</i>, <i>S. aureus</i>, <i>Enterococcus</i> spp. and <i>N. gonorrhoeae</i></p> <p>ESKAPE programme: pyrrolocytosine lead compounds (RX-P2177) - <i>N. gonorrhoeae</i></p> | <p>Delafloxacin (Baxdela®) - GNB (including <i>Enterobacteriaceae</i> and <i>P. aeruginosa</i>) and GPB (including MRSA, group A and group B <i>Streptococcus</i> spp. and <i>E. faecalis</i>) - Adaptation (additional indication) - cUTI</p> <p>Meropenem/vaborbactam (Vabomere®) - GNB and GPB - Adaptation (additional target population: paediatric patients)</p> <p>Minocycline (Minocin®) - GNB - Adaptation (high-dosing regimen)</p> <p>Minocycline (Minocin®) - GNB - Adaptation (additional target population: renally impaired patients)</p> <p>Oritavancin (Orbactiv®) - GPB - Adaptation (new formulation with a shorter infusion time, less volume and ability to reconstitute with saline)</p> <p>Oritavancin (Orbactiv®) - GPB - Adaptation (additional target population: paediatric patients)</p> | | <p>Delafloxacin (Baxdela®)*** - GNB (including <i>Enterobacteriaceae</i> and <i>P. aeruginosa</i>) and GPB (including MRSA, group A and group B <i>Streptococcus</i> spp. and <i>E. faecalis</i>) - Adaptation (additional indication) - CABP</p> <p>Meropenem/vaborbactam (Vabomere®) - CRE - Adaptation (additional indications for infections caused by CRE) - acute pyelonephritis, cUTI, cIAI, HABP, VABP and bacteraemia</p> | |

CABP = Community-acquired bacterial pneumonia
 cIAI = Complicated intra-abdominal infection
 cUTI = Complicated urinary tract infection
 CRE = Carbapenem-resistant *Enterobacteriaceae*
 GNB = Gram-negative bacteria
 GPB = Gram-positive bacteria
 HABP = Hospital-acquired bacterial pneumonia
 VABP = Ventilator-associated bacterial pneumonia

** Delafloxacin (Baxdela®) received FDA market approval in October 2019 for the treatment of CABP.

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

A.2.4 Three candidates targeting critical and/or urgent priorities

Melinta's clinical pipeline includes an adapted medicine in Phase III, for its marketed product meropenem/vaborbactam (Vabomere®) that targets CRE. Its ESKAPE programme includes two pre-clinical candidates: one that targets resistant strains of *Enterobacteriaceae*, *A. baumannii*, and *P. aeruginosa*; and another that targets *N. gonorrhoeae*. These pathogens are among those that are considered critical and/or urgent R&D priorities for limiting AMR, as identified by WHO and/or the US Centers for Disease Control and Prevention (CDC).

A.3 Intellectual capital sharing

As an SME, Melinta was not scored for this indicator, in line with the external stakeholder consensus defined by the Foundation.

A.4 Access plan for two of two projects; no stewardship plans

Melinta has two late-stage R&D projects targeting priority pathogens. Melinta has a licensing

agreement covering both projects that enables the Menarini Group to market the successful products in 68 countries in Europe, Asia-Pacific, and CIS. Additionally, Melinta and Eurofarma Laboratórios, one of the largest pharmaceutical companies in Brazil and present in more than 20 countries in Latin America, entered into an agreement for the development and commercialisation of delafloxacin in Brazil. Melinta does not report specific clauses regarding affordability or accessibility in its agreements, or any stewardship plan.

B RESPONSIBLE MANUFACTURING

As an SME, Melinta is not evaluated in this Research Area. It has antibacterial products on the market. The Benchmark notes that Melinta reports having conducted environmental risk-assessments for its nine suppliers of antibacterial APIs and/or drug products. These assessments included estimations of the presence of antibac-

terial APIs in waste streams. The assessments were carried out in order to develop a specific strategy for each supplier and to ensure a harmonised company-wide global strategy. Melinta was not scored on these activities

C APPROPRIATE ACCESS & STEWARDSHIP

As an SME, Melinta is not evaluated in this Research Area. It does, however, have antibacterial and/or antifungal products on the market. The Benchmark notes that Melinta reports making its antibacterials available outside the United States, including in access countries,[†] through partnerships with other pharmaceutical companies.

Melinta also has some strategies in place to mitigate conflict of interest (COI) for its educational programmes aimed at HCPs. Specifically, two of Melinta's five AMR-related educational programmes aimed at HCPs are accredited by an independent body that evaluates potential COI.

Melinta adapts marketing materials to ensure the appropriate use of antibacterial and/or antifungal medicines. Its marketing materials reflect emerging resistance trends and include guidelines for HCPs to raise awareness of AMR and address appropriate use.

Further, Melinta is active in one AMR surveillance programme, and publishes its results openly. Melinta is also active in SENTRY, a long-term AMR surveillance programme. This is a multinational programme that is managed by JMI laboratories with support from Melinta, among other companies. Its results are shared in an open-access data platform. Melinta was not scored for these activities.

[†] 102 low- and middle-income countries where better access to medicine is most needed. See Appendix VI.

Merck & Co, Inc

Large R&D-based pharmaceutical company

Stock exchange: NYSE • Ticker: MRK • HQ: New Jersey, USA • Employees: 69,000

PERFORMANCE

Merck & Co, Inc is middle-performing in its evaluated Research Areas when compared to other large R&D-based pharmaceutical companies in scope.

R&D: Middle-performing. Pipeline consists of 12 projects for medicines and vaccines for priority pathogens. It has commitments to expanding access and affordability and is active in intellectual capital sharing.

Responsible Manufacturing: Performs well. It has a comprehensive environmental risk-management strategy for own sites and suppliers, however reports less information than the leaders on the progress in the implementation of discharge limits.

Appropriate Access: Performs less well. Discloses limited information on where it registers its relevant products. It partners with organisations including Association Africaine des Centrales d'Achats de Médicaments Essentiels (ACAME) and Developing Countries Vaccine Manufacturers Network (DCVMN) to ensure continuous supply.

Stewardship: Middle-performing. It has educational programmes with broad conflict of interest (COI) mitigation. It is involved in multiple surveillance programmes and publicly shares results. It does not report adapting its brochures and/or packaging to facilitate appropriate use.

SALES AND OPERATIONS

Therapeutic areas: Cardiovascular diseases; Diabetes; Infectious disease; Oncology; Women's health

Business segments: Animal Health; Pharmaceuticals

Product categories: Animal health; Innovative medicines; Vaccines

Manufacturing & supply: No information available

M&A since 2018: None in the antibacterial and/or antifungal sectors

PIPELINE for diseases in scope

Pipeline size: 12 projects for priority pathogens* (9 antibacterial medicines; 2 antibacterial vaccines; 1 antibacterial and antifungal medicine combination)

Development stages: 5 clinical projects, including V114, a Phase III 15-valent pneumococcal vaccine candidate, which has been reported to be non-inferior to Pfizer's Prevnar 13® and includes 2 additional pneumococcal serotypes, and 7 discovery/pre-clinical projects

Novelty: No novel clinical-stage medicine projects

Regulatory approvals: 2, for ceftolozane/tazobactam (Zerbaxa®) for the treatment of HAP/VABP in June 2019 and for relebactam/imipenem/cilastatin (Recarbrio®), for the treatment of cIAI and cUTI in July 2019

Access plans: Unknown if its 5 late-stage R&D projects have project-specific access plans, but the company has a general commitment to increasing affordable access to antibiotics.

Stewardship plans: Unknown if its 4 late-stage R&D medicine projects have project-specific stewardship plans, but the company has a general statement that it supports hospitals in strengthening antimicrobial stewardship programmes.

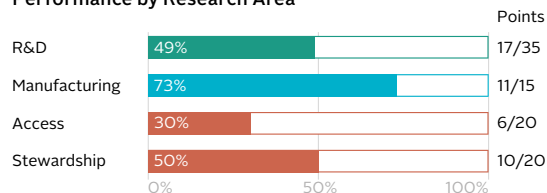
* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

** Listed on the 2019 WHO EML (Section 6).

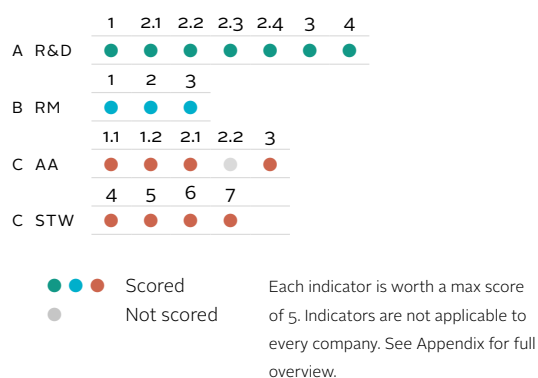
Performance in the Benchmark



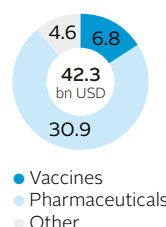
Performance by Research Area



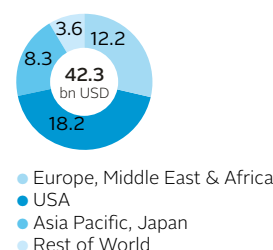
How Merck & Co, Inc was evaluated



Revenues by product (2018)



Revenues by region (2018)



PORTFOLIO for diseases in scope

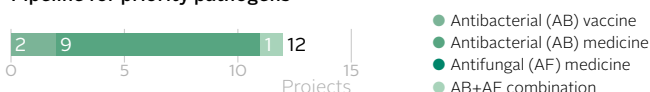
Mid-sized portfolio: At least 25 products (20 unique INNs): 15 antibacterial medicines; 5 antibacterial vaccines; 5 antifungal medicines

Essential medicines: 32% (8) of products are on the 2019 WHO EML

AWaRe medicines:** 1 Access group; 2 Watch group

Anti-TB medicines:** 1 product

Pipeline for priority pathogens



Products on the market



All companies were assessed based on data available in the public domain, including information the companies have made publicly available. This was supplemented by data submitted directly to the Benchmark by the companies. Merck & Co, Inc declined to submit data to the 2020 AMR Benchmark.

OPPORTUNITIES FOR MERCK & CO, INC

Remain engaged in R&D for antibacterial medicines and vaccines. Merck & Co, Inc is one of the few large research-based pharmaceutical companies still active in R&D for antibacterial medicines and vaccines. It is critical for the development and commercialisation of new products that large research-based pharmaceutical companies remain engaged in this space, either through acquisitions and in-licensing or through discovery.

Follow up to public commitments and increase public disclosure on environmental risk management. Following up on its commitments as a signatory to the Industry Roadmap for Progress on Combating AMR, Merck & Co, Inc can work with stakeholders to develop a practical mechanism to publicly disclose (1) a list of its suppliers and waste-treatment plants and (2) the results of environmental audits and the levels of antibacterial discharge from its own sites and the sites of its suppliers.

Expand registration and ensure adequate supply of antibacterial medicines in more access countries. Merck & Co, Inc can disclose more information regarding the access countries in which it has filed its antibacterial medicines for registration and to which it ensures a continuous supply.

Scale up UK pilot and fully decouple sales incentives from sales volumes. In order to mitigate the risk of inappropriate use of its antibacterial and/or antifungal medicines, Merck & Co, Inc can build on its current pilot in the UK and fully decouple sales incentives for sales volumes.

Publicly share raw data from its surveillance programme SMART. Merck & Co, Inc can share publicly (e.g., with the AMR Register) the raw data collected for its long-term, multinational surveillance programme SMART.

CHANGES SINCE 2018

- Received FDA approval in July 2019 for relebactam/imipenem/cilastatin (Recarbrio®) for the treatment of adults with complicated urinary tract and complicated intra-abdominal bacterial infections.
- Received FDA approval in June 2019 for ceftolozane/tazobactam (Zerbaxa®) for the treatment of hospital-acquired and ventilator-associated bacterial pneumoniae.
- Started a pilot in January 2019 where it would not reward its sales agents based on antibacterial sales volumes in UK hospitals to help prevent the inappropriate use of its antibacterial medicines.
- Reflects emerging resistance trends and guidelines for healthcare professionals (HCPs) in its marketing materials from 2018 onwards to address appropriate use.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 No information on relevant R&D investments

Merck & Co, Inc does not report publicly, or to the Benchmark, how much it invested in R&D for antibacterial medicines, antifungal medicines and/or vaccines in 2017 and 2018.

A.2.1 One of the largest pipelines evaluated

Compared to the large research-based pharmaceutical companies evaluated, this pipeline is among the largest. The company reports 12 projects targeting priority pathogens in its pipeline, 11 of which target bacterial pathogens, including

two vaccine and nine medicine projects. The other project, in discovery stage, targets both bacterial and fungal pathogens. Of the 12 projects, three are in discovery stage, four are in pre-clinical development and five are in clinical development. Two of its clinical candidates, ceftolozane/tazobactam (Zerbaxa®) and imipenem/cilastatin/relebactam (Recarbrio®), were approved by the FDA in June and July 2019, respectively. Merck & Co, Inc disclose that they run an active in-house antibacterial discovery programme, demonstrating its ongoing commitment to early-stage discovery work. It also

states that it generally does not publicly disclose candidates in Phase I or earlier.

A.2.2 No clinical-stage novel projects

Merck & Co, Inc's clinical-stage medicine pipeline for priority pathogens consists of both new and adapted R&D projects. It does not currently include candidates that are considered novel. However, during the period of analysis, Merck & Co, Inc received a market approval for a new, non-novel candidate, cilastatin/imipenem/relebactam (Recarbrio®), for the treatment of complicated urinary tract and intra-abdominal

Pipeline targeting priority pathogens: 12 As at 16 October 2019

| Discovery | Pre-clinical | Phase I | Phase II | Phase III | Approval |
|---|---|---------|----------|---|---|
| Compound screening ALIS (MOA) - <i>M. tuberculosis</i> | ATP synthase inhibitor 1 mo GLP safety studies - <i>M. tuberculosis</i> | | | Fidaxomicin (Dificid®) - <i>C. difficile</i> - (Adaptation - paediatric) - <i>C. difficile</i> -associated diarrhoea | Relebactam/imipenem/cilastatin (Recarbrio®)*** - GNB (including CRE) - cIAI and cUTI (Approved July 2019, FDA) |
| Partnership with Orchid Pharma, India - Bacteria & fungi | Diarylquinoline - <i>M. tuberculosis</i> | | | Tedizolid (Sivextro®) - GPB - Adaptation (additional indications) - HABP and VABP | Ceftolozane/tazobactam (Zerbaxa®) - GNB - Adaptation (additional indications) - HABP and VABP (Approved June 2019, FDA) |
| Protein synthesis inhibitor - <i>M. tuberculosis</i> | <i>In vivo</i> pre-clinical pharmacokinetic/pharmacodynamic dose ranging project - <i>M. tuberculosis</i> | | | ♦ Pneumococcal conjugate vaccine V114 - <i>S. pneumoniae</i> | |
| | ♦ <i>Shigella</i> vaccine | | | | |

♦ = Vaccine

cIAI = Complicated intra-abdominal infection

CRE = Carbapenem-resistant *Enterobacteriaceae*

cUTI = Complicated urinary tract infection

FDC = Fixed-dose combination

GNB = Gram-negative bacteria

GPB = Gram-positive bacteria

HABP = Hospital-acquired bacterial pneumonia

VABP = Ventilator-associated bacterial pneumonia

*** Relebactam/imipenem/cilastatin (Recarbrio®)

Adaptation for additional indications (HABP and VABP) met its primary endpoint in Phase III trials in September 2019.

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

infections.

A.2.3 Two vaccines in the pipeline

Merck & Co, Inc reports two vaccine projects in its pipeline. These include one new project (to prevent *Shigella* spp. infections) and one adapted project (against *S. pneumoniae*). Its *Shigella* vaccine is being developed through Hilleman Laboratories, a joint-venture partnership between Merck & Co, Inc and Wellcome Trust.

A.2.4 Three candidates targeting critical and/or urgent priorities

Merck & Co, Inc has three candidates targeting critical and/or urgent priority pathogens that qualify for analysis. All candidates are for antibacterial medicines in clinical development: fidaxomicin (Dificid®), in Phase III and which targets *C. difficile*; ceftolozane/tazobactam (Zerbaxa®),

recently approved for HABP and VABP and which targets CRPA; and imipenem/cilastatin/relebactam (Recarbrio®), which was recently approved for cIAI and cUTI and targets CRE. These pathogens are among those that have been identified as critical and/or urgent R&D priorities for limiting AMR by WHO and/or the US Centers for Disease Control and Prevention (CDC).

A.3 Three intellectual capital sharing initiatives

Its three relevant initiatives include being part of Hilleman Laboratories, a joint-venture partnership between Merck & Co, Inc and Wellcome Trust. The joint venture is responsible for the development of a *Shigella* vaccine, among others. In addition, Merck & Co, Inc reports a similar research centre based in Spain, collaborating with the University of Granada and receiving

funding from the regional government of Andalusia. Further, the company is part of the TB Drug Accelerator Programme, a consortium of research institutions and pharmaceutical companies that is developing new treatments for tuberculosis (TB).

A.4 Commits to expanding access and affordability practices

Merck & Co, Inc does not publicly report any specific access or stewardship plans for its five late-stage medicine and vaccine projects targeting priority pathogens. The company has made a general commitment to expanding access to its products through broad registration and to improving affordability and it supports the appropriate and responsible use of them.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Comprehensive environmental risk-management; less information on discharge limits for own sites and suppliers

Merck & Co, Inc reports a comprehensive strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, with an aim to limit AMR. This includes audits generally every 1–2 years, depending on risk. The company reports setting discharge limits for antibacterials manufactured at its sites based on PNECs to limit AMR (or more stringent PNECs).

Merck & Co, Inc expects third-party suppliers of antibacterial APIs and drug products to follow its standards and guidelines, including limits. The company reports being in the process of reviewing suppliers' operations to assess good practice in controlling releases of antibacterials into the environment and reports having provided them with the limits their discharges should meet. It expects external private waste-treatment plants to comply with its environmental standards and

guidelines, but there is limited information on how plants are audited. Merck & Co, Inc reports using no external private wastewater-treatment plants. Wastewater is either treated on-site before being discharged to surface-water bodies or sent to local municipal wastewater-treatment plants.

B.2 Publicly discloses some information on environmental risk management

Merck & Co, Inc publishes some components of its environmental risk-management strategy. Further, it is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. The underlying methodology was summarised in an open-access journal article co-authored by Alliance members including Merck & Co, Inc. Merck & Co, Inc does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private waste-treatment plants; (2) a list of these suppliers and waste-treatment plants; or

(3) the levels of antibacterial discharge from its own sites.

B.3 Has system to maintain production quality for own and suppliers' sites; no requests for official corrective action

Merck & Co, Inc reports having a system to maintain high-quality antibacterial production, consistent with international GMP standards. The company reports requiring suppliers to abide by regulatory and company quality standards, regardless of geography, including submitting suppliers to a qualification process prior to establishment of a commercial agreement. Audits are risk-based and the company reports tracking implementation of corrective and preventive actions. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Merck & Co, Inc's own sites or any subsidiaries.[†]

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries[†]

C.1.1 Filed to register relevant on-patent products in 3 access countries on average

Merck & Co, Inc performs less well than its peers in this area, as it publicly discloses limited information regarding the access countries in which it has filed relevant on-patent products for registration. It does report that one antibacterial ceftolozane/tazobactam (Zerbaxa®) has been filed for registration in at least 30 access countries.

C.1.2 Limited information on registration filings for relevant off-patent products

Merck & Co, Inc reports no evidence of filing its relevant off-patent products for registration in

access countries. It does report that other antibacterials, such as imipenem/cilastatin, have been filed for registration in several access countries.

C.2.1 Basic strategy for ensuring affordability

For its relevant on-patent products, Merck & Co, Inc, considers affordability when setting prices. It works with governments and non-governmental organisations to build effective vaccination delivery programmes. It uses tiered pricing based on factors such as the country's level of development, actual health spending and the number of people at risk of infection in the population. However, it does not disclose the products or

countries to which this pricing strategy applies. Merck & Co, Inc does not disclose how it plans to increase the affordability of such products over the next five years.

C.2.2 Pricing strategies for off-patent products Companies were not scored for this indicator as the available data was insufficient for a comparative analysis. Merck & Co, Inc, does report that it takes socioeconomic factors into account when determining prices for off-patent antibacterial or antifungal medicines or vaccines.

C.3 Some strategies to ensure the continuous supply of relevant products

Merck & Co, Inc performs less well than other large research-based pharmaceutical companies evaluated, as it discloses limited information publicly on the steps it takes to ensure the continuous supply of its relevant products to access countries. It discloses some strategies for achieving this aim. It partners with various organizations including the African Association

of Essential Drugs National Purchasing Centres (ACAME) for Sub-Saharan Africa and the Developing Countries Vaccine Manufacturers Network (DCVMN). To mitigate against falsified medicines reaching the supply chain, it has several strategies, including product security features, publication of authorised distributors on its website, awareness-raising initiatives and its Merck Anti-Counterfeiting operations to address large-scale criminal enterprises.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Broad strategy to mitigate COI for all educational programmes

The Benchmark analysed five AMR-related educational programmes for HCPs from Merck & Co, Inc. Merck & Co, Inc reports broad COI mitigation for all five programmes. To mitigate COI for three programmes, it provides financial resources to independent third parties to develop the programmes. Of the two programmes developed by the company, one has all three COI mitigation strategies looked for by the Benchmark: (1) content is developed independently from its marketing department (it is developed by independent third parties); (2) a pledge not to provide financial or material incentives to participants; and (3) it does not use branded materials. However, for the remaining programme, it is unclear whether content is developed independently from its marketing department or whether it uses branded materials.

C.5 Adapts marketing materials to address appropriate use

Merck & Co, Inc engages in practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines via its marketing practices. Under a global policy, all of Merck & Co., Inc's marketing materials reflect emerging resistance trends and include guidelines for HCPs to raise awareness of AMR and address appropriate use. To this aim, it has developed its Star of Stewardship principles for marketing teams to follow. Under this guidance, all marketing materials must include, e.g., specific indications, treatment duration and dose. After the period of analysis, the company publicly announced that it had started a pilot in January 2019 where it would not reward its sales agents based on antibacterial volumes sold in UK hospitals.

C.6 No information on brochure and/or packaging adaptations to facilitate appropriate use

There is no information regarding Merck & Co, Inc's adaptations in its brochures and/or packaging to facilitate appropriate use of its antibacterial and/or antifungal medicines by patients beyond regulatory requirements.

C.7 Active in multiple AMR surveillance programmes; openly publishes results

Merck & Co, Inc is active in multiple long-term AMR surveillance programmes. Three programmes are international: the Study for Monitoring Antimicrobial Resistance Trends (SMART); the Program to Assess Ceftolozane/Tazobactam Susceptibility (PACTS); and Surveillance of Tedizolid Activity and Resistance (STAR). These programmes run in 63, 28 and 14 countries respectively. Two programmes are national: CANWARD in Canada; and the BSAC Resistance Surveillance Programme in the UK. All five programmes only share their results in peer-reviewed open-access journal articles. Merck & Co, Inc. does not report making antibacterial and/or antifungal consumption data available to national governments or other public health authorities.

DIAGNOSTICS, ANIMAL HEALTH & AGRICULTURE

Activities in this area are not scored by the Benchmark. This information is provided given the importance of diagnostics, animal health and agriculture on the topic of AMR.

Merck & Co, Inc is the only company in scope that is involved in antibacterials for use in animal health and it was an original signatory to the Health for Animals Antibiotic Commitment. Its Position Statement on Animal Health states that it supports the responsible use of antibacterials to treat and improve the health of animals by: (1) conducting research to develop alternatives to antibacterials for animal use; (2) working with regulatory agencies to establish withdrawal periods and submitting data related to resistance development as part of the approval process for antibacterials used in food-producing animals; (3) providing veterinarians, commer-

cial production operations, farmers, ranchers and feed companies with guidelines on resistance management, appropriate dosage, and length of usage to support the appropriate use of antibacterials; and (4) supporting the adherence to guidelines on the prudent use of antibacterials developed by the World Organization for Animal Health (OIE) and adopted jointly by the American Veterinary Medical Association, Federation of Veterinarians of Europe and Canadian Veterinary Medical Association.

Moreover, Merck & Co, Inc is teaming up with the Association of American Veterinary Medical Colleges (AAVMC) through its Animal Health division on an international grant programme designed to help mitigate AMR in animals. The programme is focused on building networks and using communication technology to increase

awareness, share ideas and support innovative approaches to improving veterinary medical education at universities around the world.

Motif Bio plc

Small/medium-sized enterprise

Stock exchange: LSE; NASDAQ • Ticker: MTFB • HQ: London, UK • Employees: 7

PERFORMANCE

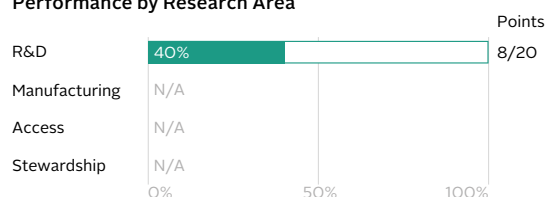
Motif Bio performs less than average in Research & Development when compared to other small and medium-sized enterprises in scope.

R&D: Motif Bio has four antibacterial projects for priority pathogens in its pipeline. It commits to developing access plans for its late-stage projects to address affordability in access countries.

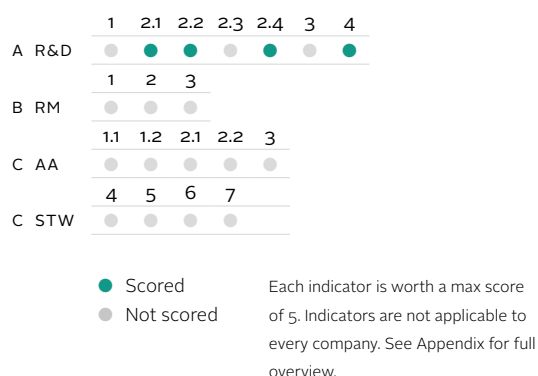
Performance in the Benchmark



Performance by Research Area



How Motif Bio was evaluated



SALES AND OPERATIONS

Therapeutic areas: Multidrug-resistant (MDR) Gram-positive bacteria

Products on the market: None

R&D grants received since 2016: At least USD 120,000, awarded from one funder (Cystic Fibrosis Foundation). This award was granted in January 2018 to fund *in vitro* testing that will help to advance the development of iclaprim for the treatment of lung infections in patients with cystic fibrosis.

Financing and Investment Structure: Motif Bio is a publicly listed company. It completed its IPO in November 2016 on the NASDAQ stock exchange, raising USD 25 million. It is also listed on the London Stock Exchange.

M&A since 2018: None in the antibacterial and/or antifungal sectors

Revenues

(2018)



PIPELINE for diseases in scope

Pipeline size: 4 projects for priority pathogens* (4 antibacterial medicines)

Development stages: 2 clinical projects for iclaprim, for the treatment of acute bacterial skin and skin structure infections and hospital-acquired and ventilator-associated bacterial pneumonia, and 2 pre-clinical projects

Novelty: No novel clinical-stage medicine projects

Regulatory approvals: 0 approvals for priority pathogens

Access plans: 2 of 2 late-stage R&D projects with project-specific access plans, both of which are commitments to develop equitable pricing strategies in low- and middle-income countries, as well as to target registration based on public health need and disease prevalence

Stewardship plans: Neither of its 2 late-stage R&D medicine projects have project-specific stewardship plans.

Pipeline for priority pathogens



* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

OPPORTUNITIES FOR MOTIF BIO

Operationalise stewardship plans for iclaprim. Motif Bio is developing one antibacterial candidate (iclaprim) in late-stage clinical development. Motif Bio can develop specific plans to ensure that iclaprim will be appropriately used globally after market approval. As examples of stewardship plans, the company can commit to decouple sales incentives from sales volumes and/or become involved in antibacterial surveillance activities.

CHANGES SINCE 2018

- Announced a partnership with the NIH in August 2019 to evaluate iclaprim activity against *L. monocytogenes*.
- Required by the FDA in June 2019 to conduct further study of iclaprim to evaluate potential risk of elevated transaminases.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 R&D investments

Motif Bio invested USD 40.5 million in the development of antibacterial medicines in 2017 and 2018. As with all other small and medium-sized enterprises (SMEs) evaluated, Motif Bio was not scored in this indicator.

adapted R&D projects. It does not currently include candidates that are considered novel. However, Motif Bio is developing iclaprim for the treatment of acute bacterial skin and skin structure infections, as well as hospital-acquired and ventilator-associated pneumonia.

A.3 Intellectual capital sharing

As an SME, Motif Bio was not scored for this indicator, in line with the external stakeholder consensus defined by the Foundation.

A.2.1 Pipeline size of four projects

Motif Bio reports four projects targeting priority pathogens in its pipeline. The company focuses on antibacterial medicine development, and has two projects in pre-clinical development and two in Phase III of clinical development. One of these projects has been submitted for market approval.

A.2.3 Vaccines in the pipeline

Motif Bio is not eligible for this indicator as it is not active in vaccine development.

A.4 Commits to addressing access for two of two projects; no stewardship plans

Motif Bio has committed to addressing affordability for its two late-stage R&D projects targeting priority pathogens. The company commits to filing iclaprim for registration based on public health needs and disease prevalence. It also commits to addressing the affordability of its products in low- and middle-income countries with pricing strategies that take affordability into account. The company makes a general commitment to improving stewardship but does not provide details on stewardship programmes.

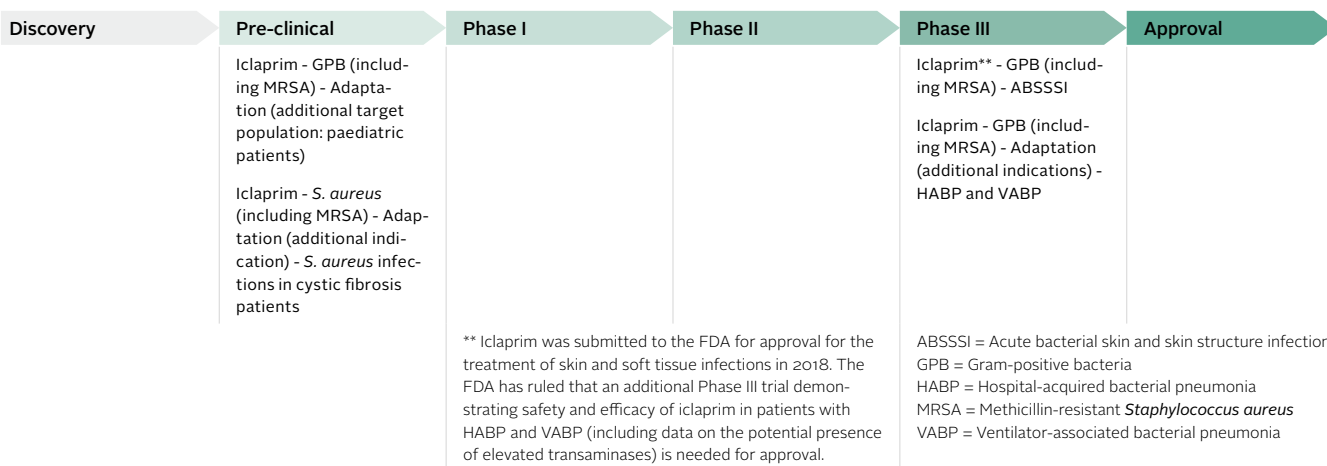
A.2.2 No clinical-stage novel projects

Motif Bio's clinical-stage medicine pipeline for priority pathogens consists of both new and

A.2.4 No candidates targeting critical and/or urgent priorities

Motif Bio does not have any candidate targeting pathogens considered 'critical' and/or 'urgent' R&D priorities for limiting AMR, as defined by WHO and/or the US Centers for Disease Control and Prevention (CDC).

Pipeline targeting priority pathogens: 4 As at 16 October 2019



B RESPONSIBLE MANUFACTURING

As an SME, Motif Bio is not evaluated in this Research Area. It has no antibacterial products on the market.

C APPROPRIATE ACCESS & STEWARDSHIP

As an SME, Motif Bio is not evaluated in this Research Area. It has no antibacterial and/or antifungal products on the market.

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

Mylan NV

Generic medicine manufacturer

Stock exchange: NASDAQ • Ticker: MYL • HQ: Hatfield, UK • Employees: 35,000

PERFORMANCE

Mylan performs well overall in its evaluated Research Areas when compared to other generic medicine manufacturers in scope.

Responsible Manufacturing: Performs well. Reports environmental risk-management strategy for own sites, including completed risk assessments based on discharge limits and commitments for future supplier evaluation.

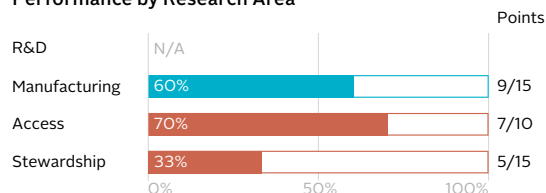
Appropriate Access: Performs well. Files for registration for all relevant off-patent products in access countries. Reports pricing strategies that account for socioeconomic conditions. Reports strategies to ensure continuous supply to access countries.

Stewardship: Middle-performing. Its educational programmes have comprehensive conflict of interest (COI) mitigation. It has no marketing or sales practices that aim to address appropriate use and it does not adapt its brochures or packaging.

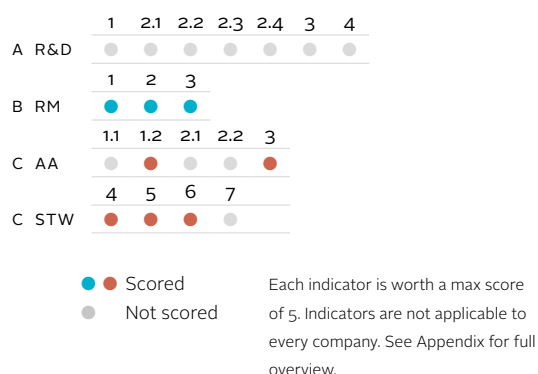
Performance in the Benchmark



Performance by Research Area



How Mylan was evaluated



SALES AND OPERATIONS

Therapeutic areas: Anaesthesia; Cardiovascular diseases; Dermatology; Gastroenterology; Infectious diseases; Metabolic diseases; Oncology; Pain management; Respiratory diseases; Women's health

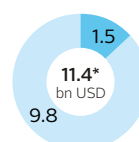
Business segments: North America; Europe; Rest of World

Product categories: Biosimilars; Consumer health; Generic medicines and innovative medicines

Manufacturing & supply: Mylan reports that it supplies its antibacterial and antifungal medicines across 75 countries, 38 of which are low- and middle-income countries.

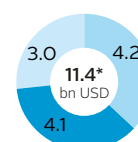
M&A since 2018: None in the antibacterial and/or antifungal sectors

Revenues by product (2018)



● Infectious diseases
● Other pharmaceuticals

Revenues by region (2018)



● Europe
● North America
● Rest of World

* Segments do not add up to 11.4 bn USD due to rounding.

