

# Biotechs are saving the world from superbugs. Can they also save themselves?

JUNE 2021

Biotechs or small- and medium-sized enterprises (SMEs) are developing the bulk of new antibiotics, which are urgently needed to replace those that are losing their effectiveness due to rising rates of resistance. Yet, SMEs struggle to secure the financing and resources needed to develop and commercialise these much-needed medicines, and face bankruptcy as a result, leaving promising candidates stuck in development. This paper examines how SMEs are navigating the tough conditions in the antibiotic market. It draws on new data and discussions with CEOs, investors and experts working on drug resistance, and builds on industry trends identified in the Antimicrobial Resistance Benchmark.

## ACKNOWLEDGEMENTS

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

### FUNDERS

UK Foreign, Commonwealth and Development Office  
The Dutch Ministry of Health, Welfare and Sport  
Wellcome Trust  
AXA Investment Managers



Ministry of Health, Welfare and Sport



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The Access to Medicine Foundation is grateful to the following people for their thoughtful reviews of earlier drafts of this paper: Karen Gallant and Kevin Outterson (CARB-X); Jean-Pierre Paccaud (GARDP); Hatim Sati (WHO); Oliver Williams (Wellcome Trust).

### 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.

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## About this paper

### A look at how SMEs are navigating the tough antibiotic market

- ▶ Small- and medium-sized enterprises (SMEs) are developing the bulk of new antibiotics and antifungal medicines.
- ▶ Despite the urgent need for the new products SMEs are developing against superbugs, they face funding shortfalls and risk bankruptcy, potentially leaving new medicines stranded on the lab bench.
- ▶ The Access to Medicine Foundation examines how SMEs are navigating the tough antibiotic and antifungal market while reforms and policy solutions ramp up.
- ▶ The Foundation will use its findings to advance ongoing discussions and the policies for how best to fix the market. It aims to highlight opportunities being developed by SMEs and why new incentives for engaging in antibacterial and antifungal R&D should prioritise appropriate global access to products emerging from pipelines.

### How does this relate to the Benchmark?

This paper is published as part of the 2021 Antimicrobial Resistance Benchmark research programme. This is the first of two reports that the Benchmark will publish in 2021. The second report will use 19 metrics to rank some of the world's largest research-based pharmaceutical companies and generic medicine manufacturers on their efforts to tackle drug resistance. SMEs play a unique role in antibacterial and antifungal research and development, leading in novel projects, and generally have few products on the market. They have limited capacity, specifically when compared to large research-based pharmaceutical companies and are therefore examined separately.

### How was the paper developed?

The conclusions in this paper have been drawn following an analysis of data on company partnerships and pipelines, and informed by discussions with C-level executives of SMEs, investors and experts working on drug resistance, including reviews of earlier drafts of the paper. It was further informed by a systematic review of information published by SMEs and their partners (between January 2021-May 2021), and builds on industry trends identified in the 2018 and 2020 Antimicrobial Resistance Benchmark reports. Data on the antibacterial pipeline is from the World Health Organization's comprehensive report 'Antibacterial Agents in Clinical and Preclinical Development', published on April 15 2021 (55 late-stage antibiotic projects); and the antifungal pipeline is from the 2020 AMR Benchmark (3 late-stage antifungal projects). Information from these various sources was cross-checked directly with companies and their partners to ensure accuracy.

## SCOPE OF THE RESEARCH

### SMEs

24 SMEs active in late-stage antibacterial and antifungal R&D with access and stewardship plans as identified by WHO and the Antimicrobial Resistance Benchmark (see Appendix I for full list). Two additional SMEs (Bugworks™ Research Inc and Qpex