PORTFOLIO for diseases in scope

Comparatively large portfolio: At least 173 products (89 unique INNs): 138 antibacterial medicines; 34 antifungal medicines; 1 antibacterial and antifungal medicine combination

Essential medicines: 32% (56) of products are on the 2019 WHO EML

AWaRe medicines*: 26 Access group; 13 Watch group; 1 Reserve group

Anti-TB medicines*: 6 (incl. 1 Watch group, 2 Reserve group)

Products on the market



The number of products is based on data from public sources, IQVIA, and data submitted by the company. It may not account for Mylan's entire portfolio.

* Listed on the 2019 WHO EML (Section 6).

OPPORTUNITIES FOR MYLAN

Expand availability and affordability of delamanid and pretomanid. Mylan in-licensed two (out of three) of the new multidrug-resistant tuberculosis (MDR-TB) medicines approved in over half a century: delamanid from Otsuka and pretomanid from the TB Alliance. Mylan should, as reportedly planned, continue to expand the availability of these medicines by ensuring that it files for registration in the remaining applicable access countries, prioritising those with a high burden of MDR-TB, and where it has the right to register. Per its reported commitment, Mylan should continue to collaborate with its partners to support accelerated registration and increased affordability.

Expand registration and ensure adequate supply of antibacterial medicines to access countries. Mylan can file for registration and ensure adequate supply of antibacterial medicines on the 2019 WHO EML, within its current portfolio (e.g. the forgotten antibiotics benzylpenicillin, chloramphenicol, cloxacillin, colistin, dicloxacillin, flucloxacillin, fosfomycin, nitrofurantoin, phenoxymethylpenicillin and trimethoprim) in more access countries.

Expand its environmental risk-management strategy, including discharge limits, to third-party suppliers and external private waste-treatment plants. Mylan has an environmental risk-management strategy and auditing processes for its own manufacturing sites, including discharge limits. The company can ensure that these limits, as well as the strategy, extend fully to the sites of third-party suppliers and external private waste-treatment plants, including auditing and discharge-monitoring processes.

Decouple sales incentives from sales volumes and/or avoid deploying sales agents. In order to mitigate the risk of inappropriate use of its antibacterial and/or antifungal medicines, Mylan can decouple sales incentives from sales volumes and/or avoid deploying sales agents, as appropriate.

CHANGES SINCE 2018

- Partnered with the TB Alliance in April 2019 to provide access to investigational TB treatments, including a global license to manufacture and commercialise pretomanid.
- Conducted environmental risk assessments at own sites using the AMR Industry Alliance framework and PNECs; started promoting the framework and limits among suppliers in July 2019.
- First company to receive WHO prequalification in 2018 for the antifungal flucytosine, on the 2019 WHO EML, for the treatment of cryptococcal meningitis.
- Granted a license from Otsuka Pharmaceuticals to prioritise access to delamanid (Deltysba®) for multidrug-resistant TB (MDR-TB) in South Africa, India and other high burden TB countries.
- Involved in two AMR surveillance programmes in India from 2018 onwards. It supports the Revised National TB Control Programme and a study on ICU patients.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer (GMM), Mylan is not evaluated in this Research Area. Mylan reports a collaboration with the TB Alliance to market and manufacture, respectively, the new anti-TB drug pretomanid, developed by the non-profit TB Alliance as part of two combination regimens: one with the medicines bedaquiline and linezolid (BPAL regimen)

for the treatment of extensively drug-resistant or MDR-TB that is treatment-intolerant or non-responsive and another with the medicines bedaquiline, moxifloxacin and pyrazinamide (BPmZ regimen), for drug-sensitive and MDR-TB. FDA approval for pretomanid was obtained on August 2019.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Environmental risk-management strategy for own sites

Mylan reports a strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, which includes audits. The company reports setting discharge limits for all antibacterials manufactured at its sites based on PNECs to limit AMR (or more stringent PNECs), as published by the AMR Industry Alliance. It has used these limits to conduct an initial risk assessment at its own sites.

Mylan has not yet implemented its strategy with third-party suppliers of antibacterial APIs and/or drug products. The company has committed to promoting and implementing the AMR Industry Alliance manufacturing framework, including supplier assessments. After the period of analysis, Mylan notified its suppliers in writing of the framework expectations and discharge limits. There is limited information on the requirements the company makes of external private

waste-treatment plants in terms of environmental strategy, audits and antibacterial discharge limits.

B.2 Publicly discloses some information on environmental risk management

Mylan publishes some components of its environmental risk-management strategy. Further, it is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. Mylan does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private waste-treatment plants; (2) a list of these suppliers and waste-treatment plants; or (3) the levels of antibacterial discharge from its own sites.

B.3 Has system to maintain production quality for own and suppliers' sites; regulator requested official corrective action

Mylan reports having a system to maintain high-quality antibacterial production, consistent with international GMP standards. This includes yearly internal audits and tracking of corrective actions. In April 2018, an FDA drug quality inspection identified non-conformities with cGMP at one of the company's sites producing antibacterials, resulting in an official request for corrective action. The company reports that the site has taken corrective actions. Mylan reports requiring suppliers to abide by regulatory and company quality standards. This includes submitting suppliers to a qualification process, after which a quality agreement is established. It reports conducting risk-based audits of suppliers that hold them to the same standards as internal sites and collaborating with suppliers to implement corrective and preventive actions.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries**

C.1.1 Registering on-patent products

Mylan was not eligible for this indicator as it does not have on-patent antibacterial or antifungal medicines or vaccines in its portfolio.

C.1.2 Filed to register relevant off-patent products*** in 4.8 access countries on average

Mylan is a middle-performing company when it comes to filing relevant off-patent products for registration. It reports filing all its relevant off-patent products (10/10 antibacterial and antifungal medicines) for registration in access countries. Its antibacterial ceftazidime, used for conditions including pneumonia and meningitis, has been filed in ten access countries. Ceftazidime is followed by the antibacterials amoxicillin and ceftriaxone, filed by Mylan in eight and seven access countries, respectively

C.2.1 Pricing strategies for on-patent products

Mylan was not eligible for this indicator, as it does not have on-patent antibacterial or antifungal medicines or vaccines in its portfolio.

C.2.2 Pricing strategies for off-patent products Companies were not scored for this indicator as the available data was insufficient for a comparative analysis. Mylan reports that it considers the socioeconomic conditions within each market in its pricing strategies for off-patent antibacterial or antifungal medicines or vaccines. These strategies include negotiations with customers, public/private partnerships and tender programmes. Mylan reports that in 2018 it provided 59 billion doses of medicine to over 165 countries at an average price of USD 0.19 per dose.

C.3 Several strategies to ensure the continuous supply of relevant products

Mylan's performance is stronger than other generic medicine manufacturers evaluated when it comes to taking steps to ensure the continuous supply of its relevant products to access countries. It reports several strategies to achieve this aim. It has a Rapid Response Advanced Planning system that looks 24 months ahead and regular meetings with external stakehold-

ers to discuss forecasting. To address the secure supply of ingredients, it has a global supply network of over 40 sites, makes use of dual sourcing and maintains safety and strategic stocks. To mitigate against falsified medicines reaching the supply chain, Mylan has several strategies, including using track-and-trace serialisation for its products. Plus, it ensures that contract manufacturers with whom it works also include its 2D data matrix on its products. Mylan also supplies six forgotten antibiotics† (chloramphenicol, flucloxacillin, nitrofurantoin, sulfamethoxazole/ trimethoprim, teicoplanin, and tobramycin) to access countries.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Comprehensive strategy to mitigate COI for all educational programmes

The Benchmark analysed four AMR-related educational programmes for healthcare professionals (HCPs) from Mylan. Mylan reports comprehensive COI mitigation for all four programmes. All programmes have all three COI mitigation strategies looked for by the Benchmark: (1) content is developed independently from its marketing department (i.e., the department does not give editorial input); (2) a pledge not to provide financial or material incentives to participants; and (3) a policy not to use branded materials.

C.5 Reports no information on sales practices or marketing materials that address appropriate use

Mylan does not report whether marketing materials for antibacterial and antifungal medicines take AMR trends and guidelines into account. The company also does not report appropriate sales practices such as decoupling sales agents' incentives from sales volumes.

C.6 Does not adapt brochures and/or packaging to facilitate appropriate use

Mylan does not provide evidence of adapting its brochures and/or packaging to facilitate appropriate use of its antibacterial and/or antifungal medicines by patients beyond regulatory requirements.

C.7 Antimicrobial surveillance

As a GMM, Mylan is not eligible for this indicator as GMMs have a limited role in AMR surveillance activities. The Benchmark notes that Mylan is active in two AMR surveillance programmes, both in India. It supports the Revised National TB Control Programme. Plus, in June 2019, it reportedly began supporting a multi-center retrospective study of antimicrobial resistance in ICU patients across India. The company reports that results will be published in a peer-reviewed medical journal.

** 102 low- and middle-income countries where better access to medicine is most needed. See Appendix VI.

*** See Appendix VII.

† A set of older off-patent antibacterials that are not always marketed or available, due to economic reasons, lack of

awareness and lack of demand but are still considered effective as a treatment for bacterial infections. See Appendix VII for citation.

Nabriva Therapeutics plc

Small/medium-sized enterprise

Stock exchange: NASDAQ • Ticker: NBRV • HQ: Dublin, Ireland • Employees: 110

PERFORMANCE

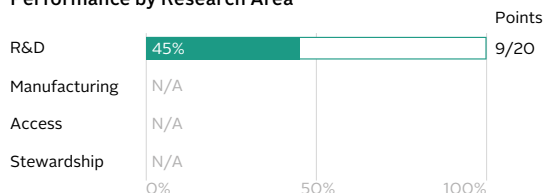
Nabriva performs on average in Research & Development when compared to other small and medium-sized enterprises in scope.

R&D: Nabriva has seven antibacterial projects for priority pathogens in its pipeline, including one late-stage candidate that is considered novel: lefamulin (Xenleta™), for community-acquired bacterial pneumonia. Granted approval in 2019 for one antibacterial medicine. Reports no project-specific plans for access or stewardship.

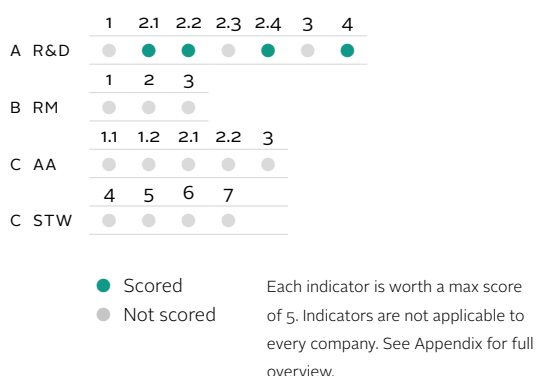
Performance in the Benchmark



Performance by Research Area



How Nabriva was evaluated



SALES AND OPERATIONS

Therapeutic areas: Anti-infectives

Products on the market: Lefamulin (Xenleta™) received FDA approval in August 2019, after the period of analysis, to treat community-acquired bacterial pneumonia.

R&D grants received since 2016: None

Financing and investment structure: Nabriva is a publicly listed company. It completed its IPO in September 2015, following one funding series and four venture rounds. Its lead investors were Orbimed, Phase 4 Ventures and Vivo Capital. From its inception in 2006 through August 2019, Nabriva has raised USD 537 million, of which USD 54 million was from non-dilutive sources (grants, business development).

M&A since 2018: In July 2018, Nabriva acquired Zavante Therapeutics, including its lead antibacterial drug candidate, an intravenous injectable form of fosfomycin (Contepo™) for the treatment of complicated urinary tract infections, including acute pyelonephritis.

Revenues

(2018)



PIPELINE for diseases in scope

Pipeline size: 7 projects for priority pathogens* (7 antibacterial medicines)

Development stages: 5 clinical projects, including BC-7013, a Phase I clinical candidate that is a semi-synthetic pleuromutilin derivative for the topical treatment of uncomplicated skin and skin structure infections, and 2 discovery/pre-clinical projects

Novelty: 1 novel project, lefamulin (Xenleta™), which was approved for the treatment of community-acquired bacterial pneumonia after the period of analysis and belongs to a new chemical class of antibacterials and has a new mode of action

Regulatory approvals: 1, for lefamulin (Xenleta™) for the treatment of community-acquired bacterial pneumonia in 2019

Access plans: None of its 3 late-stage R&D projects have project-specific access plans.

Stewardship plans: None of its 3 late-stage R&D medicine projects have project-specific stewardship plans.

Pipeline for priority pathogens



All companies were assessed based on data available in the public domain, including information the companies have made publicly available. This was supplemented by data submitted directly to the Benchmark by the companies. Nabriva declined to submit data to the 2020 AMR Benchmark.

OPPORTUNITIES FOR NABRIVA

Develop and implement access and stewardship plans for lefamulin (Xenleta™). Nabriva received FDA approval for lefamulin in August 2019. Nabriva can work with partners to ensure that this product is widely available and affordable in access countries, while appropriately used globally. Stewardship is particularly important because lefamulin is the first of a new class of antibacterials. As examples of access plans, the company can commit to an equitable pricing strategy and/or look for out-licensing opportunities with multiple manufacturers in low- and middle-income countries. As examples of stewardship plans, the company can commit to decouple sales incentives from sales volumes.

Develop access and stewardship plans for IV fosfomycin for injection (Contepo™). Nabriva has already submitted IV fosfomycin for injection for market approval in Europe and plan to re-submit its NDA to the US FDA in the last quarter of 2019. Nabriva can work with partners to develop plans to ensure that IV fosfomycin will be available, affordable and appropriately used after FDA approval. As examples of access plans, the company can commit to an equitable pricing strategy and/or look for out-licensing opportunities with multiple manufacturers in low- and middle-income countries. As examples of stewardship plans, the company can commit to decouple sales incentives from sales volumes and/or become involved in antibacterial surveillance activities.

CHANGES SINCE 2018

- Received FDA approval in August 2019 for lefamulin (Xenleta™) for the treatment of community-acquired bacterial pneumonia.
- Resubmitted NDA for IV fosfomycin (Contepo™) to the FDA in December 2019.
- Acquired Zavante Therapeutics in July 2019, including its lead antibacterial drug candidate, an intravenous injectable form of fosfomycin for the treatment of complicated urinary tract infections, including acute pyelonephritis.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 R&D investments

Nabriva invested USD 131.9 million in the development of antibacterial medicines in 2017 and 2018. As with all other small and medium-sized enterprises (SMEs) evaluated, Nabriva was not scored in this indicator.

A.2.1 Pipeline size of seven projects

Nabriva reports seven projects targeting priority pathogens in its pipeline. The company focuses on antibacterial medicine development, with one project in discovery stage, another project in pre-clinical development and five projects in clinical development, including one, fosfomycin (Contepo™), currently unavailable in the US, and which has been submitted for FDA market

approval. Another project, lefamulin (Xenleta™), was approved after the close of the Benchmark's period of analysis.

A.2.2 One clinical-stage novel project

Nabriva's clinical-stage medicine pipeline for priority pathogens consists of both new and adapted R&D projects. Nabriva has one late-stage antibacterial medicine project that is considered novel: lefamulin (Xenleta™), for community-acquired bacterial pneumonia, which belongs to a new chemical class and has a new mode of action. Nabriva received an approval for lefamulin for this indication after the close of the Benchmark's period of analysis.

A.2.3 Vaccines in the pipeline

Nabriva is not eligible for this indicator as it is not active in vaccine development.

A.2.4 One candidate targeting critical and/or urgent priorities

Nabriva has filed for first marketing authorisation for its adaptation of fosfomycin (Contepo™) in October 2018. This product targets *Enterobacteriaceae*, which has been identified as a critical priority for limiting AMR by WHO and as an urgent priority by the US Centers for Disease Control and Prevention (CDC).

Pipeline targeting priority pathogens: 7 As at 16 October 2019

| Discovery | Pre-clinical | Phase I | Phase II | Phase III | Approval |
|---|---|--|---|--|---|
| Pleuromutilin molecule platform – GNB and GPB | Lefamulin (Xenleta™) - Multidrug-resistant GNB (including <i>H. influenzae</i>) and GPB (including MRSA) and atypical bacteria - Adaptation (additional indications) - STIs (e.g. <i>N. gonorrhoeae</i> , <i>M. genitalium</i>), HAPB/VABP, osteomyelitis and prosthetic joint infections | BC-7013 - GPB (including MRSA and group A and group B <i>Streptococcus</i> spp.) - uSSSI Lefamulin (Xenleta™) - Multidrug-resistant GNB (including <i>H. influenzae</i>) and GPB (including MRSA) and atypical bacteria - Adaptation (additional target population: paediatric patients) | Lefamulin (Xenleta™) - Multidrug-resistant GNB (including <i>H. influenzae</i>) and GPB (including MRSA) and atypical bacteria - Adaptation (additional indication) - ABSSSI | IV fosfomycin (Contepo™)** - GNB (including ESBL-producing <i>Enterobacteriaceae</i>) and GPB - Adaptation (new dosing approach) - cUTI | Lefamulin (Xenleta™)*** - Multidrug-resistant GNB (including <i>H. influenzae</i>) and GPB (including MRSA) and atypical bacteria - CABP - Novel |

ABSSSI = Acute bacterial skin and skin-structure infection
 CABP = Community-acquired bacterial pneumonia
 cUTI = Complicated urinary tract infection
 ESBL = Extended-spectrum beta-lactamase
 GNB = Gram-negative bacteria
 GPB = Gram-positive bacteria
 HAPB = Hospital-acquired bacterial pneumonia
 MRSA = Methicillin-resistant *Staphylococcus aureus*
 STIs = Sexually transmitted infections
 uSSSI = Uncomplicated skin and skin-structure infection
 VABP = Ventilator-associated bacterial pneumonia

**IV fosfomycin (Contepo™) was first submitted to the FDA for approval in January 2019. Nabriva anticipates resubmitting to the FDA early in the fourth quarter of 2019.

***Lefamulin (Xenleta™) was approved after the period of analysis in August 2019 by the FDA.

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

A.3 Intellectual capital sharing

As an SME, Nabriva was not scored for this indicator, in line with the external stakeholder consensus defined by the Foundation.

A.4 No access or stewardship plans for late-stage R&D projects targeting priority pathogens

Nabriva has three such R&D projects. It currently reports no plans that address either the stewardship of or appropriate access to the products, upon reaching the market.

B RESPONSIBLE MANUFACTURING

As an SME, Nabriva is not evaluated in this Research Area. After the period of analysis, Nabriva gained marketing approval for one antibacterial product, lefamulin (Xenleta™). The Benchmark notes that Nabriva has published, in its annual report, the identities of all the suppliers it contracts for the manufacture of both the API and the drug product forms of lefamulin. Nabriva was not scored on these activities.

C APPROPRIATE ACCESS & STEWARDSHIP

As an SME, Nabriva is not evaluated in this Research Area. It has one antibacterial and/or antifungal product on the market: the antibacterial lefamulin (Xenleta™).

Novartis AG

Large R&D-based pharmaceutical company •

Stock exchange: SWX • Ticker: NOVN • HQ: Basel, Switzerland • Employees: 125,161

PERFORMANCE

Novartis is middle-performing in its evaluated Research Areas when compared to other large R&D-based pharmaceutical companies in scope. **R&D:** Performs low. Divested its antibacterial research programmes in 2018 but maintains an adapted project pipeline including a partnership with GARDP. It publicly shares all data for discontinued projects on Pew's SPARK platform.

Responsible Manufacturing: Performs well. Reports comprehensive environmental risk-management strategy for own sites and suppliers, but not audits to waste-treatment plants; risk assessments based on discharge limits completed at own sites and ongoing at suppliers' sites.

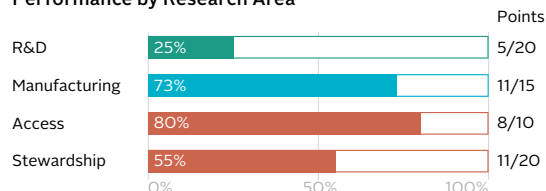
Appropriate Access: Performs well. Files its relevant off-patent products for registration in access countries. Employs strong strategies to ensure continuous supply and supplies three forgotten antibiotics.

Stewardship: Middle-performing. It has educational programmes with comprehensive conflict of interest (COI) mitigation. It adapts brochures and packaging for literacy and paediatric use for one product. Sells products through tenders and does not link incentives to the sales volume. It is not involved in AMR surveillance.

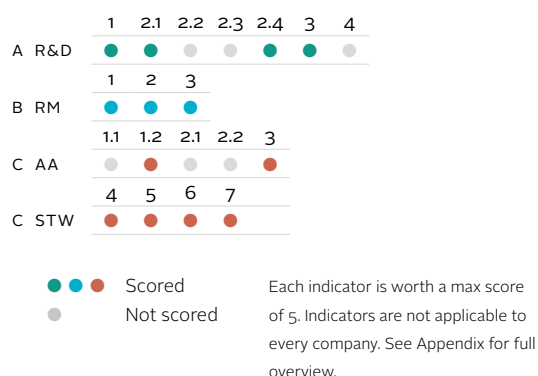
Performance in the Benchmark



Performance by Research Area



How Novartis was evaluated



SALES AND OPERATIONS

Therapeutic areas: Cardiovascular diseases; Dermatology; Immunology; Infectious diseases; Metabolic disorders; Neurology; Oncology; Ophthalmology; Respiratory diseases

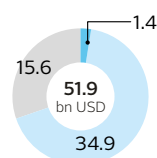
Business segments: Sandoz; Novartis Oncology; Novartis Pharmaceuticals

Product categories: Generic medicines; Innovative medicines

Manufacturing & supply: Novartis reports having 24 manufacturing sites that produce antibacterial APIs and/or drug products. It reports selling its antibacterial and antifungal medicines across approximately 140 countries, 71 of which are low- and middle-income countries.

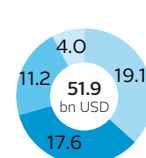
M&A since 2018: In September 2018, Novartis announced that it would divest the Sandoz US dermatology business and generic US oral solids portfolio to Aurobindo. The deal includes USD 900 million in cash and potential earn-outs of USD 100 million. In April 2019, Novartis completed the spin-off of Alcon as a separately traded company.

Revenues by product (2018)



● Anti-infectives (generics)
● Other pharmaceuticals
● Others

Revenues by region (2018)



● Europe
● USA
● Asia, Africa, Australasia
● Canada, Latin America

PIPELINE for diseases in scope

Pipeline size: 1 project for priority pathogens*

Development stages: 1 pre-clinical project

Novelty: No novel clinical-stage medicine projects

Regulatory approvals: 0 approvals for priority pathogens

Access plans: No late-stage R&D projects

Stewardship plans: No late-stage R&D projects

Pipeline for priority pathogens



PORTFOLIO for diseases in scope

Comparatively large portfolio: At least 152 products (74 unique INNs): 130 antibacterial medicines; 22 antifungal medicines

Essential medicines: 43% (66) of products are on the 2019 WHO EML

AWaRe medicines:** 29 Access group; 15 Watch group

Anti-TB medicines:** 9 (incl. 2 Reserve group)

Products on the market



The number of products is based on data from public sources, IQVIA, and data submitted by the company. It may not account for Novartis' entire portfolio.

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

** Listed on the 2019 WHO EML (Section 6).

OPPORTUNITIES FOR NOVARTIS

Follow up to public commitments and increase public disclosure on environmental risk management. Following up on its commitments as a signatory to the Industry Roadmap for Progress on Combating AMR, Novartis can work with stakeholders to develop a practical mechanism to publicly disclose (1) a list of its suppliers and waste-treatment plants and (2) the results of environmental audits and the levels of antibacterial discharge from its own sites and the sites of its suppliers.

Expand registration and ensure adequate supply of antibacterial medicines in more access countries. Novartis can file for registration and ensure adequate supply of antibacterial medicines on the 2019 WHO EML within its current portfolio (e.g. the forgotten antibiotics benzathine benzylpenicillin and fosfomycin) within its current portfolio in access countries.

Fully decouple sales incentives from sales volumes for all antibacterial and/or antifungal medicines not sold through tenders. Novartis sells most of its products through government and hospital tenders. In order to mitigate the risk of inappropriate use, Novartis can fully decouple sales incentives from sales volumes for its antibacterial and/or antifungal medicines not sold through tenders.

Engage in surveillance activities. Novartis is one of the only two large research-based pharmaceutical companies not active in surveillance activities. Novartis can engage in surveillance programmes and share publicly (e.g., through the AMR Register) the raw data from these programmes.

CHANGES SINCE 2018

- Closed its antibacterial and antiviral research programmes in July 2018 and announced a licensing agreement with Boston Pharmaceuticals for three divested antibacterial medicine projects in October 2018.
- Publicly shared data on some of its discontinued antibacterial research programmes via Pew Trusts' SPARK platform in January and May 2019
- Partnered with GARDP, in September 2018, to improve and adapt generic antibacterial medicines and increase their availability in LMICs, incl. development of heat-stable paediatric formulations.
- Initiated engagement with suppliers of antibacterial APIs and/or drug products to request them to quantify antibacterial discharge levels.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 Below average investments in relevant R&D, as proportion of pharmaceutical revenues

Novartis reports to the Benchmark how much it invested in R&D for antibacterial medicines in 2017 and 2018. As a proportion of its revenues from pharmaceuticals, these investments are below average compared to investments in such R&D made by other large research-based pharmaceutical companies evaluated in the Benchmark. The Benchmark is not able to publish further information, as the details were provided on the basis of confidentiality. Novartis is not involved in vaccines R&D.

A.2.1 One R&D project targeting a priority pathogen

Among the large research-based pharmaceutical companies evaluated, this pipeline is small in size. After licensing its infectious disease pipeline, Novartis reports one project targeting priority pathogens in its pipeline, for a medicine in pre-clinical development.

A.2.2 Novelty of pipeline

Novartis is not eligible for this indicator as it does not have any R&D candidates in clinical development.

A.2.3 Vaccines in the pipeline

Novartis is not eligible for this indicator as it is not active in vaccine development targeting priority pathogens.

A.2.4 One candidate targeting critical and/or urgent priorities

Novartis has one candidate targeting pathogens considered critical and/or urgent R&D priorities for limiting AMR, as identified by WHO and/or the US Centers for Disease Control and Prevention (CDC). Further details were provided on the basis of confidentiality.

A.3 One intellectual capital sharing initiative

Novartis shares data on the Pew Charitable Trusts' open-access Shared Platform for Antibiotic Research and Knowledge (SPARK). Through this platform, Novartis shares the results of susceptibility tests and target enzyme potency data (IC₅₀) for discontinued projects so that they can be used under a non-exclusive, royalty-free, sublicensable and transferable licence by research organisations. Novartis and GARDP partnered in September 2018 to improve and adapt existing generic antibacterial formulations and dosing regimens for newborns and children, specifically to develop heat-stable paediatric formulations against leading childhood diseases in lower-income countries.

A.4 Access and stewardship planning

Novartis is not eligible for this indicator as it has no projects in late-stage clinical development. Companies are expected to have plans in place for pipeline projects in Phase II and beyond.

Pipeline targeting priority pathogens: 1 As at 16 October 2019



** Clofazimine (Lamprene®), originally approved for the treatment of leprosy, is currently under review for WHO prequalification for tuberculosis. A Phase IIb/III trial for this additional indication was prematurely terminated by the company before the period of analysis. Novartis reports a commitment to make this tuberculosis project available with affordable pricing.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)**B.1 Comprehensive environmental risk-management for own sites and suppliers; limited oversight of waste-treatment plants**

Novartis reports a comprehensive strategy to minimise the environmental impact of waste-waters and solid waste from antibacterial manufacturing at its sites, with an aim to limit AMR. This includes audits every 2–4 years, depending on risk. The company reports setting discharge limits for all antibacterials manufactured at its sites, based on PNECs to limit AMR (or more stringent PNECs), as published by the AMR Industry Alliance. Novartis uses these PNECs to conduct risk assessments applying a mass balance approach, complemented by direct sampling and analytical testing, where needed.

Novartis expects third-party suppliers of antibacterial APIs and drug products to follow the same standards, including limits. The company reports that suppliers are audited based on risk, typically every three years. Review of antibacterial discharges has now been incorporated in the audit protocol, to be monitored in future audits. Novartis expects external private waste-treatment plants to comply with its environmental standards, but does not audit them. It does not report monitoring discharge levels of wastewater plants.

B.2 Publicly discloses some information on environmental risk management

Novartis publishes some components of its environmental risk-management strategy. Further, it is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. The underlying methodology was summarised in an open-access journal article co-authored by Alliance members including Novartis. Novartis does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private waste-treatment plants; (2) a list of these suppliers and waste-treatment plants; or (3) the levels of antibacterial discharge from its own sites.

B.3 Has system to maintain production quality for own and suppliers' sites: no requests for official corrective action

Novartis reports having a system to maintain high-quality antibacterial production, consistent with international GMP standards. This includes risk-based internal audits and tracking of corrective and preventive actions. The company reports requiring suppliers to abide by regulatory and company quality standards, as specified, e.g., in quality agreements and the Novartis Supplier Code. It reports auditing its suppliers as its own sites and having the same expectations in terms of corrective action implementation. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Novartis' own sites or any subsidiaries.[†]

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries[‡]

C.1.1 Registration of on-patent products
Novartis was not eligible for this indicator as it does not have on-patent antibacterial or antifungal medicines or vaccines in its portfolio.

C.1.2 Filed to register its relevant off-patent products§ in 11.8 access countries on average

Novartis is one of the leaders when it comes to filing relevant off-patent products for registration. It has filed 89% of its relevant products (8/9 antibacterial and antifungal medicines) for registration in access countries. Its most widely filed product in this analysis is the antibacterial medicine azithromycin, used for conditions including respiratory and skin infections. Novartis has filed its version of this product in 43 access countries. Azithromycin is followed by the antifungal fluconazole and the antibacterial medicine ceftazidime, filed by Novartis for registration in 28 and 17 access countries, respectively.

C.2.1 Pricing strategies for on-patent products
Novartis was not eligible for this indicator, as it does not have on-patent antibacterial or antifungal medicines or vaccines in its portfolio.

C.2.2 Pricing strategies for off-patent products
Companies were not scored for this indicator as the available data was insufficient for a comparative analysis.

Novartis, through Sandoz (its generic division), reports that it participates in tenders with hospitals, governments, NGOs and organizations including UNICEF, WHO and MSF. It states that it views this approach as helping to reach more patients in low-income countries, at a lower price point than via retail channels. Novartis also reports that, outside of tenders, it takes socioeconomic factors into account, such as the level of inequality and disease burden, when setting prices for new off-patent antibacterial and antifungal medicines.

C.3 Many strategies to ensure the continuous supply of relevant products

Novartis' performance is one of the strongest of the companies evaluated when it comes to taking steps to ensure the continuous supply of its relevant products to access countries. It uses 12 to 36-month forecasting and shares data with stakeholders through weekly operational meetings. To help ensure the supply of ingredients, Novartis applies a dual-sourcing strategy and its Novartis Emergency Management (NEM) and Supply Chain Management teams are trained to respond immediately to any supply shortage. Safety stocks are buffered by keeping an optimum inventory at each point of supply. To mitigate against falsified medicines reaching the supply chain, Novartis has several strategies including an anti-counterfeiting programme,

a risk-management database, in-house forensic capabilities and security features embedded on secondary packaging. Novartis also supplies the three forgotten antibiotics|| tobramycin, cefepime and cefpodoxime to access countries.

[†] Including only wholly-owned direct subsidiaries of the company. More information in Appendix I.

[‡] 102 low- and middle-income countries where better access to medicine is most needed. See Appendix VI.

[§] See Appendix VII.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Broad strategy to mitigate COI for all educational programmes

The Benchmark analysed the top five AMR-related educational programmes for healthcare professionals (HCPs) from Novartis. Novartis reports broad COI mitigation for all five programmes. Three programmes have all three COI mitigation strategies looked for by the Benchmark: (1) content is developed independently from its marketing department; (2) a pledge not to provide financial or material incentives to participants; and (3) it does not use branded materials. However, for one programme, it was unclear whether content was developed independently from its marketing department; and for the remaining programme, it was unclear whether financial or material incentives are provided to participants. After the period of analysis, the company stated that for both programmes content is developed independently from its marketing department and no financial or material incentives are given.

C.5 Adapts sales practices to address appropriate use

Novartis engages in practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines via its sales practices. Novartis does not disclose marketing practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines. It is, however, one of the two companies evaluated to report that it sells a significant portion of its antibacterial and/or antifungal medicines through tenders and does not link employees' incentives to the sales volume of these tenders.

C.6 Makes multiple adaptations to brochures and/or packaging to facilitate appropriate use

Novartis adapts brochures to facilitate the appropriate use by patients of relevant products: namely the antibacterials benzathine benzylpenicillin and amoxicillin/clavulanic acid. These adaptations take account of literacy and paediatric use. Novartis has created brochures

for benzathine benzylpenicillin in collaboration with the Pan-African Society of Cardiology for patients who may not be able to read. Novartis also created paediatric guidance for amoxicillin/clavulanic acid that focuses on correct dosing for children.

C.7 No involvement in AMR surveillance programmes or consumption data sharing

Novartis does not report any involvement in AMR surveillance programmes and it does not report making antibacterial and/or antifungal consumption data available to national governments or other public health authorities.

Otsuka Pharmaceutical Co, Ltd

Large R&D-based pharmaceutical company

Stock exchange: TSE • Ticker: 4578 (Otsuka Holdings Co, Ltd) • HQ: Tokyo, Japan • Employees: 5,700

PERFORMANCE

Otsuka is middle-performing in its evaluated Research Areas when compared to other large R&D-based pharmaceutical companies in scope. **R&D:** Middle-performing. Pipeline consists of four projects for medicines for priority pathogens. Reports commitments to access planning for one of its late-stage R&D projects and is active in intellectual capital sharing. **Responsible Manufacturing:** Performs less well. Reports a general environmental risk-management strategy for own sites without stating a specific aim to limit AMR.

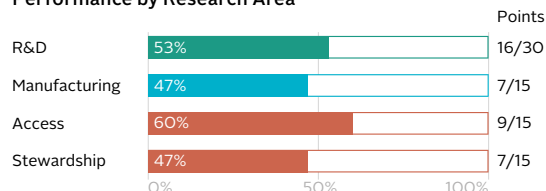
Appropriate Access: Middle-performing. Filed delamanid (Delyba®) for registration in access countries. Reports using long-term demand forecasting to ensure continuous supply.

Stewardship: Middle-performing. It has opted to not deploy sales agents to promote delamanid. It is not involved in AMR surveillance. It translates brochures for delamanid, but makes no further adaptations.

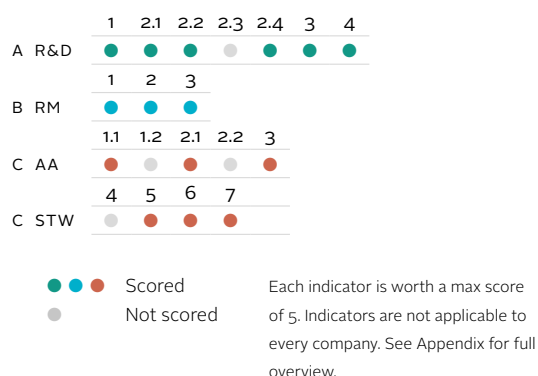
Performance in the Benchmark



Performance by Research Area



How Otsuka was evaluated



SALES AND OPERATIONS

Therapeutic areas: Cardiovascular diseases; Kidney diseases; Infectious diseases; Neurology; Oncology; Ophthalmology

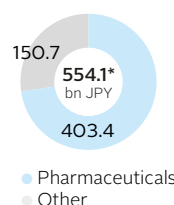
Business segments: Pharmaceuticals; Nutraceuticals

Product categories: Innovative medicines; Nutritionals

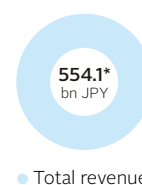
Manufacturing & supply: Otsuka reports having two manufacturing sites that produce antibacterial APIs and/or drug products. Its antibacterial medicine delamanid is available in 84 countries, 50 of which are low- and middle-income countries.

M&A since 2018: In August 2018, Otsuka completed the acquisition of Visterra for USD 430 million cash. From the Visterra pipeline Otsuka acquired, among the various projects, a preclinical stage candidate for severe *P. aeruginosa* infection.

Revenues by product (2018)



Revenues by region (2018)



*non-consolidated revenues

PIPELINE for diseases in scope

Pipeline size: 4 projects for priority pathogens* (4 antibacterial medicines)
Development stages: 2 clinical projects, including OPS-2071, a Phase II clinical candidate for the treatment of bacterial enteritis caused by *C. difficile*, and 1 preclinical project

Novelty: 1 novel project, OPC-167832, a Phase II clinical candidate for the treatment of tuberculosis (TB) that meets all four criteria set by WHO for innovativeness

Regulatory approvals: 0 approvals for priority pathogens

Access plans: 1 of 2 late-stage R&D projects with project-specific access plans, with a commitment to ensure availability and access to OPC-167832 through a partnership with the Bill & Melinda Gates Foundation

Stewardship plans: Neither of its 2 late-stage R&D medicine projects have project-specific stewardship plans.

PORTFOLIO for diseases in scope

Comparatively small portfolio: At least 1 product (1 antibacterial medicine)

Essential medicines: 1 product is on the 2019 WHO EML

AWaRe medicines:** None

Anti-TB medicines:** 1 product (1 antibacterial medicine)

Pipeline for priority pathogens



Products on the market



The number of products is based on data from public sources, IQVIA, and data submitted by the company. It may not account for Otsuka's entire portfolio.

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

** Listed on the 2019 WHO EML (Section 6).

OPPORTUNITIES FOR OTSUKA

Develop an AMR-specific environmental risk-management strategy. Otsuka can tailor its environmental risk-management strategy to AMR and implement the Common Antibiotic Manufacturing Framework and PNEC limits, as published by the Industry Alliance, of which it is a member. Otsuka can also work with stakeholders to develop a practical mechanism to publicly disclose (1) a list of its suppliers and waste-treatment plants and (2) the results of environmental audits and the levels of antibacterial discharge from its own sites and the sites of its suppliers.

Improve availability and affordability of delamanid (Delyba®). Otsuka can expand the availability of delamanid by ensuring that a file for registration is submitted (by Otsuka or delamanid's licencees) in more access countries, in particular the 30 countries with a high burden of TB. Otsuka can also improve affordability and supply to more access countries through licences with more manufacturers other than Mylan, assess where the price of other new TB medicines is lower and take into consideration the overall price of new TB regimens including multiple products.

Engage in TB surveillance activities. Otsuka can engage in a multinational, long-term surveillance programme focusing on resistance of delamanid in the countries where it markets the product. Otsuka can also encourage delamanid's licencees to engage in similar programmes in the countries where they are marketing the product.

CHANGES SINCE 2018

This section lists notable changes in companies' activities since the 2018 Benchmark. Since Otsuka was not in scope for evaluation in 2018, no changes are reported.

PERFORMANCE BY RESEARCH AREA

RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 Above average investments in relevant R&D, as proportion of pharmaceutical revenues

Otsuka reports that it invested USD 51 million in R&D for antibacterial medicines in 2017 and 2018. As a proportion of its revenues from pharmaceuticals, these investments are above average compared to investments in such R&D made by other large research-based pharmaceutical companies evaluated in the Benchmark. Otsuka does not invest in vaccines R&D. Otsuka's investment in R&D for TB medicines in 2017 is the largest reported by a Benchmark company. In addition to its own investments, Otsuka received USD 10 million for TB R&D from the Bill & Melinda Gates Foundation.

A.2.1 Pipeline size small compared to peers

Among the large research-based pharmaceutical companies evaluated, this pipeline is small in size. Otsuka reports four projects targeting priority pathogens, all of which target bacteria, including two medicine projects targeting *M. tuberculosis*, one targeting *C. difficile* and another targeting *P. aeruginosa*. Three projects

are in clinical development and one in pre-clinical development.

A.2.2 One clinical-stage novel project

Otsuka's clinical-stage medicine pipeline for priority pathogens consists of both new and adapted R&D projects. Otsuka has one late-stage antibacterial medicine project that is considered novel: OPC-167832, for pulmonary TB, which meets all four criteria set by WHO for innovativeness.

A.2.3 Vaccines in the pipeline

Otsuka is not eligible for this indicator as it is not active in vaccine development targeting priority pathogens.

A.2.4 Two candidates targeting critical and/or urgent priorities

Otsuka's pipeline includes a clinical antibacterial medicine candidate in Phase II (OPS-2071) that targets *C. difficile* and a pre-clinical candidate (VIS705) that targets *P. aeruginosa*, including multi-drug resistant strains. These pathogens have been identified by WHO and/or the

US Centers for Disease Control and Prevention (CDC) as an urgent R&D target for limiting AMR.

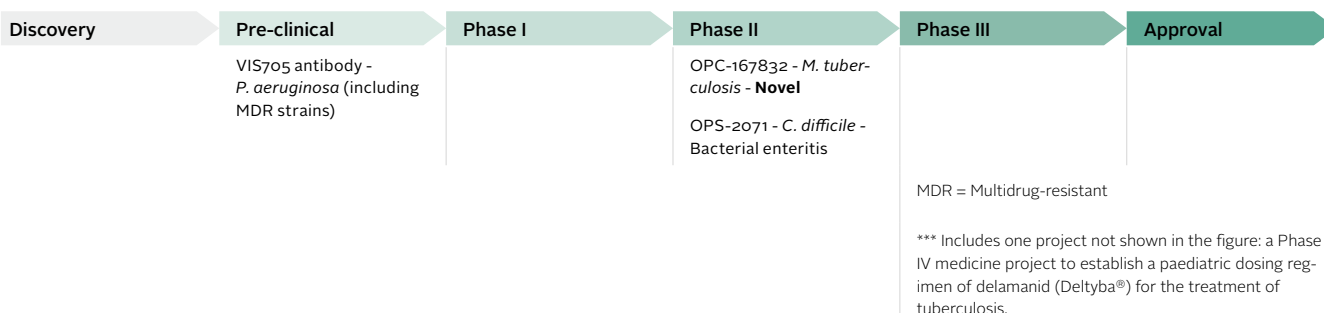
A.3 One intellectual capital sharing initiative

Otsuka commits to the stipulations set out by the Bill & Melinda Gates Foundation under the terms of its grants: namely, to provide unrestricted access, including re-use, to all peer-reviewed published research funded by the Foundation, including any underlying data sets.

A.4 Access plans for 1 of 2 projects

Otsuka has two late-stage R&D projects targeting priority pathogens, both medicines. For its project OPC-167832, Otsuka has committed itself contractually to the access plans stipulated by the Bill & Melinda Gates Foundation, which is co-developing the project. This includes commitments to make the product available and accessible at an affordable price to people most in need within developing countries. Otsuka does not report stewardship plans for either project.

Pipeline targeting priority pathogens: 4*** As at 16 October 2019



* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)**B.1 General environmental risk-management strategy for own sites**

Otsuka's general environmental strategy includes a commitment to manufacture its products in an environmentally responsible manner. However, this does not include any actions specific to delamanid (Deltiba®), the only antibacterial produced at its manufacturing sites, in both its API and drug product forms. Further, Otsuka does not report making any requirements in this regard to the third-party drug product manufacturer contracted for an intermediate step in delamanid production. There is limited information on the requirements the company makes of external private waste-treatment plants in terms of environmental strategy, audits and antibacterial discharge limits.

B.2 Publicly discloses some information on environmental risk management

Otsuka publishes some components of its environmental risk-management strategy. Further, it is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. Otsuka does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private waste-treatment plants; (2) a list of these suppliers and waste-treatment plants; or (3) the levels of antibacterial discharge from its own sites.

B.3 Has system to maintain production quality for own and suppliers' sites; no requests for official corrective action

Otsuka reports having a system to maintain high-quality antibacterial production, consistent with international standards. This includes periodic internal audits and tracking of corrective actions. The company reports requiring suppliers to abide by regulatory and company quality standards, as specified in GMP agreements. It reports auditing its suppliers and tracking implementation of corrective actions. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Otsuka's own sites or any subsidiaries.[†]

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries[‡]

C.1.1 Filed to register its one on-patent antibacterial medicine in 9 access countries

Otsuka is a middle-performing company when it comes to filing relevant on-patent products[§] for registration in access countries. It has one product that qualifies for this analysis – delamanid (Deltiba®), used for TB – which it has filed for registration in 9 access countries.

C.1.2 Registering relevant off-patent/generic products

Otsuka was not eligible for this indicator, as it does not report having relevant off-patent antibacterial or antifungal medicines or vaccines.

C.2.1 Takes socioeconomic factors into account when setting prices for on-patent products

Otsuka has one product that qualifies for this analysis: the antibacterial delamanid (Deltiba®). It demonstrates evidence of considering socioeconomic factors when setting prices. Otsuka

offers delamanid to the Global Drug Facility (GDF) at USD 1,700 per six-month course of treatment (a 98% reduction on the highest pricing tier). It is currently carrying out a technology transfer, under a licensing agreement, to Mylan India, which covers all aspects of API manufacturing. Over the next five years, Otsuka predicts that this will lead to further price reductions, and to 30,000 treatment courses being distributed.

C.2.2 Pricing strategies for off-patent products Companies were not scored for this indicator as the available data was insufficient for a comparative analysis. Otsuka does not report having off-patent antibacterial or antifungal medicines or vaccines.

C.3 Some strategies to ensure the continuous supply of relevant products

Otsuka performs less well than other large research-based pharmaceutical companies evaluated when it comes to taking steps to ensure

the continuous supply of its relevant products to access countries. It discloses some strategies for achieving this aim. It uses long-term demand forecasting and organises regular meetings to align with its supply chain team and other third parties, such as production sites. Otsuka's antibacterial delamanid (Deltiba®) is only produced in Japan, but since 2016, the company has partnered with the Global Drug Facility to supply this antibacterial to more than 100 countries, including access countries. To increase access and help ensure a secure supply of ingredients, Otsuka is currently conducting a technology transfer to Mylan. To mitigate against falsified medicines reaching the supply chain, Otsuka meets EU requirements for product serialisation and closely monitors products on markets outside the EU.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Educational stewardship activities

Otsuka is not eligible for this indicator as it reports no involvement in AMR-related educational programmes aimed at healthcare professionals (HCPs).

C.5 Does not promote its antibacterial medicine

Otsuka engages in practices that aim to address the appropriate use of antibacterial and/or antifungal medicines. It is one of the two companies evaluated to report that it does not deploy any sales agents nor develop any marketing materials to promote such products, namely for Otsuka the antibacterial delamanid (Deltiba®), because

treatment is only available in specialised centres under tightly controlled conditions.

C.6 Translates brochures to facilitate appropriate use

Otsuka adapts brochures to facilitate the appropriate use by patients of relevant products: namely its antibacterial delamanid (Deltiba®). These adaptations only take account of language needs. Otsuka has translated its Educational Risk Minimisation Materials into English, French, Spanish and Russian. These are distributed through the Global Drug Facility by MSF.

C.7 No involvement in AMR surveillance programmes but shares some consumption data

Otsuka does not report any involvement in AMR surveillance programmes. Otsuka currently shares some consumption data, about delamanid (Deltiba®) (e.g., from its compassionate use programme), with national authorities and WHO.

[†] Including only wholly-owned direct subsidiaries of the company. More information in Appendix I.

[‡] 102 low- and middle-income countries where better access to medicine is most needed. See Appendix VI.

[§] See Appendix VII.

DIAGNOSTICS, ANIMAL HEALTH & AGRICULTURE

Activities in this area are not scored by the Benchmark. This information is provided given the importance of diagnostics, animal health and agriculture on the topic of AMR.

Otsuka has its own diagnostics business and develops diagnostic devices and products. It is developing a treatment monitoring tool to determine the severity of pulmonary TB by measuring lipoarabinomannan (LAM), a major component of M. tuberculosis' cell wall. Currently, the treatment monitoring tool is only available for use in clinical research, but Otsuka is working with a third party to make the platform commercially available. The tool has received CE-marking, which is required for all in vitro diagnostic devices sold in the EU.

Pfizer Inc

Large R&D-based pharmaceutical company

Stock exchange: NYSE • Ticker: PFE • HQ: New York, USA • Employees: 92,400

PERFORMANCE

Pfizer performs well in its evaluated Research Areas, and is one of the leaders when compared to other large R&D-based pharmaceutical companies in scope.

R&D: Performs well. Pipeline consists of eight projects for medicines and vaccines for priority pathogens. Reports commitment to access and stewardship planning and is active in intellectual capital sharing.

Responsible Manufacturing: Performs well. Reports comprehensive environmental risk-management strategy for own sites and suppliers; risk assessments based on discharge limits have been completed at own sites and are ongoing at suppliers' sites.

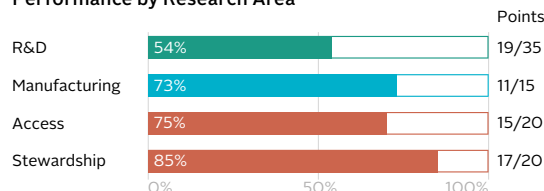
Appropriate Access: Performs well. Files its on- and off-patent products for registration in access countries. Strategies to ensure continuous supply include forecasting and data sharing to prevent shortages.

Stewardship: Performs strongly. It publicly shares raw data of its surveillance programme. Its educational programmes have comprehensive conflict of interest (COI) mitigation. Partly decouples sales incentives from volumes and adapts packaging to improve adherence to treatment.

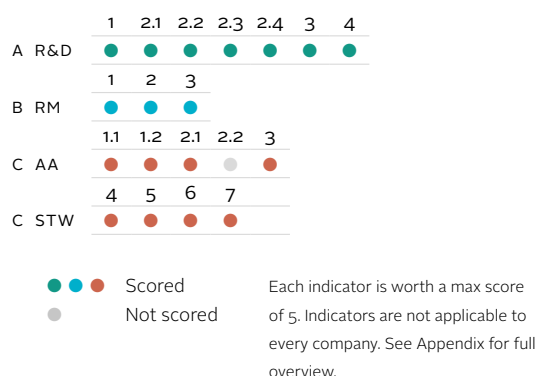
Performance in the Benchmark



Performance by Research Area



How Pfizer was evaluated



SALES AND OPERATIONS

Therapeutic areas: Cardiovascular diseases; Diabetes; Immunology; Infectious diseases; Oncology; Rare diseases

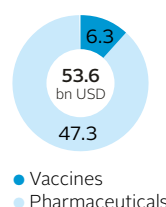
Business segments: Biopharmaceuticals; Upjohn; Hospira; Consumer Healthcare

Product categories: Biosimilars; Consumer healthcare (JV with GSK); Generic medicines; Innovative medicines (including ViiV Healthcare, JV with GSK and Shionogi); Vaccines

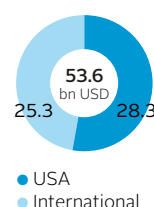
Manufacturing & supply: Pfizer supplies its antibacterial medicines, antibacterial vaccines and antifungal medicines across 182 countries, 85 of which are low- and middle-income countries.

M&A since 2018: None in the antibacterial and/or antifungal sectors

Revenues by product (2018)



Revenues by region (2018)



PIPELINE for diseases in scope

Pipeline size: 8 projects for priority pathogens* (4 antibacterial medicines; 4 antibacterial vaccines)

Development stages: 6 clinical projects, including a Phase III vaccine candidate for *C. difficile* infections and a Phase I clinical vaccine candidate for the prevention of group B *Streptococcus* infections, which are a leading cause of neonatal sepsis and meningitis globally, and 1 pre-clinical project

Novelty: No novel clinical-stage medicine projects

Regulatory approvals: 1, for ceftaroline fosamil (Zinforo®) for treating complicated skin and soft tissue infections and community-acquired bacterial pneumonia in paediatric populations in June 2019 by the EMA

Access plans: 5 of 5 late-stage R&D projects with project-specific access plans, most commonly equitable pricing strategies, including strategies developed in partnership with Gavi, the Vaccine Alliance

Stewardship plans: 2 of 2 late-stage R&D medicine projects are covered by portfolio-wide stewardship plans, including initiatives for surveillance (ATLAS) and research and education on AMR (via unrestricted grants)

PORTFOLIO for diseases in scope

Largest portfolio: At least 190 products (106 unique INNs): 157 antibacterial medicines; 5 antibacterial vaccines; 28 antifungal medicines

Essential medicines: 39% (74) products are on the 2019 WHO EML

AWaRe medicines:** 29 Access group; 14 Watch group; 3 Reserve group

Anti-TB medicines:** 13 (incl. 1 Watch group, 3 Reserve group)

Pipeline for priority pathogens



Products on the market



The number of products is based on data from public sources, IQVIA, and data submitted by the company. It may not account for Pfizer's entire portfolio.

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

** Listed on the 2019 WHO EML (Section 6).

OPPORTUNITIES FOR PFIZER

Remain engaged in R&D for antibacterial medicines and vaccines. Pfizer is one of the few large research-based pharmaceutical companies still active in R&D for antibacterial medicines and vaccines. It is critical for the development and commercialisation of new products that large research-based pharmaceutical companies remain engaged in this space, either through acquisitions and in-licensing or through discovery.

Follow up to public commitments and increase public disclosure on environmental risk management. Following up on its commitments as a signatory to the Industry Roadmap for Progress on Combating AMR, Pfizer can work with stakeholders to develop a practical mechanism to publicly disclose (1) a list of its suppliers and waste-treatment plants and (2) the results of environmental audits and the levels of antibacterial discharge from its own sites and the sites of its suppliers.

Expand registration and ensure adequate supply of its antibacterial and antifungal medicines in access countries. Pfizer can file for registration and ensure adequate supply of its antifungal medicines tavaborole (Kerydin®) and isavuconazole (Cresemba®) and the forgotten antibiotics on the 2019 WHO EML within its current portfolio (benzylpenicillin, chloramphenicol, ertapenem, nitrofurantoin and spectinomycin) in more access countries.

Scale up UK pilot and fully decouple sales incentives from sales volumes. In order to mitigate the risk of inappropriate use of its antibacterial and/or antifungal medicines, Pfizer can build on its current pilot in the UK and fully decouple incentives for sales agents from sales volumes.

Continue to publicly share raw data from its surveillance programme ATLAS. Pfizer shared publicly (with the AMR Register) the raw data collected for its long-term, multinational surveillance programme ATLAS. Pfizer can continue to share the raw data collected for this programme, and its other surveillance programmes, in the coming years.

CHANGES SINCE 2018

- Collaborated with Zipline, and Zipline's other partners, to support the Government of Ghana to deliver essential medicine products, such as vaccines, to rural Ghana, by means of medical drones.
- Provided over 7 million doses of fluconazole (Diflucan®) treatments to government and non-governmental organisations (NGOs) in access countries over the last two years (2017-2019), under the Diflucan® Partnership Program.
- Publicly announced in September 2019 the implementation of the full decoupling of incentives for sales agents from antibacterial sales volumes in the UK.
- Newly shares raw data from its ATLAS surveillance programme on an open-access data platform, and expanded the programme to cover more priority pathogens.
- Reduced the price at which it supplies its pneumococcal conjugate vaccine (PCV) to Gavi-eligible countries (and to settings designated as humanitarian emergencies by the WHO) to its lowest global price USD 2.90 per dose for multi-dose vials.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 No information on relevant R&D investments

Pfizer does not report publicly, or to the Benchmark, how much it invested in R&D for antibacterial or antifungal medicines or vaccines in 2017 and 2018.

A.2.1 Mid-sized pipeline compared to peers

Among the large research-based pharmaceutical companies evaluated, this pipeline is mid-sized. Pfizer reports eight projects targeting priority pathogens in its pipeline, all of which target bacterial pathogens, including four vaccine and four medicine projects. The majority of these candidates (6) are in clinical development.

Of the remaining projects, one is in pre-clinical development, and one, ceftazidime/avibactam (Zavicefta®), is in Phase IV.

A.2.2 No clinical-stage novel projects

Pfizer's clinical-stage medicine pipeline for priority pathogens consists entirely of adapted R&D projects. It does not currently include candidates

Pipeline targeting priority pathogens: 8[†] As at 16 October 2019

| Discovery | Pre-clinical | Phase I | Phase II | Phase III | Approval [†] |
|---|---|--|---|---|---|
| | AN10070 - <i>M. tuberculosis</i> [‡] | ◆ Group B <i>Streptococcus</i> 6-valent conjugate vaccine (PF-06760805)*** | ◆ 7-valent Pneumococcal conjugate paediatric vaccine (PF-06842433) - <i>S. pneumoniae</i> . (To be co-administered with the 13-valent pneumococcal conjugate paediatric vaccine.) | Aztreonam/avibactam (PF-06947387) - Multidrug-resistant GNB (including <i>Enterobacteriaceae</i> MBLs producers) - Adaptation (new FDC of an approved beta-lactam and beta-lactamase inhibitor) - cIAI, HABP and VABP ◆ <i>C. difficile</i> vaccine (PF-06425090) ◆ Next-generation 20-valent pneumococcal conjugate adult vaccine (PF-06482077) - <i>S. pneumoniae</i> | Ceftaroline fosamil (Zinforo®) - MRSA - Adaptation (additional target population: paediatric patients) - cSSTI and CABP (Approved June 2019, EMA) |
| *** After the period of analysis, the project has moved to Phase II. † Includes one project not shown in the figure: a Phase IV medicine project for a paediatric adaptation of ceftazidime/avibactam (Zavicefta®) for cUTI, cIAI and HABP/VABP ‡ Out-licensed to GSK, conducting research with the TB Alliance | | | | | |
| ◆ = Vaccine CABP = Community-acquired bacterial pneumonia cIAI = Complicated intra-abdominal infection cSSTI = complicated skin and soft tissue infections cUTI = Complicated urinary tract infection FDC = Fixed-dose combination HABP = Hospital-acquired bacterial pneumonia VABP = Ventilator-associated bacterial pneumonia | | | | | |

that are considered novel using WHO's criteria published in the 2018 WHO Update of antibacterial agents in clinical development. However, Pfizer is developing a fixed-dose combination of aztreonam/avibactam for complicated intra-abdominal infections and hospital-acquired and ventilator-associated pneumonia, which may offer clinical benefits.

A.2.3 Four vaccines in the pipeline

Pfizer reports four new vaccine projects, making this the second largest pipeline for new vaccines among companies evaluated. These four new projects are in clinical development and target *C. difficile*, group B *Streptococcus* and *S. pneumoniae*.

A.2.4 Three candidates targeting critical and/or urgent priorities

Pfizer's clinical pipeline includes a vaccine candidate in Phase III (PF-06425090) that targets *C. difficile*; a combination medicine candi-

date in Phase III (avibactam/aztreonam) that targets carbapenem-resistant *Enterobacteriaceae* (CRE) (including MBLs producers); and a paediatric adaptation of its medicine ceftazidime/avibactam (Zavicefta®) in Phase IV, which targets Carbapenem-resistant *P. aeruginosa* (CRPA) and CRE. These pathogens are among those that have been identified as being critical and/or urgent R&D priorities for limiting AMR, by WHO and/or the US Centers for Disease Control and Prevention (CDC).

A.3 Two intellectual capital sharing initiatives

Pfizer has two intellectual capital sharing initiatives. The first initiative involves the sharing of compounds with WIPO Re:search consortium, and the second initiative provides research brochures and other clinical study information to PATH for the repurposing of medicines to treat diarrhoeal diseases. In addition, Pfizer reports that its surveillance programme ATLAS can be

used by researchers to track and study resistance patterns.

A.4 Access plans for all 5 projects and stewardship plans for 2 of 2 medicine projects

Pfizer has five late-stage R&D medicine and vaccine projects targeting priority pathogens. It reports intending to seek equitable pricing and supply chain commitments in place for three vaccines in clinical development, via a partnership with Gavi, the Vaccine Alliance and PATH. It is unknown whether equitable pricing plans also apply to its avibactam/aztreonam and ceftazidime/tazobactam (Zinforo®) combinations. Pfizer reports that its two late-stage R&D medicine projects are covered by portfolio-wide stewardship plans, including initiatives for surveillance (ATLAS) and research and education on AMR (via unrestricted grants).

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Comprehensive environmental risk-management for own sites and suppliers

Pfizer reports a comprehensive strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, with an aim to limit AMR. This includes risk-based audits, with a minimum frequency of three years. The company reports setting discharge limits for all antibacterials manufactured at its sites, based on PNECs to limit AMR (or more stringent PNECs), as published by the AMR Industry Alliance. Pfizer reports using a mass balance approach to assess whether discharge levels meet these limits, complemented by direct sampling and analytical testing, where needed.

Pfizer expects third-party suppliers of antibacterial APIs and drug products to follow the same standards, including limits. Suppliers are set to be audited at least every five years or less (as determined by AMR-related risk). The audit protocol includes verification of how antibacterials are quantified in suppliers' wastewaters. Pfizer

expects external private waste-treatment plants to comply with its environmental standards. The plants are set to be audited on the basis of risk, but are not required to set antibacterial discharge limits.

B.2 Publicly discloses some information on environmental risk management

Pfizer publishes some components of its environmental risk-management strategy. Further, it is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. The underlying methodology was summarised in an open-access journal article co-authored by Alliance members including Pfizer. Pfizer does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private waste-treatment plants; (2) a list of these suppliers and waste-treatment plants; or (3) the levels of antibacterial discharge from its own sites.

B.3 Has system to maintain production quality for own and suppliers' sites; regulator requested official corrective action

Pfizer reports having a system to maintain high-quality antibacterial production, consistent with international GMP standards. This includes internal audits and tracking of corrective actions. In 2018, FDA drug quality inspections identified non-conformities with cGMP at two Hospira sites (a Pfizer subsidiary), resulting in an official request for corrective action. At least one of these sites produces antibacterials. The company reports that the sites have taken corrective actions. The company reports requiring suppliers to abide by regulatory and company quality standards, as specified, e.g., in quality agreements. It reports conducting risk-based audits of suppliers and having the same expectations as for its sites in terms of corrective action implementation.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries§

C.1.1 Filed to register four of 12 relevant on-patent products|| in 10+ access countries

Pfizer is a leading company when it comes to filing relevant on-patented products for registration. It files its relevant products in 11.7 access countries on average. Overall, 30% of its relevant on-patent products are filed in 10+ access countries. Its most widely filed on-patent product is the vaccine Prevnar 13®, for the prevention of pneumococcal disease, filed in 62 access countries. Prevnar 13® is followed by the antifungal

medicine Ecalta and vaccine Nimenrix, each filed by Pfizer for registration in 23 access countries.

C.1.2 Filed to register relevant off-patent products in 14.6 access countries on average

Pfizer is one of the leaders when it comes to filing relevant off-patent products for registration. It has filed 89% of its relevant products (8/9 antibacterial and antifungal medicines) for registration in access countries. Its most widely filed product in this analysis is the antifungal flu-

conazole (Diflucan®), used for diseases including those caused by *Candida* spp. Pfizer has filed its version of this product in 62 access countries. Fluconazole is followed by the antibacterials tigecycline (Tygacil®) and azithromycin (Zithromax®), filed by Pfizer for registration in 33 and 15 access countries respectively.

C.2.1 Takes socioeconomic factors into account when setting prices

When setting prices for on-patent products, Pfizer considers socioeconomic factors, namely

§ 102 low- and middle-income countries where better access to medicine is most needed. See Appendix VI.

|| See Appendix VII.

local economic conditions, average income of the population and GDP growth. Six products were included for analysis: 1 antibacterial medicine; 2 antifungal medicines; 3 vaccines. For its antibacterial medicine, ceftazidime/avibactam (Zavicefta®), it has a pricing strategy based on the factors above, which it applies in 30 access countries. For its vaccines, Pfizer has a six-tiered pricing policy based on GNI per capita, as well as other factors such as the vaccine's predicted impact on health, potential contribution to economic growth, and governments' commitment to birth-cohort coverage. Its policy includes tiers for countries supported by pooled-procurement agencies, such as Gavi the Vaccines Alliance. Pfizer does not disclose how it plans to increase the affordability of these products over the next five years.

C.2.2 Pricing strategies for off-patent products Companies were not scored for this indicator as the available data was insufficient for a comparative analysis. Pfizer does report that it applies differential pricing policies in emerging markets. Pfizer states that it donates its antibacterial azithromycin (Zithromax®) to 39 countries, through the WHO-run SAFE strategy (Surgery, Antibiotics, Facial cleanliness, and Environmental improvements) with the aim of eliminating trachoma by 2020.

C.3 Several strategies to ensure the continuous supply of relevant products

Pfizer is a leading company compared to other large research-based pharmaceutical companies evaluated, when it comes to taking steps to ensure the continuous supply of its relevant products to access countries. It discloses some strategies for achieving this aim. It has 24 to 36-month forecasting to schedule produc-

tion, as well as a five-year long-range volume forecast (LRVF). Regular meetings are held to ensure inventory levels are maintained and it shares data with either the Food and Drug Administration (FDA) or with individual countries' Ministries of Health, to help prevent shortages. Pfizer is one of Zipline's partners helping to support the Government of Ghana with a delivery drone system that delivers medical products, including routine vaccines, to citizens in rural Ghana. Pfizer is a member of International Federation of Pharmaceutical Manufacturers and Associations' (IFPMA) 'Fight the Fakes' campaign, which aims to mitigate against falsified medicine reaching the supply chain. Pfizer also has other strategies, including an Online Pharmacy Disruption Program to tackle counterfeit sales, unique product identifiers to aid tracking and tracing and it has a counterfeit awareness page on its website.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Comprehensive strategy to mitigate COI for all educational programmes

The Benchmark analysed the top five AMR-related educational programmes for healthcare professionals (HCPs) from Pfizer. Pfizer reports a comprehensive COI mitigation for all five programmes: by providing financial resources to independent third parties to develop all programmes.

C.5 Adapts marketing materials and sales practices to address appropriate use

Pfizer engages in practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines, both via its marketing practices and sales remuneration. At least some of Pfizer's marketing materials reflect emerging resistance trends and include guidelines for HCPs to raise awareness of AMR and address appropriate use: for all antibacterials and its antifungal isavuconazole (Cresemba®), by using data

from the ATLAS surveillance programme in the materials. Pfizer reports that it partly decouples incentives (that are based on national-level sales targets) for sales agents from sales volumes to help prevent the inappropriate use of such medicines. After the period of analysis, the company publicly announced that it would not reward its sales agents based on antibacterial volumes sold in the UK.

C.6 Adapts packaging to facilitate appropriate use; takes account of adherence to treatment

Pfizer adapts its packaging to facilitate appropriate use by patients of relevant products: namely its antibacterial azithromycin (Zithromax®). This adaptation takes account of adherence to treatment. Pfizer adapts the packaging of azithromycin, named the Z-Pak, which aims to facilitate patient adherence by organising the pill intake for each day, so that the patient knows exactly

which pill(s) to take on which day until the Z-Pak is completed.

C.7 Active in multiple AMR surveillance programmes; one openly shares raw data

Pfizer is active in multiple long-term AMR surveillance programmes, including the ATLAS programme. This is updated every six months with data from across 73 countries and is the only programme in the Benchmark that shares not only its results, but also its raw data in the AMR Register, an open-access data platform. The SENTRY programme, which is managed by JMI laboratories with support from Pfizer, collects isolates from 60 centres in 29 countries. Pfizer does not report making antibacterial and/or antifungal consumption data available to national governments or other public health authorities.

DIAGNOSTICS, ANIMAL HEALTH & AGRICULTURE

Activities in this area are not scored by the Benchmark. This information is provided given the importance of diagnostics, animal health and agriculture on the topic of AMR.

Pfizer reports that its programmes in diagnostics are primarily in 'companion' diagnostics development that are required by the FDA and other regulatory agencies for associated drug approvals. While Pfizer does not have its own diagnostics division, the company reports that it works with third parties to complement AMR product development with diagnostic tests whenever possible. Pfizer reports that it supports COMBACTE-CARE, a European network that addresses the diagnostic challenges for the

epidemiological and clinical studies of carbapenem-resistant bacteria. The company has also entered into collaborations with diagnostic manufacturers to support commercial availability of susceptibility tests for its new antibacterials.

Polyphor Ltd

Small/medium-sized enterprise

Stock exchange: SWX • Ticker: POLN • HQ: Allschwil, Switzerland • Employees: 70

PERFORMANCE

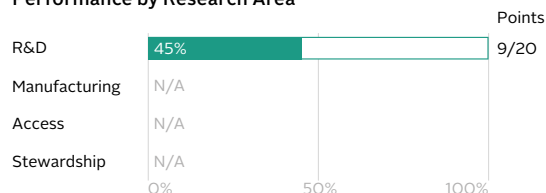
Polyphor performs on average in Research & Development when compared to other small and medium-sized enterprises in scope.

R&D: Polyphor has three antibacterial projects in its pipeline that target priority pathogens. Reports no project-specific plans for access or stewardship.

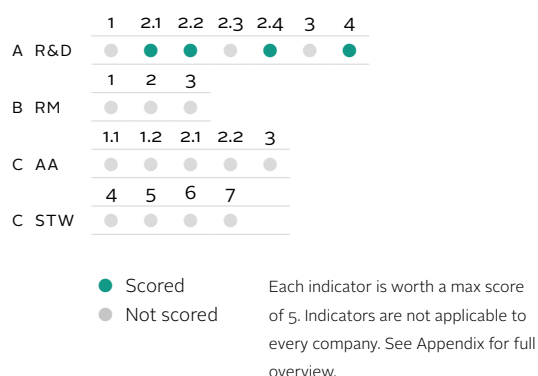
Performance in the Benchmark



Performance by Research Area



How Polyphor was evaluated



SALES AND OPERATIONS

Therapeutic areas: Antibiotics; Immuno-oncology compounds

Products on the market: None

R&D grants received since 2016: Up to USD 13.4 million, awarded by three funders (CARB-X; Innovative Medicines Initiative; Wellcome Trust). Its latest award, from CARB-X, worth USD 5.6 million, came in February 2019 to support the pre-clinical and early clinical development of Polyphor's OMPTA candidate, through the completion of the Phase I clinical trial.

Financing and investment structure: Polyphor is a publicly listed company. It completed its IPO in May 2018, raising CHF 155 million following three venture rounds raising CHF 59 million. Post IPO equity by Novo Holdings' Repair Impact Fund amounts to CHF 6.8 million.

M&A since 2018: None in the antibacterial and/or antifungal sectors

Revenues

(2018)



PIPELINE for diseases in scope

Pipeline size: 3 projects for priority pathogens* (3 antibacterial medicines)

Development stages: 3 pre-clinical projects, incl. murepavadin, formerly in Phase III clinical stage for the treatment of hospital-acquired and ventilator-associated bacterial pneumonia caused by *P. aeruginosa* infections

Novelty: 1 novel project, murepavadin, in development for the treatment of *P. aeruginosa* infections that belongs to a new chemical class of antibacterials and has a new drug target, mode of action and no known cross-resistance to other antibacterial classes

Regulatory approvals: 0 approvals for priority pathogens

Access plans: At analysis, its 1 late-stage R&D project lacked a project-specific access plan.

Stewardship plans: At analysis, its 1 late-stage R&D medicine project lacked a project-specific stewardship plan.

Pipeline for priority pathogens



* Priority pathogens: bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease

Control and Prevention (CDC). See Appendix V.

OPPORTUNITIES FOR POLYPHOR

Develop access and stewardship plans for its R&D projects when they reach Phase II in clinical development. After the end of the period of analysis (in July 2019), Polyphor closed the Phase III clinical studies for its antibacterial candidate murepavadin (on account of higher than expected rates of acute kidney injury). During the period of analysis, while the project was still in Phase III, Polyphor did not report any access or stewardship plans. When its R&D antibacterial projects (murepavadin and others from its OMPTA platform) reach Phase II in clinical development, Polyphor can work with partners and funders (including the Wellcome Trust and CARB-X) to develop plans to ensure that these products will be available, affordable and appropriately used after market approval. As examples of access plans, the company can commit to an equitable pricing strategy and/or look for out-licensing opportunities with multiple manufacturers in low- and middle-income countries. As examples of stewardship plans, the company can commit to decouple sales incentives from sales volumes and/or become involved in antibacterial surveillance activities.

CHANGES SINCE 2018

- Halted Phase III trials for murepavadin for HABP and VABP in May 2019 due to high incidence of acute kidney injury in patients; re-started pre-clinical trials.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 R&D investments

Polyphor reports it invested between USD 21 and 50 million in its entire pipeline, including the development of antibacterial medicines and one oncology project.

A.2.1 Pipeline size of three projects

Polyphor reports three projects targeting priority pathogens in its pipeline. The company is focused on antibacterial medicine development, and has two of its projects in pre-clinical development and a third one which was, at analysis, in Phase III of clinical development. After the end of the period of analysis (in July 2019), the clinical studies were closed and the project reverted back to pre-clinical development, on account of higher than expected rates of acute kidney injury.

A.2.2 One novel project

At analysis, Polyphor's candidate murepavadin, in development for the treatment of bacterial infections caused by *P. aeruginosa*, including

hospital-acquired and ventilator-associated bacterial pneumonia, was in Phase III clinical development. This candidate was considered novel, since it met all criteria set by WHO for innovativeness, including belonging to a new chemical class and having a new target, mode of action and no cross-resistance to other antibacterial classes.

A.2.3 Vaccines in the pipeline

Polyphor is not eligible for this indicator as it is not active in vaccine development.

A.2.4 Two candidates targeting critical and/or urgent priorities

Polyphor's pre-clinical pipeline includes a medicine (murepavadin) that targets CRPA and an adapted project to develop an aerosol formulation of this same product. Its project POL7306, also in pre-clinical development, targets Gram-negative ESKAPE critical priority pathogens.

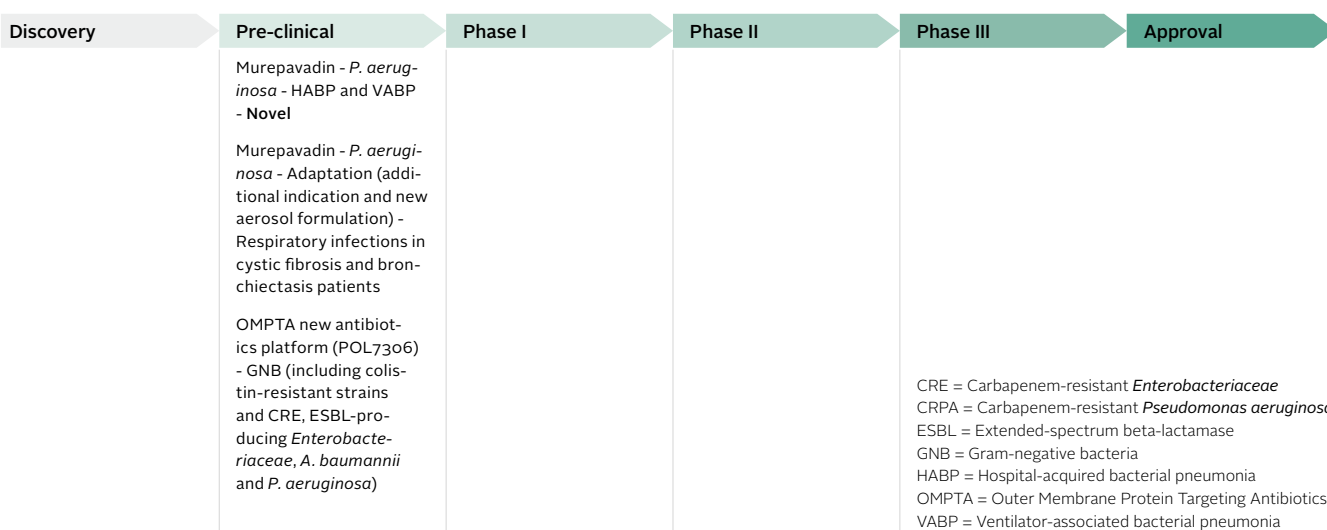
A.3 Intellectual capital sharing

As a small and medium-sized enterprise (SME), Polyphor was not scored for this indicator, in line with the external stakeholder consensus defined by the Foundation.

A.4 No access or stewardship plans for its late-stage R&D project targeting a priority pathogen

At analysis, Polyphor's candidate murepavadin, in development for the treatment of bacterial infections caused by *P. aeruginosa*, including hospital-acquired and ventilator-associated pneumonia, was in Phase III clinical development. After the end of the period of analysis (in July 2019), the clinical studies were closed and the project reverted back to pre-clinical development, on account of higher than expected rates of acute kidney injury. The company reported no plans that address either the stewardship of or appropriate access to the product, upon reaching the market.

Pipeline targeting priority pathogens: 3 As at 16 October 2019



* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

B RESPONSIBLE MANUFACTURING

As an SME, Polyphor is not evaluated in this Research Area. It has no antibacterial products on the market.

C APPROPRIATE ACCESS & STEWARDSHIP

As an SME, Polyphor is not evaluated in this Research Area. It has no antibacterial and/or antifungal products on the market.

Sanofi

Large R&D-based pharmaceutical company

Stock exchange: EPA • Ticker: SAN • HQ: Paris, France • Employees: 104,226

PERFORMANCE

Sanofi performs less well in its evaluated Research Areas when compared to other large R&D-based pharmaceutical companies in scope. **R&D:** Performs less well. Transferred its infectious diseases R&D unit to Evotec in 2019 but maintains a pipeline of six medicines and vaccines projects that target priority pathogens. Reports access plans for two late-stage vaccine projects.

Responsible Manufacturing: Performs well. Reports comprehensive environmental risk-management strategy for own sites and suppliers, however reports less information than the leaders on the progress in the implementation of discharge limits.

Appropriate Access: Middle-performing. Files its relevant vaccines in access countries. It discloses limited information regarding the access countries in which it has filed its relevant off-patent antibacterial and antifungal medicines for registration. It discloses several strategies on how it ensures the continuous supply of its products including forecasting and safety stocks.

Stewardship: Performs less well. Its educational programmes have some conflict of interest (COI) mitigation. It is active in surveillance in France, but does not share data publicly. It does not adapt its brochures or packaging to facilitate appropriate use.

SALES AND OPERATIONS

Therapeutic areas: Cardiovascular diseases; Diabetes; Infectious diseases; Neurology; Rare diseases; Urology

Business segments: Sanofi Pasteur; Primary Care; Consumer Healthcare; Sanofi Genzyme; Winthrop

Product categories: Consumer healthcare; Generic medicines; Innovative medicines; Vaccines

Manufacturing & supply: No information available

M&A since 2018: In July 2018, Sanofi completed the transfer of its infectious diseases R&D unit, including licensing, to Evotec for USD 70 million cash and guaranteed financial commitment for five years. In October 2018, Sanofi completed the divestment of its European generic business Zentiva to Advent International for USD 2.38 billion.

PIPELINE for diseases in scope

Pipeline size: 6 projects for priority pathogens* (2 antibacterial medicines and 4 antibacterial vaccines)

Development stages: 6 clinical projects, including a Phase III clinical trial to create a shorter and simpler rifapentine dosing regimen for the treatment of latent and active tuberculosis (TB) compared to existing six-month treatments

Novelty: No novel clinical-stage medicine projects

Regulatory approvals: 0 approvals for priority pathogens

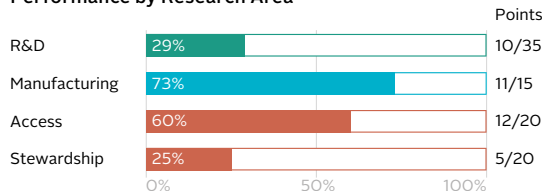
Access plans: 2 of 4 late-stage R&D projects with project-specific access plans, both of which include plans for WHO prequalification for vaccine projects.

Stewardship plans: Its 1 late-stage R&D medicine project lacks a project-specific stewardship plan.

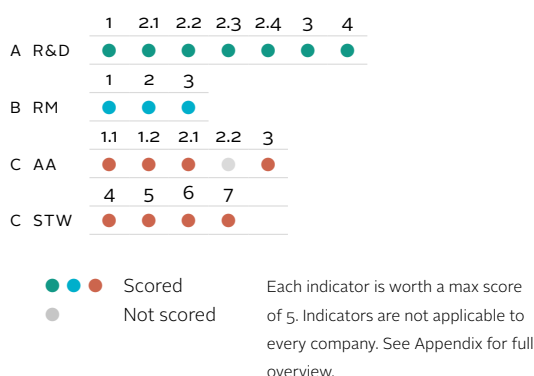
Performance in the Benchmark



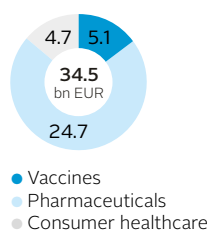
Performance by Research Area



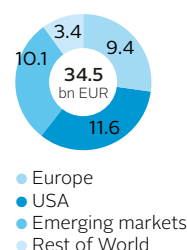
How Sanofi was evaluated



Revenues by product (2017-18)



Revenues by region (2017-18)



PORTFOLIO for diseases in scope

Mid-sized portfolio: At least 102 products (53 unique INNs): 86 antibacterial medicines; 13 antibacterial vaccines; 3 antifungal medicines

Essential medicines: 50% (51) products are on the 2019 WHO EML

AWaRe medicines:** 9 Access group; 13 Watch group; 2 Reserve group

Anti-TB medicines:** 12 products

Pipeline for priority pathogens



Products on the market



* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

** Listed on the 2019 WHO EML (Section 6).

All companies were assessed based on data available in the public domain, including information the companies have made publicly available. This was supplemented by data submitted directly to the Benchmark by the companies. Sanofi declined to submit data to the 2020 AMR Benchmark.

OPPORTUNITIES FOR SANOFI

Maintain engagement on AMR and increase disclosure of AMR strategies and activities. While Sanofi transferred its infectious diseases R&D unit to Evotec in July 2018 and did not submit data for the Benchmark, it is a key player to limit drug-resistant infections, with an active R&D pipeline of vaccines and 51 marketed antibacterial and/or antifungal medicines on the 2019 WHO EML. Sanofi can disclose more information (publicly and/or through the Benchmark) about its strategies to improve access and stewardship to the medicines within its portfolio, including their availability in access countries and its steps to mitigate the risk of inappropriate use.

Follow up to public commitments and increase public disclosure on environmental risk management. Following up on its commitments as a signatory to the Industry Roadmap for Progress on Combating AMR, Sanofi can work with stakeholders to develop a practical mechanism to publicly disclose (1) a list of its suppliers and waste-treatment plants and (2) the results of environmental audits and the levels of antibacterial discharge from its own sites and the sites of its suppliers.

Decouple sales incentives from sales volumes and/or avoid deploying sales agents. In order to mitigate the risk of inappropriate use, Sanofi can decouple sales incentives from sales volumes and/or avoid deploying sales agents, as appropriate, for its antibacterial and/or antifungal medicines.

CHANGES SINCE 2018

- Transferred its infectious diseases R&D unit, including the majority of R&D assets and 100 employees, to Evotec in July 2018.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 No information on relevant R&D investments

Sanofi does not report publicly, or to the Benchmark, how much it invested in R&D for antibacterial medicines, antifungal medicines and/or vaccines in 2017 and 2018.

A.2.1 Pipeline size small compared to peers

Among the large research-based pharmaceutical companies evaluated, this pipeline is small in size. Sanofi reports six projects targeting priority pathogens in its pipeline, all of which target bacterial pathogens, including four vaccine and two medicine projects. All six projects are in clinical development.

A.2.2 No clinical-stage novel projects

Sanofi's clinical-stage medicine pipeline for priority pathogens consists entirely of adapted R&D projects. It does not currently include can-

didates that are considered novel. However, Sanofi is developing a water-dispersible fixed-dose combination of isoniazid/rifapentine for the treatment of latent TB infection in children.

A.2.3 Four vaccines in the pipeline

Sanofi reports four vaccine projects in its pipeline, including two new projects: one next-generation pneumococcal conjugate vaccine being co-developed with SK Bioscience; one TB recombinant subunit vaccine being co-developed with Statens Serum Institute, Valneva, and the International Aids Vaccine Initiative (IAVI); and two adapted projects. All vaccine candidates are in clinical development.

A.2.4 No candidates targeting critical and/or urgent priorities

Sanofi does not have any candidate targeting pathogens considered critical and/or urgent

R&D priorities for limiting AMR, as defined by WHO and/or the US Centers for Disease Control and Prevention (CDC).

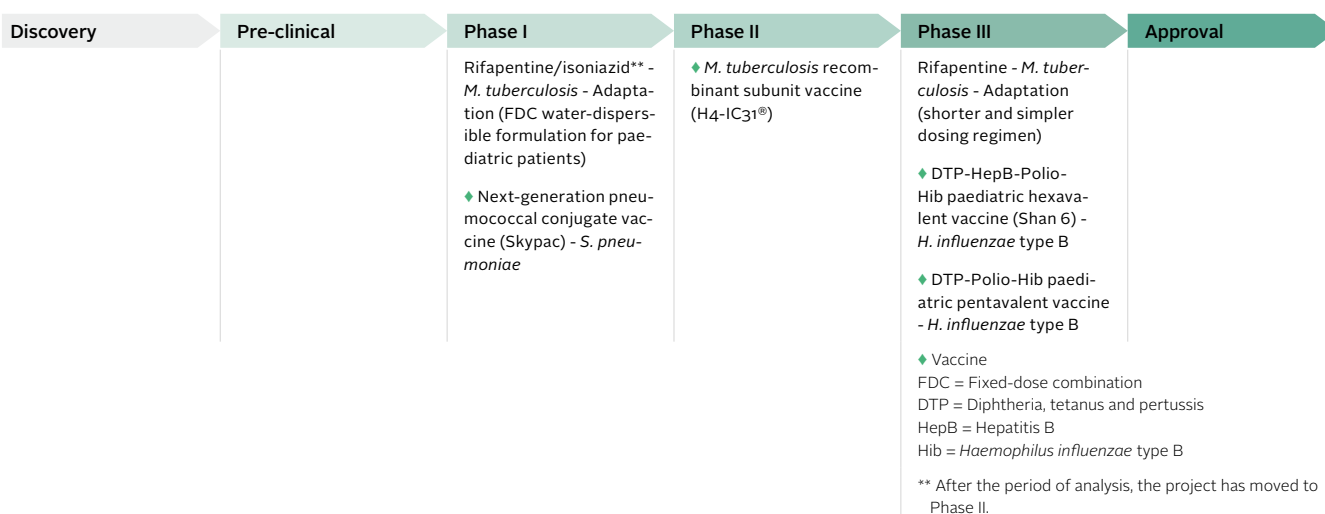
A.3 No intellectual capital sharing practices

The company does not report any intellectual capital sharing initiatives.

A.4 Access plans for two of four projects

Sanofi has four late-stage R&D projects targeting priority pathogens, of which two have access plans. It is applying for WHO prequalification for its TB vaccine and its DTP-HepB-Polio-Hib vaccine. Submitting products to WHO's prequalification process allows for UN procurement and accelerates registration processes in countries with weak national regulatory authorities. Its one medicine candidate does not have an access or stewardship plan in place.

Pipeline targeting priority pathogens: 6 As at 16 October 2019



* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)**B.1 Comprehensive environmental risk-management with less information on discharge limits for own sites and suppliers**

Sanofi has a comprehensive strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, with an aim to limit AMR. This includes audits every three years. The company reports setting discharge limits for antibacterials manufactured at its sites based on PNECs to limit AMR (or more stringent PNECs), having first covered API sites and currently moving into drug product sites.

Sanofi expects third-party suppliers of antibacterial APIs and drug products to follow a specified set of standards. Its suppliers are covered by a programme that aims to review management practices with respect to discharge of antibacterials to the environment. Sanofi prioritised these suppliers for auditing in 2017 and 2018, and reports that corrective action plans were issued. There is limited information on whether Sanofi requires suppliers to set antibacterial discharge

limits. It expects external private waste-treatment plants to comply with its environmental standards, but there is limited information on how plants are audited. The company does not report whether it requires the wastewater plants to set antibacterial discharge limits.

B.2 Publicly discloses some information on environmental risk management

Sanofi publishes some components of its environmental risk-management strategy. Further, it is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. The underlying methodology was summarised in an open-access journal article co-authored by Alliance members including Sanofi. Sanofi does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private waste-treatment plants; (2) a list of these suppliers and waste-treatment plants; or (3) the levels of antibacterial discharge from its own sites.

B.3 Has system to maintain production quality for own and suppliers' sites: no requests for official corrective action

Sanofi reports having a system to maintain high-quality antibacterial production, consistent with international GMP standards. This includes risk-based internal audits and tracking of corrective and preventive actions. The company reports requiring suppliers to abide by regulatory and company quality standards. This includes submitting suppliers to a qualification process, after which a quality technical agreement is established and routine audits are conducted. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Sanofi's own sites or any subsidiaries.***

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries†

C.1.1 Filed to register two of its five on-patent products in 10+ access countries

Sanofi is one of the leaders when it comes to filing relevant on-patent products‡ for registration. It files its products in 20.4 access countries on average. Overall, 40% of its relevant on-patent products are filed in 10+ access countries (2/5). Its most widely filed relevant on-patent products are the vaccines Hexaxim® (for DTP-Hib-Polio-Hep B) and Shan5™ (for DTP-Hib-Hep B), filed for registration in 59 and 43 access countries, respectively.

C.1.2 Limited information on registration filings for off-patent products

Sanofi performs less well than its peers in this area, as it discloses limited information regarding the access countries in which it has filed its relevant off-patent products (antibacterial and antifungal medicines) for registration.

C.2.1 Takes socioeconomic factors into account when setting prices

When setting prices for on-patent products,

Sanofi considers socioeconomic factors, including Gross National Income (GNI) per capita. Five products were included for analysis, all vaccines. Sanofi has tiered pricing policies through which its vaccines are made available to pooled-procurement agencies, including WHO, Gavi the Vaccines Alliance and the United Nations Children's Fund (UNICEF). Sanofi has made a general commitment to ensuring the prices of its vaccines are sustainable and equitable. Sanofi does not disclose how it plans to increase the affordability of these products over the next five years.

C.2.2 Pricing strategies for off-patent products
Companies were not scored for this indicator as the available data was insufficient for a comparative analysis. Sanofi reports that it aims to consider unequal living conditions in its pricing strategies. It does not disclose whether it considers affordability or socioeconomic factors when setting prices for off-patent antibacterial or antifungal medicines or vaccines.

C.3 Several strategies to ensure the continuous supply of relevant products

Sanofi is a middle-performing company compared to other large research-based pharmaceutical companies evaluated when it comes to taking steps to ensure the continuous supply of its relevant products to access countries. It has short-term (up to 36 months) and long-term (36 months to 5/10 years) forecasting for demand planning and inventories of finished goods to last between two and three months in order to avoid stockouts. It has developed a Procurement Risk Management Model to address the full range of procurement risks and to guarantee appropriate risk assessment and mitigation. Sanofi engages in capacity building through the training and employment of local staff in line with International GMP. It has strategies in place to reduce distribution of falsified medicines and an Anti-Counterfeiting Laboratory.

*** Including only wholly-owned direct subsidiaries of the company. More information in Appendix I.

† 102 low- and middle-income countries where better access to medicine is most needed. See Appendix VI.

‡ See Appendix VII.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Some COI mitigation for all educational programmes

The Benchmark analysed two AMR-related educational programmes for healthcare professionals (HCPs) from Sanofi. Sanofi reports some COI mitigation for these two programmes. Both programmes have two of three COI mitigation strategies looked for by the Benchmark: (1) a pledge not to provide financial or material incentives to participants; and (2) it does not use branded materials. However, it is unclear whether content for these programmes is developed independently from Sanofi's marketing department.

C.5 No information on marketing or sales practices that aim to address appropriate use

There is no information regarding Sanofi's engagement in practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines, either regarding its marketing materials or its sales practices.

C.6 No information on brochure and/or packaging adaptations to facilitate appropriate use

There is no information regarding Sanofi's adaptations in its brochures and/or packaging to facilitate appropriate use of its antibacterial and/or antifungal medicines by patients beyond regulatory requirements.

C.7 Active in one AMR surveillance programme

Sanofi is active in one long-term AMR surveillance programme. The programme is run by the National Reference Centre for Pneumococci (NRCP) with the French Regional Pneumococcal Observatories. It runs periodically and focuses on *S. pneumoniae* in France. The NRCP only shares the results of the programme through peer-reviewed journal articles. However, these articles are not open access. The programme covers 10 antibacterials and includes 400 health facilities. Sanofi does not report making antibacterial and/or antifungal consumption data available to national governments or other public health authorities.

Scynexis

Small/medium-sized enterprise

Stock exchange: NASDAQ • Ticker: SCYX • HQ: New Jersey, USA • Employees: 24

PERFORMANCE

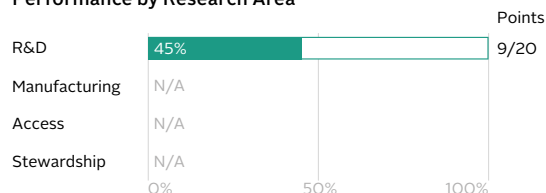
Scynexis performs on average in Research & Development when compared to other small and medium-sized enterprises in scope.

R&D: Scynexis has five antifungal projects in its pipeline, including one clinical-stage antifungal medicine project that is considered novel: ibrexafungerp, for the treatment of various fungal infections, including acute vulvovaginal candidiasis. Reports commitment to increase access to its products through expanded access programmes.

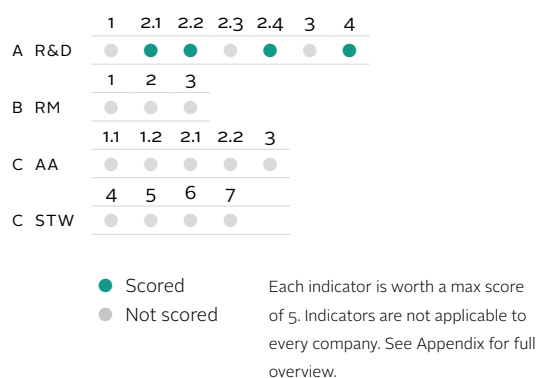
Performance in the Benchmark



Performance by Research Area



How Scynexis was evaluated



SALES AND OPERATIONS

Therapeutic areas: Multiple serious fungal infections

Products on the market: None

R&D grants received since 2016: None

Financing and investment structure: Scynexis is a publicly listed company. It completed its IPO in May 2014 raising USD 62 million, following one venture round raising USD 11.4 million.

M&A since 2018: None in the antibacterial and/or antifungal sectors

Revenues

(2018)



PIPELINE for diseases in scope

Pipeline size: 5 projects for priority pathogens* (1 antifungal medicine for 5 indications)

Development stages: 5 clinical projects, 4 of which are Phase III clinical trials (including 2 open label studies) and an additional study in Phase II for invasive candidiasis

Novelty: 1 novel project, ibrexafungerp, a Phase III clinical candidate for the treatment of various fungal infections, including acute vulvovaginal candidiasis, that belongs to a new chemical class of antifungals.

Regulatory approvals: 0 approvals for priority pathogens

Access plans: No project-specific access plans are in place for its 5 late-stage R&D projects, but the company has a general approach to increasing access through expanded access programmes.

Stewardship plans: None of its 5 late-stage R&D medicine projects have project-specific stewardship plans.

Pipeline for priority pathogens



- Antibacterial (AB) vaccine
- Antibacterial (AB) medicine
- Antifungal (AF) medicine
- AB+AF combination

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

OPPORTUNITIES FOR SCYNEXIS

Expand access plans and develop stewardship plans for ibrexafungerp. Scynexis has developed expanded access plans for ibrexafungerp that will enable seriously ill patients not enrolled in its clinical studies to have access to the investigational product. Scynexis can expand its access plans by committing to an equitable pricing strategy and/or looking for multiple licensees in low- and middle-income countries. Scynexis has not developed stewardship plans for ibrexafungerp yet. As examples of stewardship plans, the company can commit to decouple sales incentives from sales volumes and/or become involved in antifungal surveillance activities.

CHANGES SINCE 2018

This section lists notable changes in companies' activities since the 2018 Benchmark. Since Scynexis was not in scope for evaluation in 2018, no changes are reported.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 R&D investments

Scynexis invested USD 39.9 million in the development of antifungal medicines in 2017 and 2018. As with all other small and medium-sized enterprises (SMEs) evaluated, Scynexis was not scored in this indicator.

A.2.1 Pipeline size of five projects

Scynexis reports five projects targeting *Candida* spp. in its pipeline for different indications for its candidate ibrexafungerp. The company is focused entirely on antifungal medicine development. Four projects are in Phase III of clinical development and one is in Phase II.

A.2.2 One clinical-stage novel project

Scynexis' clinical-stage medicine pipeline for priority pathogens consists of both new and adapted R&D projects. Scynexis has one clinical-stage antifungal medicine project that is considered novel: ibrexafungerp, for the treatment of various fungal infections, including acute vulvovaginal candidiasis, that belongs to a new chemical class.

cal-stage antifungal medicine project that is considered novel: ibrexafungerp, for the treatment of various fungal infections, including acute vulvovaginal candidiasis, that belongs to a new chemical class.

A.2.3 Vaccines in the pipeline

Scynexis is not eligible for this indicator as it is not active in vaccine development.

A.2.4 One candidate targeting critical and/or urgent priorities

Scynexis' clinical pipeline includes one new, novel candidate (ibrexafungerp/SCY-078) in Phase III that targets multi-drug resistant *C. auris*, which is listed since November 2019 as an urgent pathogen by the US Centers for Disease Control and Prevention (CDC).

A.3 Intellectual capital sharing

As an SME, Scynexis was not scored for this indicator, in line with the external stakeholder consensus defined by the Foundation.

A.4 General access commitments for five of five projects; no stewardship plans

Scynexis has five late-stage R&D projects targeting priority pathogens, all for different indications for ibrexafungerp. Scynexis has developed expanded access plans for ibrexafungerp that will enable seriously ill patients not enrolled in its clinical studies to have access to the investigational product. It does not report on any stewardship plans.

Pipeline targeting priority pathogens: 5 As at 16 October 2019

| Discovery | Pre-clinical | Phase I | Phase II | Phase III | Approval |
|-----------|--------------|---------|--|--|----------|
| | | | Ibrexafungerp - <i>Candida</i> spp. - Invasive candidiasis | Ibrexafungerp - <i>Candida</i> spp. - Acute vulvovaginal candidiasis - Novel Ibrexafungerp - <i>Candida</i> spp. - Adaptation (additional indication) - Refractory invasive fungal infections Ibrexafungerp - <i>Candida</i> spp. - Adaptation (additional indication) - Recurrent vulvovaginal candidiasis Ibrexafungerp - <i>Candida</i> spp. (including <i>C. auris</i>) - Adaptation (additional indication) - Candidiasis | |

B RESPONSIBLE MANUFACTURING

As an SME, Scynexis is not evaluated in this Research Area. It has no antibacterial products on the market.

C APPROPRIATE ACCESS & STEWARDSHIP

As an SME, Scynexis is not evaluated in this Research Area. It has no antibacterial and/or antifungal products on the market.

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

Shionogi & Co, Ltd

Large R&D-based pharmaceutical company

Stock exchange: TSE • Ticker: 4507 • HQ: Osaka, Japan • Employees: 5,120

PERFORMANCE

Shionogi performs well in its evaluated Research Areas when compared to other large R&D-based pharmaceutical companies in scope.

R&D: Middle-performing. Pipeline consists of eight projects for medicines and vaccines for priority pathogens. It reports plans for access for its one late-stage R&D project. No intellectual capital sharing initiatives were reported.

Responsible Manufacturing: Performs strongly. Reports comprehensive environmental risk-management strategy for own sites and suppliers; risk assessments based on discharge limits have been completed at own sites and are ongoing at suppliers' sites.

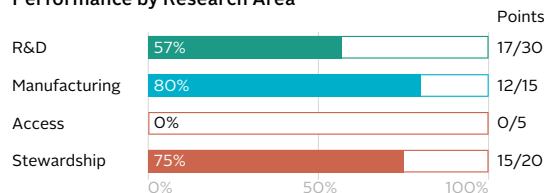
Appropriate Access: Performs low. It markets antibacterial and antifungal medicines mainly in Japan. It reports no strategies on how it ensures the continuous supply of its products to access countries.

Stewardship: Performs well. It has educational programmes with broad conflict of interest (COI) mitigation. It is active in surveillance and publicly shares results. It fully decouples sales incentives from volumes. It adapts brochures for paediatric use in Japan only.

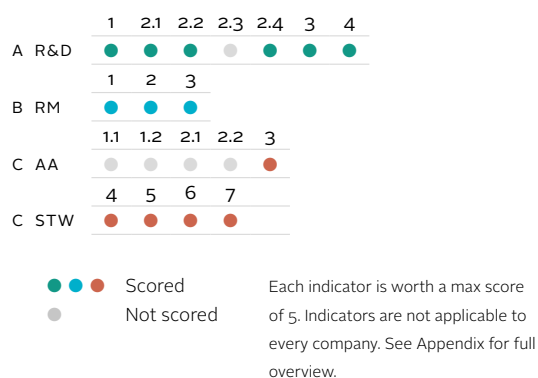
Performance in the Benchmark



Performance by Research Area



How Shionogi was evaluated



SALES AND OPERATIONS

Therapeutic areas: Diabetes; Infectious diseases; Haematology; Neurology; Pain management

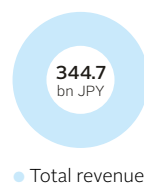
Business segment: Prescription Drugs

Product Categories: Innovative medicines (including ViiV Healthcare, JV with Pfizer and GSK)

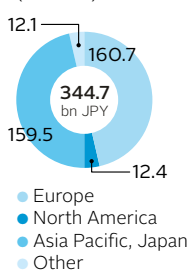
Manufacturing & supply: Shionogi reports having one manufacturing site that produces antibacterial APIs and/or drug products. It supplies more than 40 million defined daily doses (DDDs) of antibacterial medicines to date.

M&A since 2018: In July 2019, Shionogi announced that it will out-license COT-143 to the AMR Centre. COT-143 is a humanised monoclonal antibody targeting the PcrV protein of *P. aeruginosa*.

Revenues by product (2017-18)



Revenues by region (2017-18)



PIPELINE for diseases in scope

Pipeline size: 8 projects for priority pathogens* (6 antibacterial medicines and 2 antifungal medicines)

Development stages: 1 clinical project, cefiderocol, which has been submitted for EMA and FDA approval for the treatment of multidrug-resistant (MDR) Gram-negative infections, and 7 discovery/pre-clinical projects

Novelty: No novel clinical-stage medicine projects

Regulatory approvals: 0 approvals for priority pathogens

Access plans: Its 1 late-stage R&D project with a project-specific access plan.

Stewardship plans: Its 1 late-stage R&D medicine project lacks a project-specific stewardship plan.

PORTFOLIO for diseases in scope

Comparatively small portfolio: At least 7 products (7 unique INNs): 7 antibacterial medicines

Essential medicines: 29% (2) products are on the 2019 WHO EML

AWaRe medicines:** 2 Access group

Anti-TB medicines:** None

Pipeline for priority pathogens



Products on the market



The number of products is based on data from public sources, IQVIA, and data submitted by the company. It may not account for Shionogi's entire portfolio.

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

** Listed on the 2019 WHO EML (Section 6).

OPPORTUNITIES FOR SHIONOGI

Develop access and stewardship plans for cefiderocol (Fetroja®). Cefiderocol was approved by the FDA in November 2019. Shionogi can swiftly develop plans to ensure that cefiderocol is widely available and affordable in access countries, while appropriately used globally. As examples of access plans, the company can commit to an equitable pricing strategy and/or look for out-licensing opportunities with multiple manufacturers in low- and middle-income countries. As examples of stewardship plans, it can take steps to ensure the continuous supply of this product and/or include it into its antibacterial surveillance activities

Follow up to public commitments and increase public disclosure on environmental risk management. After the period of analysis, Shionogi published information, disaggregated per antibacterial product, on whether its own sites and (anonymised) suppliers met the expectations of the CAMF and discharge limits. Building on this positive step and following up on its commitments as a signatory to the Industry Roadmap for Progress on Combating AMR, Shionogi can work with stakeholders to develop a practical mechanism to publicly disclose (1) a list of its suppliers and waste-treatment plants and (2) the results of environmental audits and the levels of antibacterial discharge from its own sites and the sites of its suppliers.

Expand supply of antibacterial medicines to access countries. Shionogi can consider expanding supply of antibacterial medicines in its current portfolio on the 2019 WHO EML to access countries (eg. sulfamethoxazole/trimethoprim and vancomycin).

Publicly share raw data from its four surveillance programmes in Japan. Shionogi can share publicly (e.g., with the AMR Register) the raw data collected for its surveillance programme in Japan, such as SIDERO-WT and the Shionogi Japanese Surveillance Studies Programme.

CHANGES SINCE 2018

- Received FDA approval in November 2019 for cefiderocol (Fetroja®) for the treatment of complicated urinary tract infections.
- Received, in March 2018, a CARB-X award of USD 4.7 million to support development of a new beta-lactam antibacterial medicine targeting carbapenem-resistant *Enterobacteriaceae* (CRE) infections.
- Published its AMR-specific environmental risk-management strategy for antibacterial manufacturing in its EHS report.
- Extended its AMR-specific environmental risk-management strategy to suppliers and assesses whether their antibacterial discharge levels are below limits during audits.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 Highest investments in relevant R&D, as proportion of pharmaceutical revenues

Shionogi reports that it invested USD 133 million in R&D for antibacterial and antifungal medicines in 2017 and 2018. As a proportion of its revenues from pharmaceuticals, these investments are the highest compared to investments in such R&D made by other large research-based

pharmaceutical companies evaluated in the Benchmark. Shionogi does not invest in vaccine development.

A.2.1 Mid-sized pipeline compare to peers

Among the large research-based pharmaceutical companies evaluated, this pipeline is mid-sized. Shionogi reports eight projects targeting priority pathogens in its pipeline. It is one of the two

large research-based pharmaceutical companies within the scope of the Benchmark to have both antibacterial and antifungal projects (all medicine projects). The company's projects are mostly in discovery stage or pre-clinical development (7 out of 8), with one project, cefiderocol, that has been submitted for market approval by the EMA and FDA.

Pipeline targeting priority pathogens: 8 As at 16 October 2019

| Discovery | Pre-clinical | Phase I | Phase II | Phase III | Approval |
|--|--|---------|----------|--|----------|
| Antibacterial programme 1 - GNB (including CRE and ESBL-producing <i>Enterobacteriaceae</i>) Antibacterial programme 2 - GNB (including CRE and ESBL-producing <i>Enterobacteriaceae</i>) Antifungal programme 1 - <i>Candida</i> spp. (and <i>Aspergillus</i> spp.) Antifungal programme 2 - <i>Candida</i> spp. (and <i>Aspergillus</i> spp.) Anti-tuberculosis programme - <i>M. tuberculosis</i> | Antibody (COT-143) - <i>P. aeruginosa</i> S-004992 - <i>M. tuberculosis</i> | | | Cefiderocol (S-649266)*** - GNB (including multidrug-resistant <i>Enterobacteriaceae</i> , <i>P. aeruginosa</i> and <i>A. baumannii</i>) - bloodstream infections, cUTI, sepsis, HAP, HCAP and VABP | |
| CRE = Carbapenem-resistant <i>Enterobacteriaceae</i> CRPA = Carbapenem-resistant <i>P. aeruginosa</i> cUTI = Complicated urinary tract infection ESBL = Extended-spectrum beta-lactamase GNB = Gram-negative bacteria GPB = Gram-positive bacteria HAPB = Hospital-acquired bacterial pneumonia HCAP = Healthcare-associated pneumonia VABP = Ventilator-associated bacterial pneumonia | | | | | |
| ***Cefiderocol received FDA market approval on November 2019 for treatment of cUTI. | | | | | |

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

A.2.2 No clinical-stage novel projects

Shionogi's clinical-stage medicine pipeline for priority pathogens consists of one new R&D project. It does not currently include candidates that are considered novel. However, Shionogi has applied for EMA and FDA market approval for cefiderocol, a siderophore cephalosporin antibacterial for the treatment of multi-drug resistant infections caused by Gram-negative bacteria as well as complicated urinary tract infections and hospital-acquired and ventilator-associated pneumonia.

A.2.3 Vaccines in the pipeline

Shionogi is not eligible for this indicator as it is not active in vaccine development targeting priority pathogens.

A.2.4 Four candidates targeting critical and/or urgent priorities

Shionogi's clinical pipeline includes the medicine cefiderocol, active against Carbapenem-resistant *A. baumannii* (CRAB), Carbapenem-resistant *P. aeruginosa* (CRPA) and CRE. It has been submitted for first marketing authorisation to both the FDA and EMA. Shionogi also has three further candidates in its discovery and pre-clinical pipeline targeting pathogens considered critical and/or urgent R&D priorities for limiting AMR, as identified by WHO and/or the US Centers for Disease Control and Prevention (CDC).

A.3 No intellectual capital sharing practices

The company does not report any intellectual capital sharing initiatives.

A.4 Access plan for its late-stage R&D project targeting a priority pathogen

Shionogi has one such R&D project. It reports to run a global compassionate use programme for cefiderocol. Shionogi has affiliate companies in a limited number of countries and is also currently seeking partners to help increase access. It reports a commitment to discuss stewardship strategies with the access country governments.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)**B.1 Comprehensive environmental risk-management for own sites and suppliers**

Shionogi reports a comprehensive strategy to minimise the environmental impact of waste-waters and solid waste from antibacterial manufacturing at its sites, with an aim to limit AMR. This includes audits every five years. The company reports setting discharge limits for all antibacterials manufactured at its sites, based on PNECs to limit AMR (or more stringent PNECs), as published by the AMR Industry Alliance or the EMA. It reports using analytical testing to validate its antibacterial deactivation procedure and having plans to develop a monitoring system in the near future.

Shionogi expects third-party suppliers of antibacterial APIs and drug products to follow the same standards, including limits. Audits are set to take place at least every five years and suppliers have been requested to provide information to Shionogi on whether their discharges are below the PNECs or, where PNECs are not available, below EMA environmental emission stand-

ards. The company reports that on-site audits have been conducted for all Japanese-based suppliers and corrective actions requested when their antibacterial discharge levels were found to be above the limits. Shionogi also expects external private waste-treatment plants to comply with its environmental standards and guidelines and reports auditing them once a year. All solid waste and wastewater sent to these plants is set to be incinerated.

B.2 Publicly discloses some information on environmental risk management

Shionogi publishes some components of its environmental risk-management strategy. Further, it is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. Shionogi does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private waste-treatment plants; (2) a list of these suppliers and waste-treatment plants; or (3) the levels of antibacterial discharge from its own sites. After the period of analysis,

Shionogi published, in its 2019 EHS report, some information on how its strategy and individual discharge limits are being implemented at its own and suppliers' sites.

B.3 Has system to maintain production quality for own and suppliers' sites; no requests for official corrective action

Shionogi reports having a system to maintain high-quality antibacterial production, consistent with international GMP standards. This includes risk-based internal audits and tracking of corrective actions. The company reports requiring suppliers to abide by regulatory and company quality standards, as specified in quality agreements. It reports auditing its suppliers at its sites and having the same expectations in terms of corrective action implementation. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Shionogi's own sites or any subsidiaries.[†]

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries[‡]

C.1 - C.2 Registration and pricing

Shionogi was not eligible for this indicator as it does not have relevant on-patent[§] or off-patent marketed products in its portfolio for which it has the global rights to market or distribute. It reports that the patent on its antibacterial medicine doripenem (Doribax®, Finibax®) has expired and has been licenced out to Takeda for markets other than Japan, Taiwan and Korea. Shionogi also reports that it has marketing rights for the antibacterial cefiderocol and that it currently runs a global compassionate use programme.

C.3 No measures to ensure continuous supply of products

Shionogi does not take steps to ensure continuous supply of antibacterial medicines to access countries.

[†] Including only wholly-owned direct subsidiaries of the company. More information in Appendix I.

[‡] 102 low- and middle-income countries where better access to medicine is most needed. See Appendix VI.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Broad strategy to mitigate COI for all educational programmes

The Benchmark analysed three AMR-related educational programmes for healthcare professionals (HCPs) from Shionogi. Shionogi reports broad COI mitigation for all three programmes. Two programmes have all three COI mitigation strategies looked for by the Benchmark: (1) content is developed independently from its marketing department; (2) a pledge not to provide financial or material incentives to participants; and (3) it does not use branded materials. However, for the remaining programme, it is unclear whether financial or material incentives are provided to participants. After the period of analysis, the company stated that no payments were given to participants.

C.5 Adapts marketing materials and sales practices to address appropriate use

Shionogi engages in practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines, both via its mar-

keting practices and sales remuneration. At least some of Shionogi's marketing materials reflect emerging resistance trends and include guidelines for HCPs to raise awareness of AMR and address appropriate use: namely for the antibacterials doripenem (Finibax®) and flomoxef (Flumarin®). Shionogi is the only large-research-based pharmaceutical company evaluated that reports fully decoupling incentives for sales agents from sales volumes to help prevent the inappropriate use of its antibacterials.

C.6 Adapts brochures to facilitate appropriate use; takes account of paediatric needs

Shionogi adapts brochures in Japan to facilitate the appropriate use by patients of relevant products: namely for its antibacterial cefcapene pivoxil (Flomox®). This adaptation takes account of paediatric use. Shionogi has created a brochure that is easy to understand thanks to simple illustrations. The brochure is tailored to the treatment of children to improve paediatric use.

C.7 Active in multiple AMR surveillance programmes; openly publishes results

Shionogi runs four long-term AMR surveillance programmes. The number of pathogens (species) tested in these programmes varies from ten to 16. One of the programmes, SIDERO-WT, focuses on resistance against Gram-negative bacteria in 13 countries and is repeated every year. The other three programmes focus on antibacterial drug susceptibility in Japan. For example, the Shionogi Japanese Surveillance Studies Programme has run since 1992 and tests 43 antimicrobials. Only the results of these four programmes are shared through peer-reviewed open-access journal articles. Shionogi does not report making antibacterial and/or antifungal consumption data available to national governments or other public health authorities.

Summit Therapeutics

Small/medium-sized enterprise

Stock exchange: LSE; NASDAQ • Ticker: SUMM; SMMT • HQ: Oxfordshire, UK • Employees: 61

PERFORMANCE

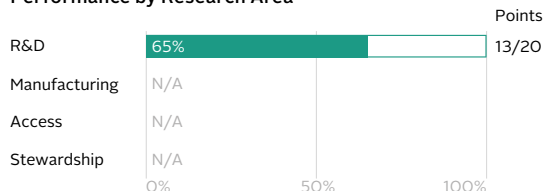
Summit performs above average in Research & Development when compared to other small and medium-sized enterprises in scope.

R&D: Summit has three antibacterial projects in its pipeline that target priority pathogens, including one late-stage candidate that is considered novel: ridinilazole, for *C. difficile* infections. Reports an access plan with a licensing agreement to expand availability to access countries.

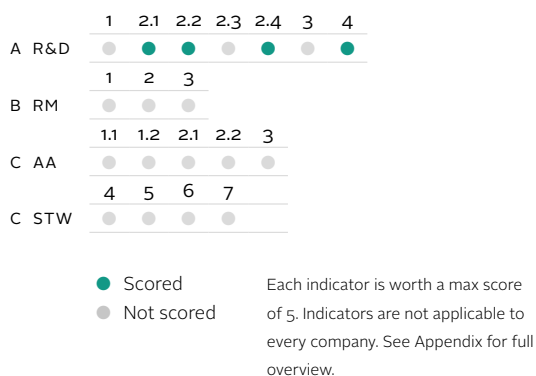
Performance in the Benchmark



Performance by Research Area



How Summit was evaluated



SALES AND OPERATIONS

Therapeutic areas: Antibiotics

Products on the market: None

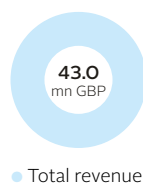
R&D grants received since 2016: At least USD 68.2 million, awarded by two funders (CARB-X; BARDA). Its latest award, from BARDA, was increased in June 2019, bringing the total value to USD 63.7 million to support patient enrolment and dosing in the ongoing Phase III clinical trials of ridinilazole.

Financing and investment structure: Summit is a publicly listed company. It completed its IPO in October 2004 on the London Stock Exchange, raising GBP 15 million. In 2015, it was listed on the NASDAQ stock exchange, raising USD 34 million.

M&A since 2018: None in the antibacterial and/or antifungal sectors

Revenues

(2018)



PIPELINE for diseases in scope

Pipeline size: 3 projects for priority pathogens* (3 antibacterial medicines)

Development stages: 1 clinical project, ridinilazole, a Phase III clinical candidate for the treatment of *C. difficile* infections, and 2 discovery/pre-clinical projects

Novelty: 1 novel project, ridinilazole, a Phase III clinical candidate for the treatment of *C. difficile* infections that belongs to a new chemical class of antibacterials and has a new drug target, mode of action and no known cross-resistance to other antibacterial classes

Regulatory approvals: 0 approvals for priority pathogens

Access plans: Its 1 late-stage R&D project has a project-specific access plan that is a licensing agreement to expand availability to access countries, though this plan does not address affordability.

Stewardship plans: Its 1 late-stage R&D medicine project lacks a project-specific stewardship plan.

Pipeline for priority pathogens



* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

OPPORTUNITIES FOR SUMMIT

Improve access plans and develop stewardship plans for ridinilazole. Summit has committed to ensure access and stewardship plans are in place for its antibacterial candidate in late-stage development, ridinilazole, through its agreement with the Wellcome Trust. So far, Summit has entered into a regional licensing agreement for ridinilazole with Eurofarma Laboratorios for 21 countries in Latin America, including 13 access countries. Summit can improve its access plans for access countries by committing to an equitable pricing strategy and/or looking for licensees across other regions of the world. Summit has not developed worldwide stewardship plans for ridinilazole yet. As examples of stewardship plans, the company can commit to decouple sales incentives from sales volumes and/or become involved in antibacterial surveillance activities.

CHANGES SINCE 2018

- Initiated Phase III clinical trials for ridinilazole in February 2019, with data expected in 2021.
- Expanded its R&D pipeline in April 2019 to include the discovery-stage DDS-04 series project targeting *Enterobacteriaceae*, identified via its proprietary Discuva Platform.
- Entered into a new exclusive license and commercialisation agreement in December 2017 with Eurofarma Laboratórios SA in Latin America for ridinilazole. Eurofarma is responsible for regulatory approvals in the territory (Brazil and 20 other Latin American countries) and Summit retains commercial rights worldwide.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 R&D investments

Summit invested USD 56 million in the development of antibacterial medicines in 2017 and 2018. As with all other small and medium-sized enterprises (SMEs) evaluated, Summit was not scored in this indicator.

A.2.1 Pipeline size of three projects

Summit reports three projects targeting priority pathogens in its pipeline. The company focuses on antibacterial medicine development, with its three projects equally divided between discovery, pre-clinical and clinical (Phase III) stages of development.

A.2.2 One clinical-stage novel project

Summit's clinical-stage medicine pipeline for priority pathogens consists of one new R&D project. Summit has one late-stage antibacterial medicine project that is considered novel: ridinilazole, for *C. difficile* infections, which meets all criteria set by WHO for innovativeness,

including belonging to a new chemical class and having a new target, mode of action and no cross-resistance to other antibacterial classes.

A.2.3 Vaccines in the pipeline

Summit is not eligible for this indicator as it is not active in vaccine development.

A.2.4 Three candidates targeting critical and/or urgent priorities

Summit's pipeline includes one clinical medicine candidate in Phase III (ridinilazole) that targets *C. difficile*; one pre-clinical medicine candidate (SMT-571) that targets *N. gonorrhoeae*; and a discovery platform (DDS-04) that targets *Enterobacteriaceae*, including ESBL-producing *Enterobacteriaceae* and CRE. These pathogens are among those that are considered critical and/or urgent R&D priorities for limiting AMR, as identified by WHO and/or the US Centers for Disease Control and Prevention (CDC).

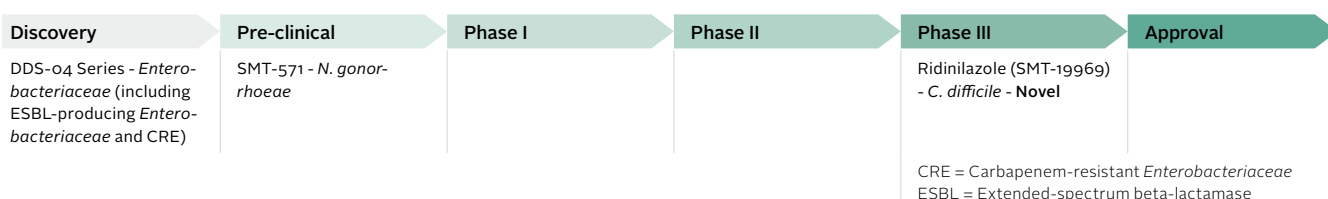
A.3 Intellectual capital sharing

As an SME, Summit was not scored for this indicator, in line with the external stakeholder consensus defined by the Foundation.

A.4 Access plan for one project; no stewardship plans

Summit has one late-stage R&D project targeting priority pathogens. Summit plans to commercialise ridinilazole with its own sales force in the USA. Other territories could be covered independently or through commercialisation agreements with third parties. For example, Summit has entered into a regional licensing agreement for ridinilazole with Eurofarma Laboratorios, one of the largest pharmaceutical companies in Brazil and present in more than 20 countries in Latin America, including 13 access countries.* Summit does not report specific clauses regarding affordability or accessibility in the agreement, or any stewardship plan.

Pipeline targeting priority pathogens: 3 As at 16 October 2019



B RESPONSIBLE MANUFACTURING

As an SME, Summit is not evaluated in this Research Area. Its most advanced antibacterial candidate is ridinilazole, and the Benchmark notes that Summit reports planning its manufacturing programmes to cover the needs of Phase III clinical trials as well as the commercial launch of ridinilazole. Within these plans, two third-party suppliers will be engaged to manufacture

the product. Summit states that it recognises the importance of reducing the impact of manufacturing discharge on antibacterial resistance and expects to develop its environmental risk-management strategy with respect to antibacterial discharge over the coming years. Summit was not scored on these activities.

C APPROPRIATE ACCESS & STEWARDSHIP

As an SME, Summit is not evaluated in this Research Area. It has no antibacterial and/or antifungal products on the market.

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

Sun Pharmaceutical Industries Ltd

Generic medicine manufacturer

Stock exchange: NSE • Ticker: SUNPHARMA • HQ: Mumbai, India • Employees: 17,501

PERFORMANCE

Sun Pharma performs low overall in its evaluated Research Areas when compared to other generic medicine manufacturers in scope.

Responsible Manufacturing: Performs less well. Reports general environmental risk-management strategy for own sites without the specific aim to limit AMR.

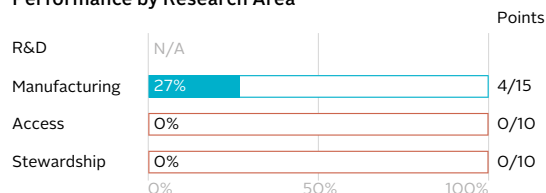
Appropriate Access: Performs low. No information is disclosed on where products are registered. No information is reported on its strategies for pricing and ensuring continuous supply.

Stewardship: Performs low. It has no marketing or sales practices that aim to address appropriate use and it does not adapt its brochures or packaging.

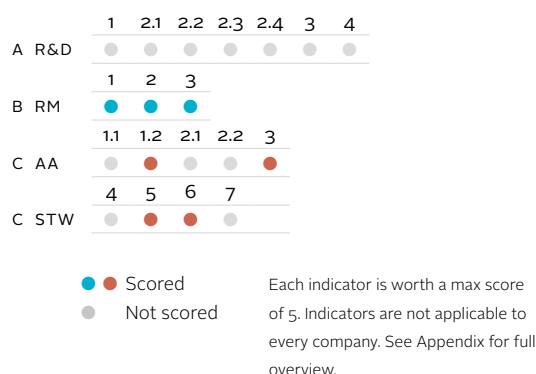
Performance in the Benchmark



Performance by Research Area



How Sun Pharma was evaluated



SALES AND OPERATIONS

Therapeutic areas: Cardiology; Dermatology; Gastroenterology; Infectious diseases; Oncology

Business segments: Formulations; OTC; APIs

Product categories: Generic medicines; Innovative medicines

Manufacturing & supply: No information available

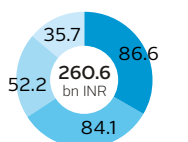
M&A since 2018: In November 2018, Sun Pharma announced the acquisition of Pola Pharma in Japan.

Revenues by product (2017-18)



● Total revenue

Revenues by region (2017-18)



● USA
● India
● Emerging markets
● Rest of World

PORTFOLIO for diseases in scope

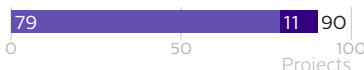
Mid-sized portfolio: At least 90 products (53 unique INNs): 79 antibacterial medicines; 11 antifungal medicines

Essential medicines: 37% (33) products are on the 2019 WHO EML

AWaRe medicines*: 14 Access group; 7 Watch group; 1 Reserve group

Anti-TB medicines*: 4 (incl. 1 Watch group)

Products on the market



● Antibacterial (AB) vaccine
● Antibacterial (AB) medicine
● Antifungal (AF) medicine
● AB+AF combination

All companies were assessed based on data available in the public domain, including information the companies have made publicly available. This was supplemented by data submitted directly to the Benchmark by the companies. Sun Pharma declined to submit data to the 2020 AMR Benchmark.

*Listed on the 2019 WHO EML (Section 6).

OPPORTUNITIES FOR SUN PHARMA

Step up engagement on AMR and increase disclosure of AMR strategies and activities. Sun Pharma is one of the generic medicine manufacturers (GMMs) with the largest portfolio of antibacterial and/or antifungal medicines, including 33 products on the 2019 WHO EML. Sun Pharma can disclose more information (publicly and/or through the Benchmark) about its strategies to improve access and stewardship to the medicines within its portfolio, including their availability in access countries and its steps to mitigate the risk of inappropriate use.

Develop an AMR-specific environmental risk-management strategy. Sun Pharma reports a commitment to manufacture its products in an environmentally responsible manner and a management system to ensure environmental regulations are met. Yet, it is unclear whether AMR is specifically taken into account. The company can develop a strategy that takes AMR into account, including discharge limits based on PNECs to limit AMR (or more stringent) at the company's own manufacturing sites, the sites of third-party suppliers and external private waste-treatment plants. The AMR Industry Alliance has developed a Common Antibiotic Manufacturing Framework and list of discharge limits that could serve as a starting point for such endeavour.

Decouple sales incentives from sales volumes and/or avoid deploying sales agents. In order to mitigate the risk of inappropriate use of its antibacterial and/or antifungal medicines, Sun Pharma can decouple sales incentives from sales volumes and/or avoid deploying sales agents, as appropriate.

CHANGES SINCE 2018

- Acquired Pola Pharma in Japan, which was announced in November 2018.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT

As a GMM, Sun Pharma is not evaluated in this Research Area.

B RESPONSIBLE MANUFACTURING

Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 General environmental risk-management strategy for own sites

Sun Pharma reports a commitment to manufacture its products in an environmentally responsible manner, supported by a management system that includes periodic audits. It is unclear how the strategy takes AMR into account or aims to minimise the environmental impact of waste-waters and solid waste from antibacterial manufacturing at its own sites, third-party suppliers of antibacterial APIs and/or drug products or external private waste-treatment plants.

B.2 Limited publicly available information on environmental risk management

Sun Pharma publishes limited information on its approach to environmental risk management, without specific references to antimicrobial resistance. It does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private waste-treatment plants; (2) a list of these suppliers and waste-treatment plants; or (3) the levels of nor limits for antibacterial discharge from its own sites.

B.3 Has system to maintain production quality for own sites; limited information on corrective and preventive action tracking

Sun Pharma reports having a system to maintain high-quality antibacterial production, consistent with international GMP standards, including internal audits to assure compliance. However, there is limited information on how corrective actions are implemented and tracked and on how the company ensures that its suppliers uphold quality standards comparable to its own. The Benchmark found no requests for official corrective action from the FDA or EMA related to non-conformities with cGMP at Sun Pharma's own sites or any subsidiaries.**

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries***

C.1.1 Registering on-patent products

Sun Pharma was not eligible for this indicator as it does not have on-patent antibacterial or antifungal medicines or vaccines in its portfolio.

C.2.1 Pricing strategies for on-patent products

Sun Pharma was not eligible for this indicator, as it does not have on-patent antibacterial or antifungal medicines or vaccines in its portfolio.

C.3 Limited information on measures to ensure continuous supply of relevant products

Sun Pharma discloses limited information on how it takes steps to ensure the continuous supply of antibacterial or antifungal medicines or vaccines to access countries. It publicly reports that it has 40 sites (manufacturing APIs and finished dose products) located in 15 countries, with trained personnel and quality systems and procedures in place. Site locations span access countries on all continents.

C.1.2 No information on registration filings for relevant off-patent products†

Sun Pharma reports no evidence of filing its relevant off-patent products for registration in access countries. However, there is evidence of sales in at least one access country.

C.2.2 Pricing strategies for off-patent products

Companies were not scored for this indicator as the available data was insufficient for a comparative analysis. There is no available evidence that Sun Pharma considers affordability or socioeconomic factors when setting prices for off-patent antibacterial or antifungal medicines or vaccines.

** Including only wholly-owned direct subsidiaries of the company. More information in Appendix I.

*** 102 low- and middle-income countries where better access to medicine is most needed. See Appendix VI.

† See Appendix VII.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Educational stewardship activities

Sun Pharma is not eligible for this indicator as there is no information regarding its involvement in AMR-related educational programmes aimed at healthcare professionals (HCPs).

C.5 No information on marketing or sales practices that aim to address appropriate use

There is no information regarding Sun Pharma's engagement in practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines, either regarding its marketing materials or its sales practices.

C.6 No information on brochure and/or packaging adaptations to facilitate appropriate use

There is no information regarding Sun Pharma's adaptations in its brochures and/or packaging to facilitate appropriate use of its antibacterial and/or antifungal medicines by patients beyond regulatory requirements.

C.7 Antimicrobial surveillance

As a GMM, Sun Pharma is not eligible for this indicator as GMMs have a limited role in AMR surveillance activities.

Tetraphase Pharmaceuticals Inc

Small/medium-sized enterprise

Stock exchange: NASDAQ • Ticker: TTPH • HQ: Massachusetts, USA • Employees: 119

PERFORMANCE

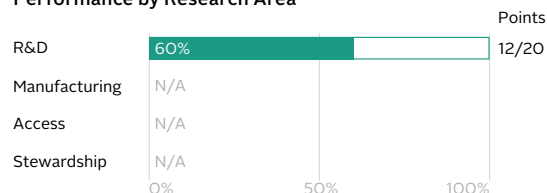
Tetraphase performs above average in Research & Development when compared to other small and medium-sized enterprises in scope.

R&D: Tetraphase has three antibacterial projects in its pipeline that target priority pathogens, including one candidate for the treatment of serious and life-threatening multidrug-resistant (MDR) bacterial infections caused by pathogens including Carbapenem-resistant *Enterobacteriaceae* (CRE) and Carbapenem-resistant *A. baumannii* (CRAB). Reports project-specific access and stewardship plans for its recently approved medicine, eravacycline.

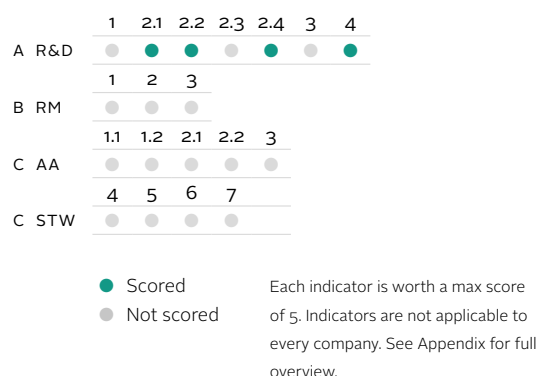
Performance in the Benchmark



Performance by Research Area



How Tetraphase was evaluated



SALES AND OPERATIONS

Therapeutic areas: Antibiotics

Products on the market: 1, eravacycline (Xerava™) approved in August 2018 for the treatment of complicated intra-abdominal infections

R&D grants received since 2016: At least USD 4 million, awarded by one funder (CARB-X). The award, worth USD 4 million, was granted in March 2017 to support its pipeline candidate TP-6076 which has demonstrated potent activity against MDR bacteria, including carbapenem-resistant *Enterobacteriaceae* and carbapenem-resistant *A. baumannii*.

Financing and investment structure: Tetraphase is a publicly listed company. It completed its IPO in March 2013 raising USD 75 million, following four funding series raising USD 95 million. Its lead investors were Excel Venture Management and Mediphase Venture Partners.

M&A since 2018: None in the antibacterial and/or antifungal sectors

PIPELINE for diseases in scope

Pipeline size: 3 projects for priority pathogens* (3 antibacterial medicines)

Development stages: 2 clinical projects, including TP-271, a Phase I clinical candidate for the treatment of respiratory disease caused by bacterial biothreats and antibacterial-resistant public health pathogens

Novelty: No novel clinical-stage medicine projects

Regulatory approvals: 1, for eravacycline (Xerava™) for the treatment of complicated intra-abdominal infections in 2018

Access plans: Its 1 late-stage R&D project has a project-specific access plan which includes a commitment to addressing affordability through licensing agreements.

Stewardship plans: Its 1 late-stage R&D medicine project has a project-specific stewardship plan which includes the development of a surveillance network for bacterial susceptibility to eravacycline.

Pipeline for priority pathogens



- Antibacterial (AB) vaccine
- Antibacterial (AB) medicine
- Antifungal (AF) medicine
- AB+AF combination

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

OPPORTUNITIES FOR TETRAPHASE

Expand the implementation of the access and stewardship plans for eravacycline (Xerava™). Tetrphase has already implement access and stewardship plans (including a license to Everest Medicines in the ASEAN region and a surveillance programme) for eravacycline, its antibacterial candidate that recently was approved. Tetrphase can also implement its commitment to addressing affordability through licensing agreements that would supply this medicine in other markets, like Latin American and Africa countries. In order to promote appropriate use of eravacycline, Tetrphase can decouple sales incentives from sales volumes and consider publicly sharing raw data collected for its long-term, multinational surveillance programme.

CHANGES SINCE 2018

- Received FDA approval in August 2018 for eravacycline (Xerava™) for the treatment of complicated intra-abdominal infections.
- Entered into a global-level development and commercialisation agreement in 2018 with Everest Medicines for eravacycline in China, Taiwan, Hong Kong, Macau, South Korea, Singapore, Thailand, Indonesia, Philippines and Malaysia.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 R&D investments

Tetrphase invested USD 156.6 million in the development of antibacterial medicines in 2017 and 2018. As with all other small and medium-sized enterprises (SMEs) evaluated, Tetrphase was not scored in this indicator.

A.2.1 Pipeline size of three projects

Tetrphase reports three projects targeting priority pathogens in its pipeline. The company focuses on antibacterial medicine development, and has two projects in clinical development, in addition to its recently approved product eravacycline (Xerava™).

A.2.2 No clinical-stage novel projects

Tetrphase's clinical-stage medicine pipeline for priority pathogens consists entirely of new R&D projects. It does not currently include candidates that are considered novel. However, Tetrphase has three clinical-stage new R&D projects, including TP-6076 for the treatment of serious and life-threatening MDR bacterial infections caused by pathogens including CRE and CRAB,

among others.

A.2.3 Vaccines in the pipeline

Tetrphase is not eligible for this indicator as it is not active in vaccine development.

A.2.4 Two candidates targeting critical priorities

Tetrphase's clinical pipeline includes one antibacterial medicine in Phase I: TP-6076, which targets CRE and CRAB. The company also has a recently approved medicine, eravacycline (Xerava™), which targets CRE, *N. gonorrhoeae* and resistant strains of *A. baumannii*. These pathogens are among those that are considered critical and/or urgent R&D priorities for limiting AMR, as identified by WHO and/or the US Centers for Disease Control and Prevention (CDC).

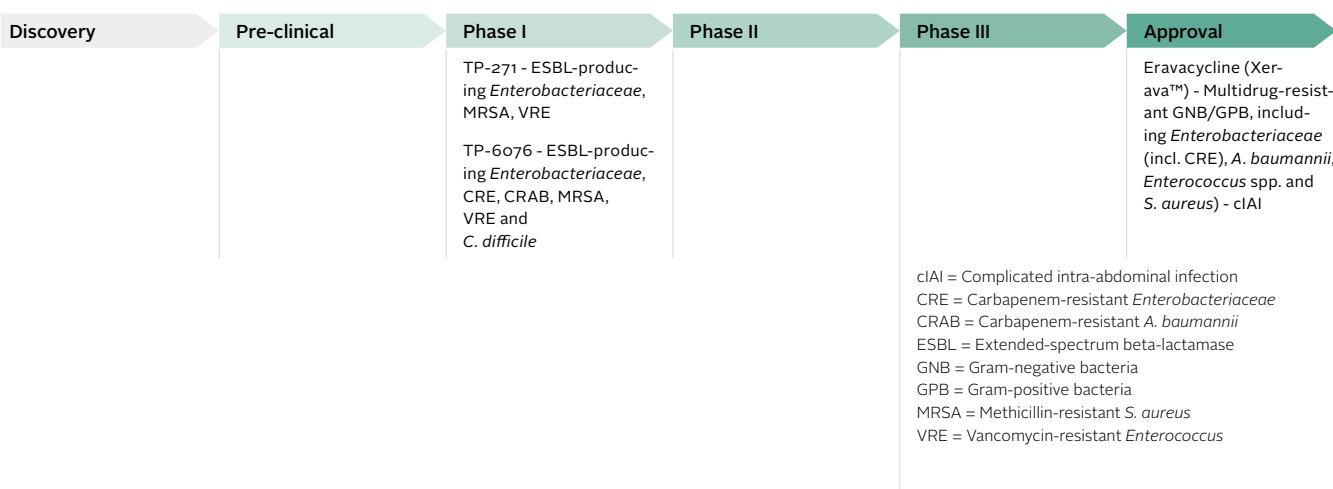
A.3 Intellectual capital sharing

As an SME, Tetrphase was not scored for this indicator, in line with the external stakeholder consensus defined by the Foundation.

A.4 Access and stewardship plan for one project

Tetrphase has one late-stage R&D project targeting a priority pathogen. Tetrphase has a licensing agreement for eravacycline (Xerava™) that enables the licensee to market the product at a competitive price in countries belonging to the Association of Southeast Asian Nations (ASEAN). Tetrphase has also committed to addressing affordability through licensing agreements that would supply this medicine in other markets. Further, Tetrphase is collaborating with International Health Management Associates (IHMA), an independent laboratory with expertise in surveillance and clinical trials, to develop a surveillance network looking at susceptibilities to eravacycline in different pathogens and clinical settings. Tetrphase provides the medicine, as well as testing strips and disks, to help hospitals and researchers test it against isolates.

Pipeline targeting priority pathogens: 3 As at 16 October 2019



* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

B RESPONSIBLE MANUFACTURING

As an SME, Tetrphase is not evaluated in this Research Area. It has one antibacterial product on the market: the antibacterial eravacycline (Xerava™).

C APPROPRIATE ACCESS & STEWARDSHIP

As an SME, Tetrphase is not evaluated in this Research Area. It has one antibacterial and/or antifungal product on the market: the antibacterial eravacycline (Xerava™). The Benchmark notes that it is active in one AMR surveillance programme, and that it openly publishes its results.

Specifically, Tetrphase reports that it is active in a long-term AMR surveillance programme, which focuses on surveillance of eravacycline against Gram-negative and Gram-positive clinical isolates globally.

Teva Pharmaceutical Industries Ltd

Generic medicine manufacturer

Stock exchange: TASE; NYSE • Ticker: TEVA • HQ: Petah Tikva, Israel • Employees: 42,535

PERFORMANCE

Teva performs well overall in its evaluated Research Areas when compared to other generic medicine manufacturers in scope.

Responsible Manufacturing: Performs well. Reports environmental risk-management strategy for own sites, including ongoing risk assessments based on discharge limits.

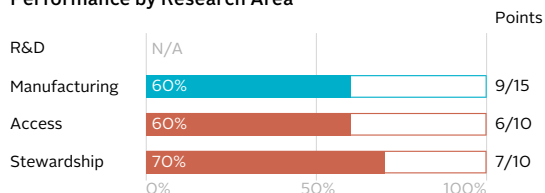
Appropriate Access: Middle-performing. Files for registration for its relevant products in access countries. It discloses strategies for pricing and to ensure supply including forecasting, global supply networks, and safety and strategic stocks.

Stewardship: Performs well. It does not deploy sales agents to promote its products. It translates packaging for three antibacterial medicines, but reports no further adaptations.

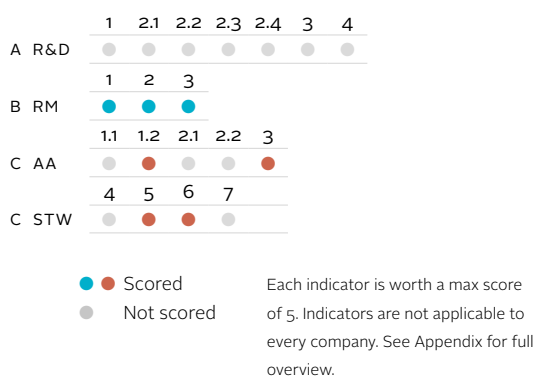
Performance in the Benchmark



Performance by Research Area



How Teva was evaluated



SALES AND OPERATIONS

Therapeutic areas: Neurology; Respiratory diseases

Business segments: North America; Europe; International Markets

Product categories: Generic medicines; Innovative medicines

Manufacturing & supply: Teva reports having 38 manufacturing sites that produce antibacterial APIs and/or drug products.

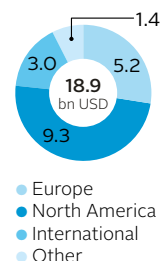
M&A since 2018: None in the antibacterial and/or antifungal sectors

Revenues by product (2018)



● Total revenue

Revenues by region (2018)



PORTFOLIO for diseases in scope

Largest portfolio: At least 202 products (117 unique INNs): 172 antibacterial medicines; 26 antifungal medicines; 4 antibacterial and antifungal combinations

Essential medicines: 37% (74) products are on the 2019 WHO EML**

AWaRe medicines*: 34 Access group; 15 Watch group and 1 Reserve group

Anti-TB medicines*: 8 (incl. 1 Watch group, 2 Reserve group)

Products on the market



The number of products is based on data from public sources, IQVIA, and data submitted by the company. It may not account for Teva's entire portfolio.

* Listed on the 2019 WHO EML (Section 6).

** The number of products is based on data from public sources and IQVIA, and

data submitted by the company. It may not account for the company's complete portfolio.

OPPORTUNITIES FOR TEVA

Expand registration and ensure adequate supply antibacterial medicines to access countries.

Teva can file for registration and ensure adequate supply of antibacterial medicines on the 2019 WHO EML list within its current portfolio (e.g. the forgotten antibiotics cloxacillin, nitrofurantoin, phenoxymethylpenicillin, fosfomycin and trimethoprim) in more access countries.

Expand its set of strategies to ensure the continuous supply of its antibacterial and/or anti-fungal medicines.

Teva implements some strategies to prevent shortages and stockouts, such as demand planning and maintaining a certain volume of products ready to donate in order to mitigate shortages and stockouts. Teva can also exchange information with external stakeholders (such as government ministries of health) to align supply with demand and set up contracts with multiple suppliers.

Implement and monitor its environmental risk-management strategy, including discharge limits, at third-party suppliers and external private waste-treatment plants. Teva has an environmental risk-management strategy and auditing processes for its own manufacturing sites, including discharge limits. The company can ensure that these limits, as well as the strategy, extend fully to the sites of third-party suppliers and external private waste-treatment plants, including auditing and discharge-monitoring processes.

Further adapt brochures and packaging. Teva already adapts its packaging by taking account of language. It can also make brochure and/or packaging adaptations that take account of literacy levels, paediatric use, adherence to treatment and environment conditions to facilitate appropriate use.

CHANGES SINCE 2018

- Recently started the Teva Access Initiative and is collaborating with five NGOs (e.g. Stop TB Partnership, the Global Drug Facility (GDF) and the IDA Foundation) to address a sustainable medicine supply in access countries.
- Newly reports not deploying sales agents to promote its antibacterial and/or antifungal medicines and does not have marketing materials for such medicines.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT

As a generic medicine manufacturer (GMM), Teva is not evaluated in this Research Area. However, the company reports investments of > USD 2.5 million in 2017-2018 in the development

of generic versions of antibacterial and antifungal medicines.

B RESPONSIBLE MANUFACTURING Evaluated: antibacterials manufacturing (APIs and drug products)

B.1 Environmental risk-management strategy for own sites

Teva reports a strategy to minimise the environmental impact of wastewaters and solid waste from antibacterial manufacturing at its sites, which includes audits. The company reports setting discharge limits for all antibacterials manufactured at its sites, based on PNECs to limit AMR (or more stringent PNECs), as published by the AMR Industry Alliance. It has used these limits to initiate risk assessments at a subset of its sites, with plans to cover the great majority of its antibacterial production by volume by the end of 2019.

Teva has not yet implemented its strategy with third-party suppliers of antibacterial APIs and/or drug products. It expects suppliers to follow its code of conduct, which includes only a general provision on appropriate management of API-containing waste. Teva expects external private waste-treatment plants to comply with its environmental standards, but there is limited information on how plants are audited. Teva reports not requiring wastewater plants to set antibacterial discharge limits.

B.2 Publicly discloses some information on environmental risk management

Teva publishes some components of its environmental risk-management strategy. Further, it is a member of the AMR Industry Alliance, which publishes a list of recommended antibacterial discharge targets. Teva does not publish: (1) the results of environmental audits, whether conducted at its own sites, the sites of suppliers or external private waste-treatment plants; (2) a list of these suppliers and waste-treatment plants; or (3) the levels of antibacterial discharge from its own sites.

B.3 Has system to maintain production quality for own and suppliers' sites; regulator requested official corrective action

Teva reports having a system to maintain high-quality antibacterial production, consistent with international GMP standards. This includes periodic risk-based internal audits and tracking of corrective actions. In July 2018, an FDA drug quality inspection identified non-conformities with cGMP at one Actavis site (a Teva subsidiary) producing antibacterial drug products, resulting in an official request for corrective action. The company reports that oral antibacterial products manufactured at this site were not impacted by the observations and that the site is taking corrective actions. The company reports requiring suppliers to abide by regulatory and company quality standards, auditing its suppliers as its sites and having the same expectations in terms of corrective action implementation.

C APPROPRIATE ACCESS & STEWARDSHIP – ACCESS

Evaluated: access activities relating to antibacterial & antifungal medicines & vaccines in 102 access countries***

C.1.1 Registering on-patent products

Teva was not eligible for this indicator as it does not have on-patent antibacterial or antifungal medicines or vaccines in its portfolio.

C.1.2 Filed to register relevant off-patent products† in 6.4 access countries on average

Teva is a middle-performing company when it comes to filing relevant off-patent products for registration. It has filed 14% of its products (1/7 antibacterial and antifungal medicines) for registration in access countries. Its most widely filed product in this analysis is the antibacterial linezolid, used for various conditions including pneumonia and skin infections. Teva has filed its version of this product for registration in approximately 50 access countries. Teva plans to file its other four antibacterial medicines and two antifungal medicines with highest volume sales in access countries during 2019-2020.

C.2.1 Pricing strategies for on-patent products

Teva was not eligible for this indicator, as it does not have on-patent antibacterial or antifungal medicines or vaccines in its portfolio.

C.2.2 Pricing strategies for off-patent products

Companies were not scored for this indicator as the available data was not sufficient for a comparative analysis. Teva does report that it donates six of its highest volume antibacterial and antifungal medicines (in terms of sales) to access countries via the US Donations Program and NGO partnerships with AmeriCares, Brother's Brother Foundation, Direct Relief International, Operation Blessings and Universal Heart.

C.3 Some strategies to ensure the continuous supply of relevant products

Teva is a middle-performing company, compared to other generic medicine manufacturers evaluated, when it comes to taking steps

to ensure the continuous supply of its relevant products to access countries. It discloses some strategies for achieving this aim. It uses an Enterprise Resource Planning (ERP) system for demand planning and maintains a certain volume of products ready to donate in order to mitigate shortages and stockouts. Teva recently started its Teva Access Initiative and is collaborating with five NGOs with the aim of enlarging its footprint and ensuring a sustainable medicine supply in more countries. To mitigate against falsified medicines reaching the supply chain, Teva's donated products go directly to its certified NGO partners and all EU Teva affiliates now implement product serialisation (as required by EU law). Teva also supplies five forgotten antibiotics‡ (benzylpenicillin, chloramphenicol, colistin, dicloxacillin and tobramycin) to some access countries.

C APPROPRIATE ACCESS & STEWARDSHIP – STEWARDSHIP

Evaluated: stewardship activities relating to antibacterial & antifungal medicines globally

C.4 Educational stewardship activities

Teva is not eligible for this indicator as it reports no involvement in AMR-related educational programmes aimed at healthcare professionals (HCPs).

C.5 Does not promote its antibacterial and antifungal medicines

Teva engages in practices that aim to address the appropriate use of antibacterial and/or antifungal medicines. It is one of the two companies evaluated to report that it does not deploy any sales agents to promote such products. As Teva does not perform any promotional activities, it does not have marketing materials for such medicines.

C.6 Translates packaging materials to facilitate appropriate use

Teva adapts packaging to facilitate the appropriate use by patients of relevant products: namely its antibacterials azithromycin, linezolid and pyridoxine. These adaptations only take account of language needs. Their packaging contains information that is translated into English, Spanish, French and Portuguese.

C.7 Antimicrobial surveillance

As a GMM, Teva is not eligible for this indicator as GMMs have a limited role in AMR surveillance activities.

*** 102 low- and middle-income countries where better access to medicine is most needed. See Appendix VI.

† See Appendix VII.

‡ A set of older off-patent antibacterials that are not always marketed or available, due to economic reasons, lack of

awareness and lack of demand but are still considered effective as a treatment for bacterial infections. See Appendix VII for citation.

Wockhardt Ltd

Small/medium-sized enterprise

Stock exchange: NSE • Ticker: WOCKPHARMA • HQ: Mumbai, India • Employees: 5,840

PERFORMANCE

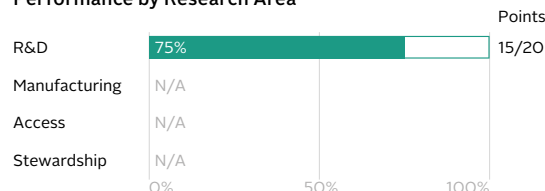
Wockhardt is a hybrid company with both an R&D pipeline and portfolio of marketed products, but is evaluated like a small and medium-sized enterprise. Wockhardt performs well in Research & Development when compared to other small and medium-sized enterprises in scope.

R&D: Wockhardt has nine antibacterial projects in its pipeline that target priority pathogens. Reports project-specific access plans for all late-stage projects.

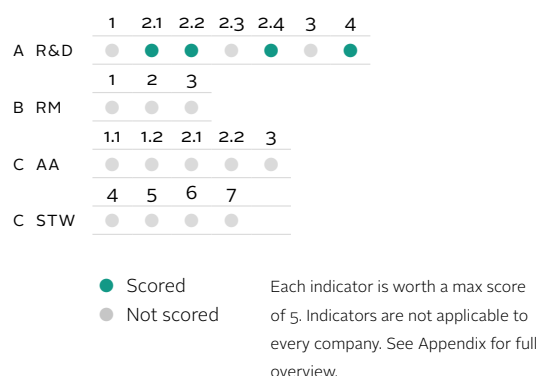
Performance in the Benchmark



Performance by Research Area



How Wockhardt was evaluated



SALES AND OPERATIONS

Therapeutic areas: Anti-infectives; Cardiovascular diseases; Dermatology; Diabetes; Pain management; Respiratory diseases

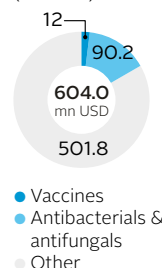
Products on the market: 59 antibacterial and antifungal products

R&D grants received since 2016: None

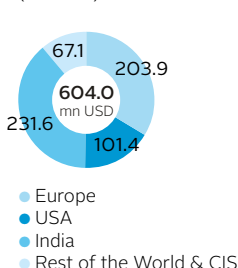
Financing and investment structure: Wockhardt is a publicly listed company. It completed its IPO in May 2004.

M&A since 2018: None in the antibacterial and/or antifungal sectors

Revenues by product (2017-18)



Revenues by region (2017-18)



PIPELINE for diseases in scope

Pipeline size: 9 projects for priority pathogens* (9 antibacterial medicines)

Development stages: 4 clinical projects, including levonadifloxacin, a Phase III clinical candidate for the treatment of acute bacterial skin and skin structure infections and three different types of bacterial pneumonia including hospital-acquired bacterial pneumonia, and 5 pre-clinical projects

Novelty: No novel clinical-stage medicine projects

Regulatory approvals: 0 approvals for priority pathogens

Access plans: 4 of 4 late-stage R&D projects with project-specific access plans, which are all commitments to register the products in India (with registration in other access countries simultaneously) but with no information on affordability

Stewardship plans: No late-stage R&D medicine projects with a project-specific stewardship plan

PORTFOLIO for diseases in scope

Wockhardt maintains a portfolio of marketed products as well as an R&D pipeline of candidates targeting priority pathogens.

Mid-sized portfolio: At least 59 products (43 unique INNs): 54 antibacterial medicines; 1 antibacterial vaccine; 3 antifungal medicines; 1 antibacterial and antifungal combination

Essential medicines: 46% (27) products are on the 2019 WHO EML

AWaRe medicines:** 7 Access group; 13 Watch group; 1 Reserve group

Anti-TB medicines:** 2 (incl. 1 Watch group)

Pipeline for priority pathogens



Products on the market



* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

** Listed on the 2019 WHO EML (Section 6).

OPPORTUNITIES FOR WOCKHARDT

Expand access plans for levonadifloxacin, cefepime/tazobactam, cefepime/zidebactam and nafithromycin. Wockhardt's access plans for its four projects in late stages of development (levonadifloxacin, cefepime/tazobactam, cefepime/zidebactam and nafithromycin) focus on filing for registration and availability. Wockhardt can expand its plans by taking affordability into consideration as well. For example, it can commit to implement equitable pricing strategies.

Publicly share raw data from its surveillance programme ASPIRE. Wockhardt can share publicly (e.g., with the AMR Register) the raw data collected for its long-term surveillance programme ASPIRE, which focuses on nosocomial clinical infections in 16 medical centres across India.

CHANGES SINCE 2018

- Recently received market approval for IV levonadifloxacin & oral alalevonadifloxacin in India.
- Involved in an AMR-related educational programme aimed at healthcare professionals (HCPs), from 2018 onwards.
- Newly reports fully decoupling incentives for sales agents from sales volumes to help prevent the inappropriate use of its antibacterial and/or antifungal medicines.

PERFORMANCE BY RESEARCH AREA

A RESEARCH & DEVELOPMENT Evaluated: medicine & vaccine pipelines for priority* bacteria & fungi

A.1 R&D investments

Wockhardt invested USD 156.1 million in Research & Development during 2017 and 2018. This figure represents its investments in the development of antibacterials and antifungals as well as medicines in other therapeutic areas. As with all other small and medium-sized enterprises (SMEs) evaluated, Wockhardt was not scored in this indicator.

A.2.1 Pipeline size of nine projects

Wockhardt reports nine projects targeting priority pathogens. The company focuses on antibacterial medicine development, and has four projects in clinical development, and five in pre-clinical development.

A.2.2 No clinical-stage novel projects

Wockhardt's clinical-stage medicine pipeline for priority pathogens consists of adapted and new R&D projects. It does not currently include candidates that are considered novel. However, it

is developing three clinical-stage new R&D projects, including a fixed-dose combination of cefepime/zidebactam for the treatment of complicated urinary tract and intra-abdominal infections and sepsis, among others.

A.2.3 Vaccines in the pipeline

Wockhardt is not eligible for this indicator as it is not active in vaccine development.

A.2.4 Four candidates targeting critical and/or urgent priorities

Wockhardt's clinical pipeline includes one combination medicine candidate in Phase II: cefepime/zidebactam targeting CRE and possibly CRPA and CRAB. The company's pre-clinical pipeline includes three further projects targeting critical R&D priorities for limiting AMR as identified by WHO and/or urgent priorities as identified by the US Centers for Disease Control and Prevention (CDC). These are: meropenem/WCK4234, targeting CRAB and CRPA;

WCK6777, targeting CRPA; and one of its beta-lactam and non beta-lactam combination projects, also targeting CRPA.

A.3 Intellectual capital sharing

As an SME, Wockhardt was not scored for this indicator, in line with the external stakeholder consensus defined by the Foundation.

A.4 Access and/or stewardship plans for four of four projects

Wockhardt has four late-stage R&D projects targeting priority pathogens. Wockhardt plans to register these projects in India and other access countries, simultaneously. However, the detailed plans do not address affordability. The company also reports that it conducts susceptibility tests for its marketed products, as well as for projects in development, which supports stewardship.

Pipeline targeting priority pathogens: 9 As at 16 October 2019

| Discovery | Pre-clinical | Phase I | Phase II | Phase III | Approval |
|-----------|---|---------|--|--|----------|
| | Beta-lactam and non beta-lactam combination project 1 - <i>Enterobacteriaceae</i> and certain carbapenem-resistant <i>Pseudomonas</i> spp. Beta-lactam and non beta-lactam combination project 2 - <i>Enterobacteriaceae</i> Cefpodoxime/WCK6395 - <i>Enterobacteriaceae</i> Meropenem/WCK4234 - <i>Enterobacteriaceae</i> , multidrug-resistant <i>P. aeruginosa</i> and carbapenem-resistant <i>A. baumannii</i> WCK6777 - <i>Enterobacteriaceae</i> and certain carbapenem-resistant <i>Pseudomonas</i> spp. | | Cefepime/tazobactam (WCK 4282) - <i>Enterobacteriaceae</i> (including ESBL-producing strains) and <i>P. aeruginosa</i> - Adaptation (new FDC of an approved beta-lactam and beta-lactamase inhibitor) - cUTI including pyelonephritis, cIAI, bloodstream infections, sepsis, HABP and VABP Nafithromycin (WCK 4873) - Multidrug-resistant <i>S. pneumoniae</i> , Group A <i>Streptococcus</i> , <i>S. aureus</i> and <i>H. influenzae</i> - CABP Cefepime/zidebactam (WCK 5222) - <i>Enterobacteriaceae</i> (including CRE), <i>P. aeruginosa</i> and <i>Acinetobacter</i> spp. - cUTI including pyelonephritis, cIAI, bloodstream infections, sepsis, HABP and VABP | IV levonadifloxacin (WCK 771) & oral alalevonadifloxacin (WCK 2349) - MRSA, VRSA, <i>S. pneumoniae</i> , Group A <i>Streptococcus</i> and <i>H. influenzae</i> - ABSSSI, CABP, HABP and VABP | |

* Bacteria and fungi that have been identified as priority R&D targets for limiting AMR, by either the WHO and/or the Centers for Disease Control and Prevention (CDC). See Appendix V.

B RESPONSIBLE MANUFACTURING

As an SME, Wockhardt is not evaluated in this Research Area. It has antibacterial products on the market. The Benchmark notes that Wockhardt reports manufacturing antibacterial APIs and/or drug products at three manufacturing sites, all of which possess on-site wastewater-treatment plants. Wockhardt also

reports that it is implementing an environmental risk-management strategy to minimise the impact of manufacturing discharge of antibacterial APIs and/or drug products at all three sites in a phased manner. It is unclear how this strategy considers the risk of AMR.

C APPROPRIATE ACCESS & STEWARDSHIP

As an SME, Wockhardt is not evaluated in this Research Area. It does, however, have antibacterial and/or antifungal products on the market. The Benchmark notes that Wockhardt has plans to register such products in access countries.***

Further, it has some strategies in place to mitigate conflict of interest (COI) for its AMR-related educational programme aimed at HCPs. Specifically, Wockhardt reports that it develops the content independently from its marketing department.

It also adapts sales practices to address the appropriate use of its antibacterial and/or anti-

fungal medicines. Wockhardt reports fully decoupling incentives for sales agents from sales volumes to help prevent the inappropriate use of its antibacterial and/or antifungal medicines.

Further, Wockhardt is active in one AMR surveillance programme, ASPIRE, a long-term programme which focuses on clinical nosocomial infections in India. Wockhardt was not scored for these activities.

*** 102 low- and middle-income countries where better access to medicine is most needed. See Appendix VI.

Appendices

| | |
|-----|---|
| 186 | Appendix I: Analysis, scoring and review process |
| 189 | Appendix II: Limitations |
| 190 | Appendix III: Scoring guidelines |
| 196 | Appendix IV: Identifying best practices |
| 197 | Appendix V: Priority pathogens included for analysis in R&D |
| 198 | Appendix VI: Access countries |
| 199 | Appendix VII: Guide to Report Cards |
| 203 | Appendix VIII: Figures |
| 204 | Appendix IX: Definitions |

APPENDIX I

Analysis, scoring and review process

PROCESS FOR ANTIMICROBIAL PORTFOLIO ANALYSIS

The product portfolio database, including medicines and vaccines, was constructed using information from various sources, including proprietary data from IQVIA, public sources from pharmaceutical companies and supplemented (where relevant) with data from company submissions. The Benchmark requested companies to provide additional data on their antibacterial and antifungal portfolio for analysis. Companies were asked to list each of their antibacterial or antifungal products' International Nonproprietary Name (INN), brand name(s), formulation(s), dose(s) and route(s) of administration.

All products on the market as of 21 June 2019 (when the data collection period ended) were eligible for inclusion in the descriptive analysis of the product portfolio. The research team verified whether R&D projects included for analysis in the R&D Research Area were approved between the date of submission and until 16 October 2019. If approved between those dates, the product was included in the company's pipeline. R&D projects with market approval dates after the end of the period of analysis on 21 June 2019 and until 16 October 2019 (the time period during which the status of R&D projects was monitored by the Benchmark) were not added to the company's marketed product portfolio. In some instances, companies did not submit their entire antibacterial and antifungal portfolio during the data collection period. Products not submitted may include products with different INNs as well as products with the same INN but marketed under different brand names (e.g. in different countries/regions). For companies that did not participate in the Benchmark's survey, the initially pre-populated database was used for all descriptive product portfolio analyses.

To ensure products were within scope and eligible for analysis – i.e. antibacterial and antifungal medicines and vaccines for human use, both systemic and topical – and that there were no duplicate products within a company's submission, the research team reviewed and validated companies' submitted portfolios. For analyses at the individual company level, product data was aggregated at the INN level, since these were used to showcase the different active antibacterial and antifungal ingredients that the company marketed (formulations, doses, routes of administration or brand names were not differentiated). INN-level aggregation was performed both in the case of products with a single INN and fixed-dose combinations (FDCs) composed of two or more single-INN elements – there-

fore, two FDCs containing, e.g., the same single-INN components but with different doses in one or more of the components, were considered equivalent and aggregated. The Benchmark also considered that different salts of the same single-INN product or FDC component were considered equivalent and aggregated. On the other hand, product modifications that resulted in significantly different chemical/pharmaceutical properties were considered non-equivalent to the original product (examples include benzathine benzylpenicillin, a type of benzylpenicillin). The Benchmark also considered that combination products differing only in components that are not antimicrobials were equivalent and hence aggregated. Lastly, co-packaging of two products already marketed by a company (single-INN or FDC) did not count as an additional product. For the analysis combining companies' portfolios (in the portfolio analysis section of this report) no further data aggregation took place, meaning a product with a given INN, marketed by more than one company, was counted as many times as the number of companies that market it. The purpose of this was to provide an overview of the antibacterial and antifungal market.

Information regarding whether or not the product was listed on the WHO Model List of Essential Medicines (EML) was also verified by the research team. This final product portfolio, including 1521 products, was compared to the 21st WHO EML, published in 2019, to assess the number of products on this list. For a product to be considered by the Benchmark as a part of the EML, the INN, the specific formulation and strength had to be listed on the EML (chapter 6 anti-infectives and chapter 19.3 vaccines). The percentage of medicines on the 2019 WHO EML for a given company was calculated as the number of the company's INN and formulation pairs for which at least one marketed strength appears on the 2019 WHO EML divided by the total number of INN and formulation pairs on the company's portfolio. Antibacterial medicines on the EML were further grouped according to the Access, Watch and Reserve (AWaRe) classification. Antituberculosis medicines were classified as: antituberculosis medicines; antituberculosis medicines with Reserve group properties, or antituberculosis medicines with Watch group properties. Products that could be linked to an EML product via a Square box were treated the same way as products that were mentioned on the EML and all alternatives listed were also included in the product portfolio database.

SUMMARY OF THE SCORING PROCESS

Companies were assessed and scored by the Benchmark in three Research Areas: Research & Development, Responsible Manufacturing and Appropriate Access and Stewardship, with each area composed of several indicators. Due to the variation between companies in scope, not all indicators were applicable to every company, as shown in the Indicators and Scoring Eligibility table in this Appendix.

The Benchmark included ongoing/active projects up until 21 June 2019 (when the data collection period ended), with two exceptions: (1) for R&D indicators, the status of R&D projects included for analysis was monitored between 21 June 2019 and 16 October 2019 (for termination or changes in clinical phase) and changes during this period were footnoted in the companies' report cards; R&D products approved up to 16 October 2019 were included as approved products for the R&D analysis. Of note, no additional R&D projects were included for analysis after 21 June 2019; (2) for stewardship indicators, such as C.4 and C.7, programmes active at some point during the period of analysis were included, regardless of their ending date. Financial data from fiscal year 2018 was used for analysis (the exact date marking the fiscal year end varies among companies).

Data review

Companies were asked to verify the accuracy of publicly sourced data and to provide additional necessary information. Prior to analysis, the Benchmark team reviewed companies' submissions for each of the Research Areas:

Research & Development: R&D projects consisting of antibacterial and antifungal medicines and vaccines were included for the overall pipeline. R&D projects eligible for scoring had to target at least one of the pre-defined priority pathogens (see Appendix V). R&D projects were classified as new or adapted. Adapted R&D projects do not involve a new chemical or biological entity (NCE or NBE); new R&D projects involve either an NCE or NBE. New medicines in clinical development were further classified as novel when they fulfilled one or more of the following criteria, defined by WHO in its 2017 analysis of the antibacterial clinical development pipeline¹: (a) it represents a new chemical class; (b) it aims at a new target; (c) it has a new mode of action; (d) it displays no cross-resistance from existing antimicrobials. Moreover, a new indicator was introduced that will analyse R&D projects targeting the most critical priority pathogens (i.e. those defined as 'Critical

or 'Urgent' the WHO and CDC lists of priority pathogens, respectively. After final submission and any necessary clarifications with the companies, all R&D projects were evaluated according to this standardised procedure.

Responsible Manufacturing: the Benchmark requested companies to share their environmental strategies and discharge limits in place to minimise risk of AMR from the manufacturing of antibacterial APIs and drug products. For public disclosure indicator B.2, the research team reviewed companies' public information on, e.g., corporate websites, annual reports and corporate social responsibility reports. In indicator B.3, the Benchmark assessed information on how companies ensure high-quality manufacturing of antibacterial APIs and drug products. This included a review of any GMP non-conformities publicly reported in (a) the FDA's Inspection Classification Database under the 'Drug Quality Assurance' project area and with classification of 'Official Action Indicated' (OAI), and (b) the EMA EudraGMP database. Inspection end date had to be within the period of analysis, 9 September 2017 to 21 June 2019, inclusive. Databases were last consulted on 16 October 2019.

Appropriate Access & Stewardship: the Benchmark requested companies to share their access and stewardship policies for antibacterials and antifungals for the Research Area on Access, specifically the indicators Registration (C 1.1 and C 1.2) and Pricing (C.2.1 and C 2.2), the Benchmark examined on- and off-patent products separately. The on-patent products antibacterial and antifungal medicines and vaccines were derived from the product portfolio as described above and were verified by the companies. The selection of off-patent products (antibacterial and antifungal medicines) was based on each company's three highest volume sales data globally and in 21 low income markets, which were provided by IQVIA Midas® based on sales data from 2017. These products were derived from the 2017 EML and were divided into six categories. Four categories were based on the 2017 WHO AWaRe Classification of Access, Watch, Access/Watch and Reserve and two categories were for Antifungal and Anti-Tuberculosis medicines. The data on the number of access countries in which a product had been filed for registration pertained to specific formulations of the products (such as tablets, capsules, or powder for injection) that IQVIA Midas® had reported to be highest volumes

sales products. Companies' policies and strategies for these on- and off patent medicines and vaccines were then analysed in the various access-related indicators.

For stewardship-related indicators, companies were asked to disclose up to five: (a) educational stewardship activities; (b) antimicrobial surveillance programmes; and (c) stewardship-oriented brochure and packaging adaptations. All adaptations (except those relating to language) were evaluated only if they went beyond regulatory requirements. It could not be evaluated whether language adaptations were beyond regulatory requirements, because these requirements were not clearly reported by all regulatory agencies. In addition, companies were asked to disclose their practices that aim to address the appropriate use of its antibacterial and antifungal medicines.

Scoring

All indicators were scored from zero to five and weighted equally. When scoring a company on a quantitative indicator, such as financial investments or R&D pipeline size, the corresponding number was first scaled across all companies in scope for scoring.

When a given indicator was not applicable to a company, the company's maximum attainable score in the corresponding Research Area was decreased by an amount equal to the number of maximum points attainable in that indicator.

Scoring was carried out based on data from a wide range of information sources including companies themselves, independent reports and databases or documents from the WHO, other multilateral organizations and Non-Governmental Organisations. For analysis and scoring of R&D projects, the Benchmark also reached out, where necessary, to external experts and, in the case of projects developed in collaboration with other partners, to the latter. For currency conversion to USD, exchange rates on the website x-rates.com were used.

Final scoring of the companies was the result of a multi-tiered analysis and quality assurance process. The quality assurance process included both systematic verification of scoring consistency and spot-checking. For each indicator, preliminary scoring results were used to make adjustments in scoring guidelines to ensure maximum variability of final results.

Review process

Following clarification and cross-check of company scores, the research team wrote the various sections of the Benchmark report. Each Research Area was reviewed by at least one externally appointed expert advisors. In addition

to this, an external editorial review of the Benchmark report was performed.

METHODOLOGY DEVELOPMENT

To develop the methodology for the 2020 Antimicrobial Resistance Benchmark, the Foundation applied its proven process for building consensus on the role of pharmaceutical companies in tackling global health priorities. Strategic guidance was provided by an Expert Committee for the Benchmark, an independent body of experts, from top-level academic centres, donor governments, local governments in low- and middle-income countries, investors and companies. The Expert Committee met in July and August 2018 to review proposals for the scope, structure and analytical approach of the Benchmark. Their recommendations helped identify ways forward where disagreement or uncertainty existed regarding areas of research.

The Expert Committee members

Hans Hogerzeil (Chair)
Gregory Frank
Nina Grundmann
Magdalena Kettis
Joakim Larsson
Marc Mendelson
Margareth Ndomondo-Sigonda
Katarina Nedog
Sarah Paulin (Observer)
Andrew Singer

Stakeholders by group

Discussions were held with representatives of a wide range of organisations, a list of which can be found in the methodology report for the 2020 Antimicrobial Resistance Benchmark, available for download at www.amrbenchmark.org.

1. WHO. (2017). Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis. Retrieved from http://www.who.int/medicines/areas/rational_use/antibacterial_agents_clinical_development/en/

INDICATORS AND SCORING ELIGIBILITY

| | IN SCOPE FOR R&D | | | | | | | | FOR RM | | | IN SCOPE FOR AA&S | | | | | | | | | | |
|--|------------------|------|------|------|------|----|----|----|--------|----|------|-------------------|------|------|----|----|----|----|----|--|--|--|
| | A1 | A2.1 | A2.2 | A2.3 | A2.4 | A3 | A4 | B1 | B2 | B3 | C1.1 | C1.2 | C2.1 | C2.2 | C3 | C4 | C5 | C6 | C7 | | | |
| Large R&D-based pharmaceutical companies | | | | | | | | | | | | | | | | | | | | | | |
| GSK | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | | | |
| Johnson & Johnson | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | | | |
| Merck & Co, Inc | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | | | |
| Novartis | ● | ● | | | ● | ● | | ● | ● | ● | | ● | | | ● | ● | ● | ● | ● | | | |
| Otsuka | ● | ● | ● | | ● | ● | ● | ● | ● | ● | ● | | ● | | ● | | ● | ● | ● | | | |
| Pfizer | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | | | |
| Sanofi | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | ● | | | |
| Shionogi | ● | ● | ● | | ● | ● | ● | ● | ● | ● | | | | | ● | ● | ● | ● | ● | | | |
| Generic medicine manufacturers | | | | | | | | | | | | | | | | | | | | | | |
| Abbott | | | | | | | | ● | ● | ● | | ● | | | ● | ● | ● | ● | | | | |
| Alkem | | | | | | | | ● | ● | ● | | ● | | | ● | | ● | ● | | | | |
| Aurobindo | | | | | | | | ● | ● | ● | | ● | | | ● | | ● | ● | | | | |
| Cipla | | | | | | | | ● | ● | ● | | ● | | | ● | ● | ● | ● | | | | |
| Fresenius Kabi | | | | | | | | ● | ● | ● | | ● | | | ● | ● | ● | ● | | | | |
| Hainan Hailing | | | | | | | | ● | ● | ● | | ● | | | ● | | ● | ● | | | | |
| Mylan | | | | | | | | ● | ● | ● | | ● | | | ● | ● | ● | ● | | | | |
| Sun Pharma | | | | | | | | ● | ● | ● | | ● | | | ● | | ● | ● | | | | |
| Teva | | | | | | | | ● | ● | ● | | ● | | | ● | | ● | ● | | | | |
| SMEs | | | | | | | | | | | | | | | | | | | | | | |
| Achaogen | | ● | ● | | ● | | ● | | | | | | | | | | | | | | | |
| Amplix | | ● | ● | | ● | | ● | | | | | | | | | | | | | | | |
| Cidara | | ● | ● | | ● | | ● | | | | | | | | | | | | | | | |
| Debiopharm | | ● | ● | | ● | | ● | | | | | | | | | | | | | | | |
| Entasis | | ● | ● | | ● | | ● | | | | | | | | | | | | | | | |
| Melinta | | ● | ● | | ● | | ● | | | | | | | | | | | | | | | |
| Motif Bio | | ● | ● | | ● | | ● | | | | | | | | | | | | | | | |
| Nabriva | | ● | ● | | ● | | ● | | | | | | | | | | | | | | | |
| Polyphor | | ● | ● | | ● | | ● | | | | | | | | | | | | | | | |
| Scynexis | | ● | ● | | ● | | ● | | | | | | | | | | | | | | | |
| Summit | | ● | ● | | ● | | ● | | | | | | | | | | | | | | | |
| Tetraphase | | ● | ● | | ● | | ● | | | | | | | | | | | | | | | |
| Wockhardt | | ● | ● | | ● | | ● | | | | | | | | | | | | | | | |

Large research-based pharmaceutical companies were eligible for scoring in every research area, with a few exceptions. Generic medicine manufacturers were eligible for scoring in the RM and AA&S research areas but not in R&D, as their main focus is the manufacturing of generic products. Small and medium-sized enterprises (SMEs) were eligible for scoring in the R&D research area, with the exception of three indicators: A.1, assessing R&D investments, A.2.3, assessing vac-

cines in the R&D pipeline and A.3, intellectual capital sharing. SMEs were not assessed for R&D investments because this is not reflective of their efforts in this area. As no SME assessed by the Benchmark was active in vaccine R&D, they were not eligible for scoring in this area. Further, in line with the external stakeholder consensus defined by the Foundation, SMEs were not eligible for scoring of their intellectual capital sharing. SMEs were not eligible for scoring in RM and AA&S

because they either did not have products on the market or had small sales volumes and were thus excluded in this iteration of the Benchmark. Any evaluation of access and/or stewardship plans for R&D projects was done in indicator A.4.

APPENDIX II

Limitations

In this section we cover the main limitations faced in the Benchmark. All limitations, methodological, process or otherwise will be reviewed by the Foundation when undertaking future Benchmarks.

GENERAL METHODOLOGICAL LIMITATIONS

As in any survey, main limitations relate to coverage, sampling, non-responder and measurement biases. To the extent possible, the Benchmark research team sought to minimise the impact of these biases in the final results. On coverage and representativeness, we attempted to ensure that coverage of our survey represented as much as possible the wider antimicrobial industry players with relevant activities across the three Research Areas. The criteria used to select companies for the Benchmark is outlined in detail in our Methodology 2019. Companies are sometimes unwilling or unable to disclose data, or, if they do, may do so only partially. For example, the content of R&D projects and pricing information may be treated more cautiously by companies.

APPLICABILITY OF FINDINGS

Disease and product scopes

The outputs analysed in this study and the findings generated from it relate only to the disease and product scopes as outlined in the Antimicrobial Resistance Benchmark Methodology 2019. The 2020 Benchmark will focus on bacterial and fungal infections, particularly those identified as particular threats due to resistance, called priority pathogens, as determined by WHO and the CDC for the R&D research area. For the Responsible Manufacturing research area, the focus through stakeholder and expert review committee consensus was to focus on company's initiatives and activities around antibacterial APIs and drug products. The Appropriate Access and Stewardship research area assessed included companies' antibacterial and antifungal medicines and vaccines for Appropriate Access and antibacterial and antifungal medicines for Stewardship.

Company comparability

The results and findings of this Benchmark relate to a subset of companies especially in the generic and biotechnology industry, the latter referred to as small and medium-sized enterprises (SMEs). Within SMEs, our findings represent a specific subset of companies involved namely in the clinical development of medi-

cines targeting bacterial or fungal pathogens in an attempt to align our company selection with other international agencies active in this space such as the Pew Charitable Trusts and the World Health Organization. Hence, findings in this category of companies should therefore not be taken to be representative of all SMEs involved in antibacterial and antifungal product development given the large volume of such SMEs coming onto the market in the development of infectious disease medicines and vaccines.

Among the large research-based pharmaceutical companies and generic medicine manufacturers, companies were selected based on their antibacterial sales volume or value of their sales. Large research-based pharmaceutical companies were also selected for their antibacterial pipelines that have at least one antibacterial medicine or vaccine candidate targeting a priority pathogen in phase II or more advanced of clinical development and with an anti-infective product portfolio. Generic medicine manufacturers were also selected based on whether they are a large vendor of active pharmaceutical ingredients (APIs). The Benchmark findings on this category of companies should therefore be taken in this context.

Depending on the research area being analysed, different company types might be included in the analysis. For instance, within the R&D research area, indicators on the pipeline are applicable to both large research-based pharmaceutical companies and SMEs but not to generic medicine manufacturers. Both company types are quite different with vastly different business models. In the Benchmark analysis, we adjusted for these variations between company types, company size, and company portfolio whenever relevant and possible. Further, the Benchmark provides key information about companies' antibacterial and antifungal business in several sections of the report, which readers should take into account as important context when interpreting the Benchmark findings.

Different factors may affect companies' capacity for reporting information. Some companies have submitted only a selection of their antibacterial and antifungal business to the Benchmark. Hence, the data presented in the "Portfolio Analysis" section of this report and on individual company report cards may not necessarily represent their entire portfolio resulting in a potential underreporting of the number of essential medicines on the 2019 WHO EML. Different companies also use different nomenclature and have different ways of categorising information. For example, when calculating the value of antibacterial and antifungal R&D investments or revenue from antibacterial and antifungal sales, such disaggregated data might not be

readily available. In an effort to minimise variability in interpretation and ensure data consistency, a glossary of definitions was published in the Benchmark Methodology 2019.

Data Availability

As in all survey methodologies, the data of the Benchmark is dependent on company submissions as the source data as well as on data available in the public domain. To mitigate any reporting bias and for scoring purposes, every effort was made to triangulate company-submitted data by verifying it against public sources, such as company annual reports, WHO reports, and clinical trial registries. Insofar triangulation was not possible, data submitted by the companies was used for scoring. For example, in the R&D research area, while clinical stage projects could be verified with publicly available data, information on discovery and preclinical stage projects was often obtained from company submissions. Both sets of information were used for analysis and scoring. Hence, the comprehensiveness and level of detail available in public sources and in the data submitted by the companies are thus limiting factors in the Benchmark analysis. Furthermore, some information was submitted by companies on the basis of confidentiality, thus making the Benchmark's ability to analyse and report conclusions across several indicators challenging.

¹The PEW Charitable Trusts. (March, 2016). Antibiotics Currently in Clinical Development.

APPENDIX III

Scoring guidelines

A RESEARCH & DEVELOPMENT

A.1 R&D INVESTMENTS

R&D investments (including in-kind) dedicated to the development of antibacterial and antifungal medicines and vaccines targeting priority pathogens in fiscal years 2017 and 2018.

- 5-2 The percentage of the company's (total) revenue derived from pharmaceuticals that it then invests (spends) in the development of antibacterial and/or antifungal medicines and/or vaccines.

This number is scaled across all companies that disclose their investments.

- 1 The company invests into the development of antibacterial and/or antifungal medicines and/or vaccines but does not disclose the amount.
- 0 The company does not disclose the economic investment in the development of antibacterial and antifungal medicines and vaccines for pathogens in scope.

N/A GMMs and SMEs are not scored in this indicator.

A.2.1 PIPELINE SIZE

The size of a company's R&D pipeline targeting priority pathogens, including antibacterial and antifungal medicines and vaccines (including new chemical/biological entities and adaptations) developed in-house or through collaborations.

- 5-1 The sum of medicines and vaccines in development, or having received approval, during the period of analysis that targets the priority pathogens.

This number is scaled across all companies and scored.

- 0 The company has no relevant R&D activity within the scope of this indicator.

N/A GMMs are not scored in this indicator.

A.2.2 NOVELTY OF PIPELINE

The novelty of new investigational clinical antibacterial and antifungal medicines targeting priority pathogens that the company is developing (in-house or through collaborations). A new product candidate in development is defined as containing at least one new component (entity) not previously approved.

A novel candidate meets at least one of the four WHO innovativeness criteria: (1) new chemical class; (2) new target; (3) new mode of action; or (4) absence of cross-resistance. Antibacterial candidates are assessed using WHO's report Antibacterial agents in clinical development (2019).

- 5 The company has at least one (1) new clinical-stage project that meets all four (4) WHO innovativeness criteria.
OR
At a minimum two (2) new clinical-stage projects that meet at least one (1) WHO innovativeness criterion.
- 4 The company has at least one (1) new clinical-stage project that meets at least one (1) WHO innovativeness criterion.
- 3 The company has at least three (3) new projects in its clinical pipeline but none fulfill any of the WHO innovativeness criteria.
- 2 The company has at least one (1) new project in its clinical pipeline but none fulfill any of the four WHO innovativeness criteria.
- 1 The company has no new clinical-stage projects but does have at least one (1) clinical-stage adapted project in its clinical pipeline.

N/A GMMs are not scored in this indicator.

A.2.3 VACCINES IN THE PIPELINE

The number of new vaccines that the company is developing for priority pathogens in scope (in-house or through collaborations).

- 5 The company has a large vaccine pipeline, ($n \geq 10$), mostly focused on innovative projects.
- 4 The company has a moderate vaccine pipeline, ($n \geq 3$ to $n < 10$), all innovative projects
- 3 The company has a moderate vaccine pipeline, ($n > 1$), and at least half ($\geq 50\%$) of the pipeline is focused on innovative projects.
- 2 The company has a moderate vaccine pipeline, ($n > 1$), and more than half ($> 50\%$) of the pipeline is focused on adaptive projects.

N/A The company is not engaged in vaccine development and therefore has no relevant R&D activity within the scope of this indicator. GMMs and SMEs are not scored in this indicator.

A.2.4 PROJECTS TARGETING CRITICAL PRIORITIES

The number of projects that target a 'critical' pathogen (as defined by WHO) and/or 'urgent' pathogen (as defined by the CDC). These pathogens include carbapenem-resistant (CR) *Acinetobacter baumannii*, CR *Pseudomonas aeruginosa*, CR or ESBL-producing *Enterobacteriaceae*, *Clostridioides difficile*, drug-resistant *Neisseria gonorrhoeae* and *Candida auris*.

- 5 The company has 5 or more projects targeting critical priorities.
- 4 The company has 4 projects targeting critical priorities.
- 3 The company has 3 projects targeting critical priorities.
- 2 The company has 2 projects targeting critical priorities.
- 1 The company has 1 project targeting critical priorities.
- 0 The company does not have projects targeting critical priorities.

N/A GMMs are not scored in this indicator.

A.3 INTELLECTUAL CAPITAL SHARING

The company provides evidence of sharing its intellectual capital (e.g., molecule libraries, patented compounds, processes and technologies) with research institutions and drug discovery initiatives to foster the development of products that target priority pathogens.

- 5 The company reports ten (10) or more intellectual capital sharing initiatives.
- 4 The company reports between five to nine (5-9) intellectual capital sharing initiatives.
- 3 The company reports four (4) intellectual capital sharing initiatives.
- 2 The company reports two to three (2-3) intellectual capital sharing initiatives.
- 1 The company reports one (1) intellectual capital sharing initiative.
- 0 The company does not have any intellectual capital sharing initiatives.

N/A GMMs and SMES are not scored in this indicator.

A.4 PLANNING ACCESS & STEWARDSHIP

The proportion of late-stage antibacterial and antifungal R&D projects, targeting priority pathogens, for which the company provides information about having plans in place for (1) access in countries in scope and (2) stewardship on a global basis. Late-stage R&D includes projects in Phase II and III of clinical development (developed in-house or through collaborations) and recently approved products.

- 5 The company has a detailed portfolio-wide or project-specific access plans for all late-stage medicines and vaccines, and stewardship plans for all late-stage medicines.
- 4 The company has project-specific access plans for the majority of its late clinical-stage medicines and vaccines, and stewardship plans for the majority of its late-stage medicines.
- 3 The company has project-specific access (for medicines and vaccines) and/or stewardship (for medicines) plans in place for the majority of its late-stage projects.
- 2 The company has least one late-stage project with a project-specific access (for medicines and vaccines) and/or stewardship (for medicines) plan.
- 1 The company has general commitments or policies in place to develop access and/or stewardship plans for late-stage R&D projects, but the company provides no clear evidence of such plans being applied to existing late-stage R&D candidates.
- 0 The company reports having neither access nor stewardship plans or commitments for its late-stage R&D candidates.

N/A The company does not have any late-stage projects and therefore not applicable.

B MANUFACTURING & PRODUCTION**B.1 ENVIRONMENTAL RISK-MANAGEMENT STRATEGY**

The company has an environmental risk-management (ERM) strategy to minimise the environmental impact of manufacturing discharge of antibacterials that includes:

- (i) implementation of waste-treatment practices for both liquid and solid antibacterial-containing wastes taking AMR risk into account
- (ii) on-site auditing of compliance with the strategy
- (iii) setting of antibacterial discharge limits based on predicted no-effect concentrations (PNECs) for resistance selection
- (iv) monitoring/quantification of the levels of antibacterials discharged in wastewaters to assess and manage risk that limits are surpassed

The points above apply to the company's:

- (a) owned and/or operated manufacturing sites
- (b) third-party suppliers of antibacterial active pharmaceutical ingredients (APIs) and/or drug products
- (c) external privately-owned* waste-treatment plants

Elements (i) to (iv) define the depth of the strategy and elements (a) to (c) define its breadth. There are a total of 12 elements, corresponding to the 12 combinations of 4 depth elements with 3 breadth elements. In the case of suppliers and waste-treatment plants, depth elements (iii) and (iv) were merged for the scoring process, resulting in a maximum total of 10 elements assessed by the Benchmark**. Each element was considered fully, partially or not met and assigned 1, 0.5 or 0 points, respectively. Points were summed to obtain the final score.

- 5 The company demonstrates an ERM strategy that covers 8 or more of the applicable indicator elements
- 4 The company demonstrates an ERM strategy that covers 6-7.5 of the applicable indicator elements

- 3 The company demonstrates an ERM strategy that covers 4.5-5.5 of the applicable indicator elements
- 2 The company demonstrates an ERM strategy that covers 3-4 of the applicable indicator elements
- 0 The company demonstrates an ERM strategy that covers 0-2.5 of the applicable indicator elements.
 - * Off-site plants that are more than 50% owned by private parties, which may or may not include the company itself
 - ** Some elements were not applicable to all companies. Namely, some companies reported not using private external plants for treating their wastewaters and as such were not assessed with respect to requesting these plants to set/monitor limits.

B.2 DISCLOSURE ON ENVIRONMENTAL RISK MANAGEMENT

The company publishes the following elements:

- a. components of its ERM strategy to minimise environmental impact of wastewaters and solid waste from antibacterial manufacturing
- b. results of strategy audits at the company's manufacturing sites, third-party sites manufacturing antibacterial APIs and drug products and/or external private waste-treatment plants
- c. identities of third parties manufacturing antibacterial APIs and drug products and/or of external private waste-treatment plants
- d. levels (concentrations) of antibacterial discharge and discharge monitoring/quantification technique(s)
- e. limits set for antibacterial discharge, along with methodological and evidential bases
- 5 The company publishes 5 of the 5 indicator elements
- 4 The company publishes 4 of the 5 indicator elements
- 3 The company publishes 3 of the 5 indicator elements
- 2 The company publishes 2 of the 5 indicator elements
- 1 The company publishes 1 of the 5 indicator elements
- 0 The Benchmark found none of the indicator elements published in the company's web-site*, annual report, or CSR/EHS reports
 - * Discharge limits published in the AMR Industry Alliance website were also considered for this indicator in the 2020 Benchmark, despite not qualifying as disclosure via an official individual company source.

B.3 MANUFACTURING HIGH-QUALITY ANTIBACTERIALS

The company makes commitments, has systems in place and promotes initiatives to ensure, maintain and/or improve the production of high-quality antibacterial APIs and drug products at its own and third-party manufacturing sites, in a manner consistent with the international standards developed and accepted by recognised national and international authorities.

To accomplish this, the company reports having a quality system that meets the following five elements:

- 1. it is consistent with international standards such as FDA, EU and/or WHO Good Manufacturing Practice (GMP) at all own sites manufacturing antibacterial APIs and/or drug products
- 2. it includes quality monitoring procedures, e.g. periodic auditing
- 3. it includes a system for implementation and tracking of corrective actions
- 4. it covers all of the company's third-party suppliers of antibacterial APIs and/or drug products
- 5. the authorities above, as applicable, have not publicly reported GMP non-conformities at companies' own sites or sites of wholly-owned direct subsidiaries, during the period of analysis

For the last element, the Benchmark considered non-conformities* to be either (a) inspections with a result of 'Official Action Indicated' (OAI) as made publicly available in the FDA's Inspection Classification Database under the 'Drug Quality Assurance' project area, or (b) non-compliance reports found in the EMA EudraGMP database, both referring to inspections with end date within the period of analysis, 9 September 2017 to 21 June 2019, inclusive. Databases were last consulted on 16 October 2019.

- 5 The company reports having a quality system that meets 5 of the 5 indicator elements
- 4 The company reports having a quality system that meets 4 of the 5 indicator elements
- 3 The company reports having a quality system that meets 3 of the 5 indicator elements
- 2 The company reports having a quality system that meets 2 of the 5 indicator elements
- 1 The company reports having a quality system that meets 1 of the 5 indicator elements
- 0 The company demonstrates no information on a quality system that meets any of the 5 indicator elements
 - * It was sometimes not possible to determine whether the sites affected by non-conformities produced antibacterials. Such non-conformities were nevertheless taken into account in the Benchmark assessment, since they suggest potential risks regarding how the companies' reported quality system (usually covering all sites) is being implemented at sites producing antibacterials.

C APPROPRIATE ACCESS

C.1.1 REGISTRATION OF ON-PATENT PRODUCTS

Companies are assessed according to the average number of access countries in which on-patent antibacterial and antifungal medicines and vaccines have been filed for registration.

- 5 The company files their on-patent products for registration in >40 access countries on average.
- 4 The company files their on-patent products for registration in 11-40 access countries on average.
- 3 The company files their on-patent products for registration in 6-10 access countries on average.
- 2 The company files their on-patent products for registration in 1-5 access countries on average.
- 1 The company has on-patent products that have been filed in at least one access country, but files them in less than one access country on average or there is little information available.
- 0 The company has on-patent products, but there is no evidence of filing in access countries.

C.1.2 REGISTRATION OF OFF-PATENT PRODUCTS

Companies are assessed according to the proportion of off-patent antibacterial and antifungal and anti-tuberculosis medicines filed for registration in access countries, as well as the number of countries filed for registration per product.

- 5 The off-patent products are registered in >40 access countries on average each.
- 4 The off-patent products are registered in 11-40 access countries on average each.
OR
Each product is registered in at least 1 access country and there is an average of 6-10 countries per product.
- 3 The off-patent products are registered in 6-10 countries on average.
OR
Each product is registered in at least 1 access country and there is an average of 1-5 countries per product.
- 2 The off-patent products are filed for registration in 1-5 countries on average each, but less than 100% of the products have been registered in at least one access country.
- 0 Companies have not disclosed in what countries their products have been registered.

C.2.1 PRICING OF ON-PATENT PRODUCTS

Assessments of companies are based on the pricing strategies they report per product (none, basic and good), the geographic scope where pricing strategies are applied per product (0 access countries, 1-10 access countries and >10 access countries on average) and whether or not they have a commitment with specific targets to make their products accessible for more people in the future.

- 5 The company reports good pricing strategies (including taking socioeconomic factors into account) on average for their products, these pricing strategies are applied in >10 countries on average and companies report a commitment with specific targets to make their products accessible for more people.
- 4 The company reports good pricing strategies that are applied to >10 access countries on average, but no commitment with specific targets to make products accessible for more people.
OR
The company reports basic pricing strategies that are applied to >10 access countries on average and a commitment with specific targets to make products accessible for more people.
OR
The company reports good pricing strategies that are applied to 1-10 access countries on average and a commitment with specific targets to make products accessible for more people.
- 3-1 Aggregate of assessments for pricing strategies, geographic scope of pricing strategies and commitment with specific targets to make products accessible for more people.
- 0 The company reports no pricing strategies, no geographic scope of pricing strategies and no commitment with specific targets to make products accessible for more people.

C.2.2 PRICING OF OFF-PATENT PRODUCTS (NOT SCORED)

The pricing strategies that companies report for off-patent products are described, but not assessed.

C.3 ENSURING CONTINUOUS SUPPLY

Companies are assessed according to eight criteria representing areas they can engage in to ensure the continuous supply of their products: forecasting and data sharing, procurement and shortage mitigation, capacity building (including addressing gaps in the supply chain) and geographic scope of capacity building, mitigating falsified medicines and supplying forgotten antibiotics. Companies are assessed according to the number of criteria they meet and the number of strategies they report within the 8 criteria.

- 5 The company reports strategies to meet all 8 criteria and reports multiple strategies within all 8 criteria
- 4 The company reports strategies to meet 6 or 7 criteria
OR
The company reports strategies to meet 8 criteria, but does not report multiple strategies within all 8 criteria.
- 3 The company reports strategies to meet 4 or 5 criteria
- 2 The company reports strategies to meet 2 or 3 criteria
- 0 The company reports strategies to meet 0 or 1 criteria

C STEWARDSHIP**C.4 EDUCATIONAL STEWARDSHIP ACTIVITIES**

The company has a clear strategy to mitigate any conflicts of interest (COI) in its support of antibacterial and antifungal stewardship educational activities directed at healthcare professionals.

- 5 The company engages in AMR-related educational programmes aimed at healthcare professionals (HCPs) with comprehensive conflict of interest (COI) mitigation for all of its submitted programmes (up to five programmes total). Comprehensive COI mitigation can be done either by:
 - (1) receiving accreditation from an independent body that evaluates potential COI; or
 - (2) providing an unrestricted grant to an independent third party to develop a programme; or
 - (3) implementing all three of the Benchmark's defined COI mitigation strategies. These are: (a) developing content independently from the marketing department, (b) pledging not to provide financial or material incentives to participants, and (c) not using branded materials.
 - 4 The company engages in AMR-related educational programmes aimed at healthcare professionals (HCPs) with comprehensive COI mitigation for the majority of its submitted programmes (up to five programmes total). Comprehensive COI mitigation can be done either by:
 - (1) receiving accreditation from an independent body that evaluates potential COI; or
 - (2) providing an unrestricted grant to an independent third party to develop a programme; or
 - (3) implementing all three of the Benchmark's defined COI mitigation strategies. These are: (a) developing content independently from the marketing department, (b) pledging not to provide financial or material incentives to participants, and (c) not using branded materials.
 - 3
 - The company engages in AMR-related educational programmes aimed at healthcare professionals (HCPs) with comprehensive COI mitigation for the minority of its submitted programmes (up to five programmes total). Comprehensive COI mitigation can be done either by:
 - (1) receiving accreditation from an independent body that evaluates potential COI; or
 - (2) providing an unrestricted grant to an independent third party to develop a programme; or
 - (3) implementing all three of the Benchmark's defined COI mitigation strategies. These are: (a) developing content independently from the marketing department, (b) pledging not to provide financial or material incentives to participants, and (c) not using branded materials.
 - The company engages in AMR-related educational programmes aimed at healthcare professionals (HCPs) with some COI mitigation for its submitted programmes (up to five programmes total). Some COI mitigation refers to including any of the three of the Benchmark's defined COI mitigation strategies. These are: (a) developing content independently from the marketing department, (b) pledging not to provide financial or material incentives to participants, and (c) not using branded materials.
 - o The company engages in AMR-related educational programmes aimed at healthcare professionals (HCPs) without any conflict of interest (COI) mitigation.
- N/A The company does not engage in AMR-related educational programmes aimed at healthcare professionals (HCPs).

Bullet points refer to OR situations.

C.5 RESPONSIBLE PROMOTIONAL PRACTICES

In its promotional activities for healthcare professionals, the company adopts marketing practices that advance stewardship of antibacterials and antifungals. It implements mechanisms to incentivise in-house and/or third-party sales representatives to engage in responsible marketing practices, and thus avoid overselling of antibacterials and antifungals.

- 5
 - The company does not deploy sales agents to promote any of its antibacterial and/or antifungal medicines.
 - The company only participates in tenders for the sales of all of its antibacterial and/or antifungal medicines.
 - The company fully decouples incentives for sales agents from sales volumes for all of its antibacterial and/or antifungal medicines AND provides evidence of taking into account AMR trends and guidelines in its marketing materials. Full decoupling means there is no variable pay in sales agents' total pay.

- 4 The company provides evidence of taking into account AMR trends and guidelines in its marketing materials AND fulfils at least one of the following points:
 - The company does not deploy sales agents to promote most of its antibacterial and/or antifungal medicines.
 - The company only participates in tenders for the sales of most of its antibacterial and/or antifungal medicines.
 - The company fully decouples incentives for sales agents from sales volumes for most of its antibacterial and/or antifungal medicines. Full decoupling means there is no variable pay in sales agents' total pay.
 - The company partly decouples incentives for sales agents from sales volumes for all of its antibacterial and/or antifungal medicines. Partial decoupling means (part of) the variable pay in sales agents' total pay is based on sales volumes.
 - 3
 - The company provides evidence of taking into account AMR trends and guidelines in its marketing materials.
 - The company does not deploy sales agents to promote most of its antibacterial and/or antifungal medicines.
 - The company only participates in tenders for the sales of most of its antibacterial and/or antifungal medicines.
 - The company fully decouples incentives for sales agents from sales volumes for most of its antibacterial and/or antifungal medicines. Full decoupling means there is no variable pay in sales agents' total pay.
 - The company partly decouples incentives for sales agents from sales volumes for all of its antibacterial and/or antifungal medicines. Partial decoupling means (part of) the variable pay in sales agents' total pay is based on sales volumes.
 - o The company does not report engaging in practices that aim to address the appropriate use of its antibacterial and/or antifungal medicines, either regarding its marketing materials or its sales practices.
- Bullet points refer to OR situations.

C.6 STEWARDSHIP-ORIENTED PACKAGING ADAPTATIONS

The company adapts its brochures and/or its packaging to facilitate the appropriate use of antibacterial and antifungal products by patients. The company considers needs, such as literacy or language, and adaptations that improve paediatric use and/or adherence to treatment.

- 5 The company adapts its brochures and/or packaging to take account of all needs including: literacy levels, paediatric use*, adherence to treatment and environmental conditions.
- 4 The company adapts its brochures and/or packaging to take account of at least one need, which can include: literacy levels, paediatric use*, adherence to treatment and/or environmental conditions.
- 3 The company adapts its brochure and/or packaging to take account of one of the following needs: literacy levels, paediatric use*, adherence to treatment or environmental conditions.
- 2 The company adapts its brochures and/or packaging to take account of only language needs.
- o The company does not adapt its brochures and/or packaging to facilitate the appropriate use of its antibacterial and/or antifungal medicines by patients beyond regulatory requirements.

* Adaptations for paediatric use are only assessed if the company has any products in its portfolio for paediatric use.

C.7 ANTIMICROBIAL SURVEILLANCE

The company has, supports and/or contributes to antibacterial and antifungal surveillance programmes, and/or shares antibacterial and antifungal medicine and vaccine consumption data with national governments and other public health authorities.

- 5 The company has one or multiple long-term* surveillance programmes, of which at least one shares its raw data through an open-access data platform.
- 3 The company has one or multiple long-term* surveillance programmes, of which at least one shares its results through an open-access data platform or peer-reviewed open-access journal articles.
- 2 The company has one or multiple surveillance programmes, however it does not share its results through open-access data platforms or peer-reviewed open-access journal articles.
- o The company does not report any involvement in AMR surveillance programmes.

N/A GMMs are not eligible for this indicator as they have a limited role in AMR surveillance activities.

* Long-term: surveillance programmes that are periodically repeated.

APPENDIX IV

Identifying best practices

The diffusion of best practices is one of the Benchmark's mechanisms for supporting the pharmaceutical industry in curbing AMR. Recognising those companies piloting or scaling up unique industry policies or initiatives is an important way of acknowledging those companies prepared to stand out from peers.

BEST PRACTICES

Best practices are ones that can be accepted as being the most effective way of achieving a desired end, relative to what the industry is currently doing in that area and what stakeholder expectations are. It can also be described as a benchmark. Best practices are not new practices – they have already been conceived of, applied and proven to meet at least some of the following criteria:

- Sustainability;
- Replicability;
- Alignment with external standards/stakeholder expectations; and
- Proven effectiveness.

In different areas of analysis (for example, in Research & Development vs. in Appropriate Access) how a best practice is identified may be different. A best practice need not be unique amongst companies. A best practice might be an example of a 'gold standard' of practice; a best-in-class policy; or a strategy, programme, product initiative or group of behaviours closely aligned with stakeholder expectations. Best practices should be considered as the exemplar of positive practices in the corresponding research area in comparison to those of the other companies that submitted data within the current period of analysis. These best practices are identified based on evidence of progress submitted in the data collection period and verified with public information and through consultation with experts, where appropriate.

PROCESS

To determine which of the company's practices would be highlighted as best practice, the Foundation's research team evaluated all aspects of company practices, compiling those that met the criteria used for the purpose of scoring with additional standards for each Research Area, where necessary. Practices that met these outlined criteria were reviewed and finalised by the Foundation's senior management with additional input from experts in the corresponding field, when required.

APPENDIX V

Priority pathogens included for analysis in R&D

In the Research & Development Research Area, the Benchmark assesses the size and public health value of a company's pipeline of investigational antibacterial and antifungal medicines and vaccines. This assessment is limited to medicines and vaccines targeting priority pathogens, which include families of bacteria and fungi that pose the greatest threat to human health because of their widespread resistance against the existing standard of care. The Centers for Disease Control and Prevention (CDC) and World Health Organization have published priority pathogens lists and both are covered in the R&D Research Area.

Specifically for indicator A.2.4, newly introduced in 2020, the Benchmark assesses companies' projects targeting the most critical priorities in these lists, i.e. targeting the pathogens classified in the CDC and WHO lists as 'Urgent' or 'Critical', respectively. Since November 2019, *C. auris* was listed as an 'Urgent' pathogen by the CDC.

| Pathogen | WHO Priority List ¹ | CDC Biggest Threats ² |
|--|--------------------------------|----------------------------------|
| BACTERIA | | |
| <i>Acinetobacter</i> spp. | Critical | Serious |
| <i>Campylobacter</i> spp. | High | Serious |
| <i>Clostridioides difficile</i> | | Urgent |
| <i>Enterobacteriaceae</i> | Critical | Urgent / Serious |
| <i>Enterococcus</i> spp. (<i>E. faecalis</i> & <i>E. faecium</i>) | High | Serious |
| <i>Haemophilus influenzae</i> type b (<i>Hib</i>) | Medium | |
| <i>Helicobacter pylori</i> | High | |
| <i>Mycobacterium tuberculosis</i> | R&D priority | Serious |
| <i>Neisseria gonorrhoeae</i> | High | Urgent |
| <i>Pseudomonas aeruginosa</i> | Critical | Serious |
| <i>Salmonella</i> spp. | High | Serious |
| <i>Shigella</i> spp. | Medium | Serious |
| <i>Staphylococcus aureus</i> | High | Serious / Concerning |
| <i>Streptococcus</i> (group A) | | Concerning |
| <i>Streptococcus</i> (group B) | | Concerning |
| <i>Streptococcus pneumoniae</i> | Medium | Serious |
| FUNGI | | |
| <i>Candida</i> spp. | | Serious |

REFERENCES

* WHO. (2017). Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics.

**U.S. Centers for Disease Control and Prevention (CDC). (April, 2013). Antibiotic resistance threats in the United States, 2013.

APPENDIX VI

Access countries

List of countries covered by access metrics for the 2020 Antimicrobial Resistance Benchmark – 102 countries

EAST ASIA & PACIFIC

| | |
|---------------------------|-------|
| Cambodia | LMIC |
| China | HIDBC |
| Indonesia | LMIC |
| Kiribati | LMIC |
| Korea, Dem. People's Rep. | LIC |
| Lao PDR | LMIC |
| Micronesia, Fed. Sts. | LMIC |
| Mongolia | LMIC |
| Myanmar | LMIC |
| Papua New Guinea | LMIC |
| Philippines | LMIC |
| Solomon Islands | LMIC |
| Thailand | HIDBC |
| Timor-Leste | LMIC |
| Tuvalu | LDC |
| Vanuatu | LMIC |
| Vietnam | LMIC |

EUROPE & CENTRAL ASIA

| | |
|-----------------|-------|
| Georgia | LMIC |
| Kosovo | LMIC |
| Kyrgyz Republic | LMIC |
| Moldova | LMIC |
| Tajikistan | LIC |
| Turkmenistan | HIHDC |
| Ukraine | LMIC |
| Uzbekistan | LMIC |

LATIN AMERICA & CARIBBEAN

| | |
|--------------------------|-------|
| Belize | HIHDC |
| Bolivia, Plurinat. State | LMIC |
| Brazil | HIHDC |
| Colombia | HIHDC |
| Dominican Republic | HIHDC |
| El Salvador | LMIC |
| Guatemala | MHDC |
| Guyana | MHDC |
| Haiti | LIC |

| | |
|-----------|-------|
| Honduras | LMIC |
| Mexico | HIDBC |
| Nicaragua | LMIC |
| Paraguay | HIHDC |
| Peru | HIDBC |
| Suriname | HIHDC |

MIDDLE EAST & NORTH AFRICA

| | |
|---------------------------------------|------|
| Djibouti | LMIC |
| Egypt, Arab Rep. | LMIC |
| Iraq | MHDC |
| Morocco | LMIC |
| Syrian Arab Republic | LIC |
| Tunisia | LMIC |
| Palestine, State / West Bank and Gaza | LMIC |
| Yemen, Rep. | LIC |

SOUTH ASIA

| | |
|-------------|-------|
| Afghanistan | LIC |
| Bangladesh | LMIC |
| Bhutan | LMIC |
| India | LMIC |
| Maldives | HIHDC |
| Nepal | LIC |
| Pakistan | LMIC |
| Sri Lanka | LMIC |

SUB-SAHARAN AFRICA

| | |
|--------------------------|-------|
| Angola | LMIC |
| Benin | LIC |
| Botswana | HIHDC |
| Burkina Faso | LIC |
| Burundi | LIC |
| Cabo Verde | LMIC |
| Cameroon | LMIC |
| Central African Republic | LIC |
| Chad | LIC |
| Comoros | LIC |

| | |
|-----------------------|-------|
| Congo, Dem. Rep. | LIC |
| Congo, Rep. | LMIC |
| Côte d'Ivoire | LMIC |
| Equatorial Guinea | MHDC |
| Eritrea | LIC |
| Ethiopia | LIC |
| Gabon | HIHDC |
| Gambia, The | LIC |
| Ghana | LMIC |
| Guinea | LIC |
| Guinea-Bissau | LIC |
| Kenya | LMIC |
| Lesotho | LMIC |
| Liberia | LIC |
| Madagascar | LIC |
| Malawi | LIC |
| Mali | LIC |
| Mauritania | LMIC |
| Mozambique | LIC |
| Namibia | MHDC |
| Niger | LIC |
| Nigeria | LMIC |
| Rwanda | LIC |
| São Tomé and Príncipe | LMIC |
| Senegal | LIC |
| Sierra Leone | LIC |
| Somalia | LIC |
| South Africa | MHDC |
| South Sudan | LIC |
| Sudan | LMIC |
| Swaziland | LMIC |
| Tanzania | LIC |
| Togo | LIC |
| Uganda | LIC |
| Zambia | LMIC |
| Zimbabwe | LIC |

● Newly in scope for the 2020 Benchmark

Table legend

| | |
|-------|--|
| LIC | Low-income country, World Bank income classifications (June 2018) |
| LMIC | Lower middle-income country, World Bank income classifications (June 2018) |
| LDC | Least Developed Country, UN ECOSOC LDC list (March 2018) |
| LHDC | Low Human Development Country, UNDP Human Development Indices and Indicators (September 2018) |
| MHDC | Medium Human Development Country, UNDP Human Development Indices and Indicators (September 2018) |
| HIHDC | High Inequality in Human Development Country, UNDP Human Development Indices and Indicators (September 2018) |
| HIDBC | High Infectious Disease Burden Country, IHME Global Burden of Disease Study 2017 Results |

APPENDIX VII

Guide to Report Cards

The Guide to Report Cards provides a description of each section of the Report Cards for the 2020 Antimicrobial Resistance Benchmark.

| Section | Description | Source |
|---|---|---|
| General company information (header) | Company name, Stock exchange(s), Stock exchange ticker(s), Location of headquarters, Number of employees (as FTE) | <ul style="list-style-type: none"> Annual report for the fiscal year ending 31 December 2018 or later (or, equivalently, forms 10-K or 20-F) Company website |
| Performance in the Benchmark (figure) | This figure shows the company's overall score. | <ul style="list-style-type: none"> Benchmark analysis |
| Performance by Research Area (RA) (figure) | This figure shows the company's scores for each of the RAs in which it was scored. | <ul style="list-style-type: none"> Benchmark analysis |
| How company was evaluated: (by indicator) | This figure shows the indicators that were applicable to the company. | <ul style="list-style-type: none"> Benchmark Methodology Report 2019 Benchmark analysis |
| Performance (text) | <p>This section summarises the company's overall performance in the Benchmark. It covers:</p> <ul style="list-style-type: none"> Drivers behind its scores Main areas where the company scores well or below par compared to peers | <ul style="list-style-type: none"> Benchmark analysis |
| Sales and Operations (text) | <p>The structure of this section varies per company type.</p> <p><i>For large research-based pharmaceutical companies and generic medicine manufacturers:</i></p> <p>Therapeutic areas: Therapeutic areas the company focuses on, as available in public sources, and standardised by the Benchmark across companies.</p> <p>Business segments: How the company is operationally organised, as presented in official company sources.</p> <p>Product categories: product types the company markets, as available in public sources, and standardised by the Benchmark across companies.</p> <p>Manufacturing and supply: Size of the company's manufacturing network for antibacterial active pharmaceutical ingredients (APIs) and drug products and reach of its antibacterial and antifungal product supply.</p> <p>M&A since 2018: Merger & acquisition activity since 2018 specifically relevant for antibacterial or antifungal products.</p> <p><i>For small- and medium-sized enterprises:</i></p> <p>Therapeutic areas: Therapeutic areas the company focuses on, as available in public sources, and standardised by the Benchmark across companies.</p> <p>Products on the market: Products the company currently markets.</p> <p>R&D grants received since 2016: Amount received and providers of R&D grants since 2016. Only the latest grant is described in detail.</p> <p>Financing and investment structure: Summary of financial information and main investments in the company.</p> <p>M&A since 2018: Merger & acquisition activity since 2018 specifically relevant for antibacterial or antifungal products.</p> | <ul style="list-style-type: none"> Annual report for the fiscal year ending 31 December 2018 or later (or, equivalently, forms 10-K or 20-F) Company website Press releases by company or pharmaceutical news websites Stock exchange communications Benchmark questionnaire |
| Revenues by product (figure) | This figure shows, where possible, a breakdown of the company's revenues in fiscal year 2018 into: antibacterial and antifungal medicines; antibacterial vaccines; other pharmaceuticals; other (non-pharmaceuticals). If such breakdown is not possible, categories are based on companies' business segments or may show only the total revenue. | <ul style="list-style-type: none"> Benchmark questionnaire Annual report for the fiscal year ending 31 December 2018 or later (or, equivalently, forms 10-K or 20-F) |

| | | |
|---|--|--|
| Revenues by region (figure) | <p>This figure shows a breakdown of the company's revenues by geographic region in fiscal year 2018.</p> <p>The categories are based on official company reports but may be aggregated. If no breakdown by region is possible, the figure shows only the total revenue. If this is the case for both the regional and product breakdowns, there is a single figure showing the total revenue.</p> | <ul style="list-style-type: none"> • Annual report for the fiscal year ending 31 December 2018 or later (or, equivalently, forms 10-K or 20-F) |
| Pipeline (text) | <p>This section characterises a company's R&D pipeline for priority pathogens in scope with respect to the following points:</p> <p>Pipeline size: Provides the number of projects in scope, including a breakdown by type.</p> <p>Development stages: Provides a count of the company's projects in clinical stage (listing examples), followed by a count of projects in discovery or pre-clinical stage.</p> <p>Novelty: Lists projects that are considered novel by the Benchmark, as per the WHO innovativeness criteria (see Sources column).</p> <p>Regulatory approvals: Lists regulatory approvals for projects targeting priority pathogens, as at 16 October 2019.</p> <p>Access plans: Provides the number of late-stage projects (i.e. Phase II onwards) that have project-specific or portfolio-wide access plans. Phase IV or technical lifecycle projects are excluded.</p> <p>Stewardship plans: Provides the number of late-stage projects (i.e. Phase II onwards) that have project-specific or portfolio-wide stewardship plans. Phase IV or technical lifecycle projects are excluded.</p> | <ul style="list-style-type: none"> • Benchmark analysis • The WHO innovativeness criteria are listed in: World Health Organization. (2017). Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis. • World Health Organization. (2018). Update of antibacterial agents in clinical development. • World Health Organization. (2019). Antibacterial agents in clinical development - Sep 2019 update • The Pew Charitable Trusts. Antibiotics currently in global clinical development - Sep 2019 update • The Pew Charitable Trusts. Nontraditional products for bacterial infections in clinical development - Sep 2019 update |
| Pipeline for priority pathogens (figure) | <p>This figure shows, where possible, a breakdown of the company's pipeline for priority pathogens into: antibacterial vaccines; antibacterial medicines; antifungal medicines; and projects that are combinations of antibacterial and antifungal medicines.</p> | <ul style="list-style-type: none"> • Benchmark questionnaire • Company website and clinical trials registries |
| Portfolio (text) | <p>This section characterises a company's antibacterial and antifungal product portfolio, starting with a comparative statement on the number of products in scope, including a breakdown by type.</p> <p>The total number of products considers different formulations separately and the number of unique INNs is provided in brackets. The following information is also listed, as applicable:</p> <p>Essential medicines: number and percentage of the company's products that are on the 2019 WHO EML</p> <p>AWaRe medicines: number of medicines in each WHO AWaRe group for antibacterials (Access, Watch, Reserve)</p> <p>Anti-TB medicines: number of anti-tuberculosis medicines, including breakdown by AWaRe group</p> <p>Product formulation is taken into account in all categories above. The percentage of Essential medicines for a given company was calculated as the number of the company's INN and formulation pairs for which at least one marketed strength appears on the 2019 WHO EML divided by the total number of INN and formulation pairs on the company's portfolio. The classification of products as "Anti-TB medicines" follows the 2019 WHO EML. Some of the medicines in this category may not have received market approval for this indication.</p> <p>For products with a square box, alternative products listed on ATC/DDD Index are also treated as on EML.</p> | <ul style="list-style-type: none"> • Benchmark questionnaire • Registered products identified from the EMA, FDA, and the company's website • IQVIA MIDAS® 2017 anti-infectives data • WHO EML, 21st List, 2019 (several sections, as listed in Benchmark Methodology Report 2019, Appendix II) |
| Products on the market (figure) | <p>This figure shows, where possible, a breakdown of the company's marketed products in scope into: antibacterial vaccines; antibacterial medicines; antifungal medicines; and products that are combinations of antibacterial and antifungal medicines.</p> <p>The number of products is based on data from public sources, IQVIA MIDAS®, and data submitted by the company. It may not account for the company's entire product portfolio.</p> | <ul style="list-style-type: none"> • Benchmark questionnaire • Registered products identified from the EMA, FDA, and the company's website • IQVIA MIDAS® 2017 anti-infectives data |

| | | |
|--|--|---|
| Opportunities (text) | This section outlines opportunities for the company to do more to address AMR. The opportunities listed take into account company-specific characteristics as far as possible. | <ul style="list-style-type: none"> • Benchmark analysis |
| Changes since 2018 | This section provides an update on where the company's actions to curb AMR have changed most notably since the 2018 Benchmark. It includes a selection of new or expanded commitments, strategies, activities and programmes. These may have taken place after the period of analysis and are not necessarily scored by the Benchmark. | <ul style="list-style-type: none"> • Benchmark analysis • Benchmark questionnaire • Public sources such as company website or press releases |
| Performance by RA: A. Research & Development (text) | <p>This section summarises company performance for the RA of Research & Development, by indicator. The paragraphs describe the company's performance and highlight (where available) relevant examples of its activities.</p> <p>In indicator A.2.2, novelty is analysed for clinical-stage projects only and based on the innovativeness criteria defined by the WHO (see Sources column).</p> <p>In indicator A.2.4, the assessment is based on the number of unique candidates (i.e. unique INNs) within the projects that target critical or urgent priorities.</p> <p>In indicator A.4, detailed portfolio-wide or project-specific access and stewardship plans are analysed for late-stage projects only. This includes projects in clinical Phase II or III as well as projects awaiting approval or approved during the period of analysis (2017/09/09 to 2019/06/21) but not Phase IV or technical lifecycle projects. For medicine projects, the Benchmark looks at both access and stewardship plans, whereas for vaccine projects, where overuse or inappropriate use is not a concern with respect to AMR, only access plans are considered.</p> | <ul style="list-style-type: none"> • Benchmark analysis • Benchmark Methodology Report 2019 • The WHO innovativeness criteria are listed in: World Health Organization. (2017). Antibacterial agents in clinical development: an analysis of the antibacterial clinical development pipeline, including tuberculosis. • World Health Organization. (2018). Update of antibacterial agents in clinical development • World Health Organization. (2019). Antibacterial agents in clinical development • The Pew Charitable Trusts. Antibiotics currently in global clinical development - Sep 2019 update • The Pew Charitable Trusts. Nontraditional products for bacterial infections in clinical development- Sep 2019 update |
| Pipeline targeting priority pathogens (figure) | <p>This figure shows the company's pipeline of antibacterial and antifungal medicines and vaccines targeting priority pathogens. Phase IV projects, technical lifecycle or other projects are not shown.</p> <p>Where applicable, regulatory approvals (including label extensions) are noted, including the regulatory body/location and date of approval. Data omissions due to confidentiality agreements are noted.</p> <p>Although the figure shows the pipeline as at 16 October 2019, the analysis in the R&D Performance by RA text considers the status of projects at the end of the period of analysis, on 21 June 2019.</p> | <ul style="list-style-type: none"> • Projects submitted by the company for scoring and analysis in the Benchmark, including verification/cross-reference with publicly available pipeline information. Approval data is verified using public sources, e.g. clinical trial registries or press releases by companies |
| Performance by RA: B. Responsible Manufacturing (text) | <p>This section summarises company performance for the RA of Responsible Manufacturing, by indicator. The paragraphs describe the company's performance and highlight (where available) relevant examples of its activities.</p> <p>In indicator B.2, discharge limits published in the AMR Industry Alliance website were also considered in the assessment, despite not qualifying as disclosure via an official individual company source.</p> <p>In indicator B.3, two public databases were searched: the FDA inspection classification database and the EU EudraGMP database (see Sources column). For more information, see Appendix I. Results are as at 16 October 2019.</p> | <ul style="list-style-type: none"> • Benchmark analysis • Official public company sources such as annual or CSR reports, policy documents or company websites • FDA inspection classification database (https://www.fda.gov/inspection-classification-database) • EU EudraGMP database (http://eudragmp.ema.europa.eu/inspections/displayWelcome.do) |

| | | |
|--|---|--|
| <p>Performance by RA:</p> <p>C. Access (text)</p> | <p>This section summarises company performance for each Access indicator in the RA of Appropriate Access and Stewardship. The paragraphs describe the company's performance and highlight (where available) relevant examples of its activities.</p> <p>In indicators C.1.1 and C.2.1, “on-patent products” refers to all on-patent antibacterial and antifungal medicines and vaccines that the company markets.</p> <p>In indicators C.1.2 and C.2.2, “off-patent products” refers to a company-specific set of off-patent antibacterial and antifungal medicines based on each company's highest volume sales data globally and in 21 low income markets, as provided by IQVIA Midas® 2017 database for specific product formulations. These products were firstly derived from the 2017 WHO EML and divided into six categories: four based on the 2017 WHO AWaRe classification of Access, Watch, Access/Watch and Reserve and two for antifungals and anti-tuberculosis medicines.</p> <p>Indicator C.3 considers all antibacterial and antifungal medicines and vaccines in scope for this Benchmark. This indicator includes a specific analysis for forgotten antibiotics (Pulcini et al, 2012, see Sources column).</p> | <ul style="list-style-type: none"> • Benchmark analysis • IQVIA MIDAS® 2017 anti-infectives data • WHO EML, 20th List, 2017 • Appendix II of the Benchmark Methodology Report 2019 • Pulcini C, Bush K, Craig WA, et al. Forgotten Antibiotics: An Inventory in Europe, the United States, Canada, and Australia. Clin Infect Dis. 2012;54(2):268-274. doi:10.1093/cid/cir838 |
| <p>Performance by RA:</p> <p>C. Stewardship (text)</p> | <p>This section summarises company performance for each Stewardship indicator in the RA of Appropriate Access and Stewardship. The paragraphs describe the company's performance and highlight (where available) relevant examples of its activities. Only antibacterial and antifungal medicines are in scope for this Research Area.</p> | <ul style="list-style-type: none"> • Benchmark analysis • Public sources such as accreditation body websites or independent 3rd party websites • The AMR Register (https://amr.theodi.org/) • AMR Industry Alliance website (https://www.amrindustryalliance.org/) |

APPENDIX VIII

Figures

page

| | |
|-------|--|
| 7, 12 | Figure 1: Antimicrobial Resistance Benchmark – 2020 |
| 14 | Figure 2: Benchmark Performance for large research-based pharmaceutical companies |
| 16 | Figure 3: Benchmark Performance for generic medicine manufacturers |
| 18 | Figure 4: Benchmark Performance for small and medium-sized enterprises |
| 21 | Figure 5: Eight late-stage antibiotics have both access and stewardship plans |
| 21 | Figure 6: Breakdown of the clinical antibiotic pipeline for priority bacteria and fungi |
| 23 | Figure 7: Many missed opportunities to improve access to antibiotics where need is highest |
| 25 | Figure 8: Positive shift in pharmaceutical companies' promotional practices to improve stewardship |
| 25 | Table 1: How far does responsible promotion go when it comes to deploying sales staff and linking bonuses to sales volume? |
| 27 | Figure 9: Publishing surveillance results is common practice, with sharing raw data a new gold standard |
| 28 | Figure 10: 138 projects targeting the biggest bacterial and fungal threats |
| 29 | Figure 11: 40% of products are flagged by WHO as priorities for better access and stewardship |
| 34 | Figure 12: Research & Development: how the companies perform |
| 36 | Table 2: How the Benchmark pipeline analysis complements other reports |
| 37 | Table 3: Priority bacterial and fungal pathogens for R&D and threats for human health |
| 39 | Figure 13: 138 R&D projects target priority bacterial and fungal pathogens |
| 39 | Figure 14: 54% of the pipeline is in clinical development or beyond |
| 39 | Figure 15: Breakdown of the clinical antibiotic pipeline for priority bacteria and fungi |
| 41 | Figure 16: GSK has largest pipeline of R&D projects targeting priority bacteria and fungi |
| 41 | Figure 17: Mid-level threats are main focus for large research-based pharma companies |
| 41 | Figure 18: Out of 13 small and medium-size enterprises (SMEs), Melinta has largest pipeline |
| 41 | Figure 19: Highest threat pathogens are focus for many SMEs |
| 43 | Figure 20: SMEs have more novel medicine candidates in their pipelines |
| 43 | Figure 21: Nine clinical-stage medicine candidates meet WHO criteria for innovativeness - classed as 'novel' by Benchmark |
| 43 | Table 4: Which medicines in clinical development are considered novel? |
| 45 | Table 5: Approvals between 9 September 2017 – 16 October 2019 |
| 45 | Figure 22: How has the pipeline changed since 2018? |
| 47 | Figure 23: Eight late-stage antibiotics have both access and stewardship plans |
| 47 | Table 6: Recommendations for developers of new antibacterials on how to plan for access and stewardship |
| 52 | Figure 24: Responsible Manufacturing: how the companies perform |
| 55 | Table 7: What is the scale of pharmaceutical companies' antibacterial manufacturing operations? |
| 55 | Figure 25: Twelve companies set limits but only six currently extend them to suppliers |
| 56 | Table 8: Depth and breadth of environmental risk-management strategies vary widely between companies |
| 57 | Figure 26: Companies are assessing the risk of releasing antibacterials into the environment |
| 59 | Figure 27: Seven companies extend environmental risk-management strategies to antifungal production |
| 60 | Figure 28: Which elements of their environmental risk-management strategies are published by 17 companies? |
| 61 | Figure 29: Broad adherence to GMP |
| 66 | Figure 30: Appropriate Access & Stewardship: how the companies perform |
| 69 | Figure 31: 102 low- and middle-income countries need better access to medicine. |
| 69 | Figure 32: Companies have 39 on-patent* products on the market |
| 69 | Figure 33: Companies have from 1 to 12 on-patent antibacterials and antifungals each |
| 70 | Figure 34: Only 60% of on-patent products are being registered in any of the countries where access is most needed |
| 70 | Figure 35: Registrations of on-patent products focus on large middle-income countries |
| 71 | Figure 36: Pneumococcal vaccines top registration lists |
| 71 | Figure 37: Medicine for complicated urinary tract infection is filed most widely |
| 72 | Figure 38: How widely are off-patent/generic medicines being registered where needed? |
| 73 | Figure 39: Which off-patent/generic antibacterial and antifungals are filed in more than five access countries? |
| 74 | Figure 40: Most companies apply a diverse range of pricing strategies |
| 74 | Figure 41: Which pricing strategies are reported most frequently? |
| 75 | Table 9: 14 companies produce TB medicines |
| 76 | Table 10: Which pricing strategies do companies report using for antimicrobials? |
| 77 | Figure 42: Most companies report some activity in areas that aim to ensure continuous supply |
| 78 | Table 11: How can companies help ensure the continuous supply of their antibacterial and antifungal products? |
| 79 | Figure 43: Only 30% of forgotten antibiotics are supplied to access countries |
| 79 | Figure 44: Cefepime is the most widely produced and supplied forgotten antibiotic |
| 81 | Table 12: Which surveillance programmes are companies active in? |
| 81 | Figure 45: The majority of companies are involved in AMR surveillance |
| 81 | Figure 46: AMR surveillance programmes track majority of priority pathogens* |
| 82 | Figure 47: India - a key country for tracking resistance |
| 83 | Figure 48: The majority of AMR surveillance programmes have been running for more than ten years |
| 83 | Figure 49: Half of AMR surveillance programmes are multinational |
| 83 | Figure 50: Only one company shares the raw data from AMR surveillance programmes |
| 83 | Figure 51: Pfizer represents best practice by sharing raw surveillance data |
| 84 | Figure 52: How many companies are engaging in responsible promotion? |
| 85 | Table 13: How far does responsible promotion go when it comes to deploying sales staff and linking bonuses to sales volumes? |
| 87 | Figure 53: The majority of companies are involved in AMR-related educational programmes |
| 87 | Figure 54: Comprehensive COI mitigation in place for majority of AMR-related educational programmes |
| 87 | Figure 55: What do COI mitigation strategies look like? |
| 88 | Figure 56: Companies take language needs into account most frequently in their brochures and packaging |

APPENDIX IX

Definitions

Access plan*[Working definition, used for analysis]*

An access plan is a plan set up to ensure that public health needs are taken into consideration during R&D. These plans may be developed in-house or through collaborations and include commitments, strategies, concrete provisions and other agreed-upon measures (typically developed in partnership) to enforce accountability. Access plans facilitate availability, accessibility and affordability for patients in countries within the scope of the Benchmark (e.g., registration commitments, equitable pricing strategies, sufficient supply commitments, non-exclusivity in specified territories, waiving of patent rights, royalty-free provisions and applying for WHO prequalification).

Active pharmaceutical ingredient (API)

The active pharmaceutical ingredient (API) is the active pharmaceutical component of a medicine that carries out its intended effects. Some medicines, such as combination therapies, have multiple active ingredients that target multiple disease pathways and/or symptoms. The inactive ingredients of a medicine are referred to as excipients.

Adaptive R&D*[Working definition, used for analysis]*

R&D adaptations to existing medicines and/or vaccines. This includes new formulations, new fixed-dose combinations of existing chemical or biological entities, a new target demographic, or the repurposing of an existing product for additional indications.

Affordability*[Working definition, used for analysis]*

The measure of a payer's ability to pay for a product (whether or not they are the end user). The Benchmark takes this into account when assessing pharmaceutical companies' pricing strategies.

AMR surveillance*[Working definition, used for analysis]*

The continuous and systematic collection, analysis and interpretation of antimicrobial infection and resistance-trend data needed for the planning, implementation, and evaluation of antimicrobial stewardship activities.

Antibacterial medicine*[Working definition, used for analysis]*

Antimicrobial medicine used to treat bacterial infections by directly targeting the bacteria that causes the infection or the disease process (as opposed to targeting the symptoms of the infection). See also Antibiotic medicine.

Antibacterial resistance

Antimicrobial resistance occurring specifically in bacteria. This resistance renders the medicines normally used to treat bacterial infections (e.g., urinary tract infections, pneumonia, bloodstream infections) ineffective. Sometimes also referred to as antibiotic resistance. See also antimicrobial resistance.

Antibiotic medicine*[Working definition, used for analysis]*

Equivalent to Antibacterial medicine. The term "antibiotic" is used inconsistently in the literature to denote either a drug that targets any type of microorganism in the body or, alternatively, a drug that targets bacteria specifically. Given the ambiguity, the Benchmark preferably avoids use of this term, referring to the more general category as "antimicrobial" and to the more specific one as "antibacterial".

Antifungal medicine*[Working definition, used for analysis]*

Antimicrobial medicine used to treat fungal infections by directly targeting the fungi that causes the infection (as opposed to targeting the symptoms of the infection or toxins produced by the pathogen).

Antimicrobial medicine*[Working definition, used for analysis]*

A medicine used to treat an infectious disease by directly targeting the bacteria, fungi, helminths, protozoa or viruses that cause the infection (as opposed to targeting the symptoms of the infection or toxins produced by the pathogen).

Antimicrobial resistance (AMR)

Antimicrobial resistance is the ability of microbes such as bacteria, viruses, fungi and parasites (protozoa or helminths) to grow in the presence of an antimicrobial substance (e.g., a medicine) that would normally kill them or limit their growth. Resistance is a consequence of evolution via natural or artificial selection.

Antimicrobial stewardship

A systematic and comprehensive process that aims to ensure that all aspects of prescribing, (e.g., drug, dose, duration), dispensing, and the use of antimicrobial medicines are consistent with the available evidence on how to minimise the emergence of antimicrobial resistance.

Responsible promotional practices*[Working definition, used for analysis]*

Promotional activities targeting the general public, patients and healthcare professionals in such a way that transparency, integrity, accuracy, clarity and completeness of information can be

ensured.

Appropriate use of antimicrobials

The cost-effective use of antimicrobials, which maximises clinical therapeutic effect while minimising both drug-related toxicity and the development of antimicrobial resistance [WHO Global Strategy for Containment of Antimicrobial Resistance, 2001].

Broad-spectrum antibacterial

Broad-spectrum antibacterial medicines are active against a wide range of bacterial types and may be used to treat a wide range of bacterial infections.

Capacity building

The company forms partnerships with local stakeholders to increase capacity (e.g. by training of staff or obtaining equipment and other necessary resources) in order to strengthen the supply chain.

Clinical-stage drug development*[Working definition, used for analysis]*

Clinical-stage drug development comprises phases I through III of clinical development. Products approved (or awaiting approval) between 9 September 2017 (end of the period of analysis for the previous edition of the Benchmark) and 21 June 2019 are also categorised as late-stage.

Conflict of interest (COI)*[Working definition, used for analysis]*

Within the context of pharmaceutical companies' engagement in public health-oriented initiatives, a conflict of interest potentially arises when the commercial interests of the company conflict with the primary interest of protecting and promoting public health.

Cross-resistance

Cross-resistance refers to the resistance developed to a usually effective antimicrobial medicine through exposure to a similarly acting substance. Cross-resistance can occur among human antimicrobials and is also observed between human antimicrobials and products used in animal health or agriculture (e.g., pesticides, herbicides or fungicides).

Disability-Adjusted Life Year (DALY)

The disability-adjusted life year (DALY) is a measure of disease burden that combines disease-associated mortality and morbidity. It is the sum of the number of years of life lost (YLLs) and years lived with disability (YLDs). DALYs allow comparison of disease burden across different populations and health conditions across

time. One DALY equals one lost year of healthy life.

Drug product

The finished dosage form of a medicine obtained at the end of the manufacturing process, (e.g., the tablet, capsule, or solution containing the active pharmaceutical ingredient(s), generally, but not necessarily, in association with one or more other ingredients). Also referred to as a finished drug product, finished product or formulation.

Environmental risk management (ERM)

[Working definition, used for analysis]

In the context of antibacterial product manufacturing, environmental risk management (ERM) seeks to determine and manage environmental risks resulting from the production of antibacterials, such as the emergence of antibacterial resistance, to protect human health and the environment.

Equitable pricing strategy

[Working definition, used for analysis]

A targeted pricing strategy, which aims at improving access to medicines and vaccines for those in need by taking affordability for individuals and healthcare systems into account in a manner that is locally appropriate.

Falsified medicine

A medicine which is deliberately and fraudulently mislabelled with respect to identity and/or source. Falsified medicines may contain no active ingredient, the wrong active ingredient or the wrong amount of the correct active ingredient.

Generic medicine

A medicine that is created to be the same as a known marketed brand-name drug (the originator medicine) in dosage form, strength, route of administration, quality and performance characteristics, and intended use. See also Originator medicine.

Good Manufacturing Practices (GMP)

Good manufacturing practice (GMP) is a system employed to ensure that products are consistently produced and controlled according to appropriate quality standards. Within pharmaceutical production this serves to minimise risks such as unexpected contamination, incorrect labelling or incorrect dose of the active ingredient. GMP covers all aspects of pharmaceutical production (e.g., starting materials, premises, equipment, training and personal hygiene of staff) and includes processes that provide docu-

mented proof that correct procedures are consistently followed at each step of the manufacturing process. GMP guidelines are established and overseen by regulatory agencies in individual countries or regions, as well as the WHO.

Healthcare Professional (HCP)

Any specialised worker in any branch of healthcare that provides preventive, curative or rehabilitative services to the community.

Intellectual capital

[Working definition, used for analysis]

Intellectual capital is the intangible value of a company, covering its employees (human capital), its relationships (relational capital) and the infrastructure (e.g. hardware, software, databases, processes, patents) that supports the work of its employees (structural capital). A company's intellectual capital gives it a competitive advantage. In the context of the Benchmark, the intellectual capital of a pharmaceutical company may comprise of, for example, molecule libraries, patented compounds, processes and technologies or unpublished data on pharmacological characteristics of compounds.

International non-proprietary name (INN)

The International non-proprietary name (INN) is a common, generic name selected by designated experts for the unambiguous identification of a pharmaceutical substance or active pharmaceutical ingredient. The selection process is coordinated by World Health Organization (WHO) via its INN Programme. Each INN is a unique name that is globally recognised and is public property.

Late-stage drug development

[Working definition, used for analysis]

In the context of the pharmaceutical R&D pipeline, medicine and vaccine candidates in Clinical phase II or Clinical phase III are considered to be in late-stage clinical development. Products approved (or awaiting approval) between 9 September 2017 (end of the period of analysis for the previous edition of the Benchmark) and 21 June 2019 are also categorised as late-stage by the Benchmark.

Narrow-spectrum antibacterial

Narrow-spectrum antibacterials are antibacterial medicines that are active against a selected group of bacterial types. Examples include colistin, an antibacterial that selectively targets gram-negative bacteria, and vancomycin, an antibacterial that selectively targets gram-positive bacteria.

Novel drug candidate

[Working definition, used for analysis]

A novel candidate meets at least one of the four criteria defined in WHO's report "Antibacterial agents in clinical development" (2017): (1) new chemical class; (2) new target; (3) new mode of action; (4) absence of cross-resistance. This assessment is applied only to candidates in clinical stage and validated by WHO and/or external experts.

Off-patent medicine

[Working definition, used for analysis]

A medicine whose granted patent protection has expired. Patent protection typically lasts for 20 years and is specific to each country.

On-patent/patented medicine

[Working definition, used for analysis]

A patented or on-patent medicine is one which has received exclusivity rights, allowing the patent holder to prevent or stop others from making, using, selling or importing the medicine within the country that granted the patent. The Benchmark determines patent status for its products in scope through a process that combines data from selected regulatory authority websites (e.g. FDA) and participating companies..

One Health

An approach used to design and implement public health programmes, policies, legislation and research in which multiple sectors communicate and work together to achieve better outcomes. The areas for which a One Health approach is particularly relevant include food safety, the control of zoonosis, and combating antimicrobial resistance. [WHO, 2017]

Originator medicine

The medicine that was first authorised worldwide for marketing, normally as a patented product, on the basis of its documented efficacy, safety and quality, according to requirements at the time of authorisation. The originator medicine always has a brand name; this name may, however, vary among countries.

Over-the-counter medicine

A medicine that can be purchased without prescription from a healthcare professional.

Period of analysis

[Working definition, used for analysis]

The 2020 AMR Benchmark report will assess company activities taking place during a period of analysis going from 9 September 2017 to 21 June 2019. For the R&D research area, pro-

jects need to be ongoing, approved or awaiting approval by the end of the period of analysis.

Preclinical-stage drug development

[Working definition, used for analysis]

Preclinical-stage drug development comprises the discovery and preclinical phases of drug development.

Predicted no-effect concentration (PNEC)

In the context of environmental risk assessment, the predicted no-effect concentration (PNEC) is the concentration of a substance in any environment below which adverse effects will most likely not occur. The PNEC can be based on acute (short-term) or chronic (long-term) toxicity data and usually takes account of the uncertainty in extrapolating from collected/available data to the entire ecosystem.

Priority pathogen

[Working definition, used for analysis]

Priority pathogens are pathogens for which new medicines and vaccines are highly needed. The Benchmark identified this set of priority pathogens based on the WHO priority pathogens list as of 25 February 2017 and the CDC's US Biggest Threats list as of April 2013.

Product Development Partnership (PDP)

[Working definition, used for analysis]

Product Development Partnerships (PDPs) take the form of centralised non-profit organisations that facilitate financial risk-sharing across the public and private sectors by pooling and sharing resources, both tangible and intangible, for the development of medicines, vaccines and other health tools.

Public-private partnership

[Working definition, used for analysis]

A public-private partnership (PPP) is a partnership between one or more public organisations and the private sector for providing a public asset or service, in which the private party bears significant risk and management responsibility, and remuneration is linked to performance. The Benchmark also considers a partnership between a non-profit organisation and the private sector to be a PPP.

Pull incentive

Pull incentives, in the form of extended exclusivity periods, higher reimbursement or market entry rewards, reward companies for bringing new drugs to the market through lowering the uncertainty for return on investment.

Push incentive

Push incentives, in the form of grants, partnerships or tax credits, are employed to lower the cost of and de-risk research and development of a new medicine.

Stewardship plan

[Working definition, used for analysis]

A stewardship plan is a plan set up to ensure that AMR-relevant public health needs are taken into consideration during R&D. These plans may be developed in-house or through collaborations and include commitments, strategies, concrete provisions and other agreed-upon measures (typically developed in partnership) to enforce accountability. Stewardship plans facilitate the appropriate use of antimicrobial medicines and reduce the emergence of resistance. Examples include (but are not limited to) appropriate promotional practices and conducting surveillance studies.

Substandard medicine

Also referred to as "out of specification", these are market-authorised medicines that fail to meet either quality standards or specifications, or both. [based on WHO, 2017]

Report Design

Explanation Design (Klaas van der Veen)

Photo Jayasree K. Iyer: Ilvy Njiokiktjien / VII

Photo Agency

Photo Disclaimer

The Access to Medicine Foundation gratefully respects the permission granted to reproduce the copyright material in this report. Every reasonable effort has been made to trace copyright holders and to obtain their permission for the use of copyright material. Should you believe that any content in this report does infringe any rights you may possess, please contact us at info@accesstomedicinefoundation.org or + 31 (0) 20 21 53 535.

Disclaimer

As a multi-stakeholder and collaborative project, the findings, interpretations and conclusions expressed herein may not necessarily reflect the views of all members of the stakeholder groups or the organisations they represent. The report is intended to be for information purposes only and is not intended as promotional material in any respect. The material is not intended as an offer or solicitation for the purchase or sale of any financial instrument. The report is not intended to provide accounting, legal or tax advice or investment recommendations. Whilst based on information believed to be reliable, no guarantee can be given that it is accurate or complete.

Copyright

No part of this report may be reproduced in any manner without the written permission of the Access to Medicine Foundation. The information herein has been obtained from sources which we believe to be reliable, but we do not guarantee its accuracy or completeness. All opinions expressed herein are subject to change without notice.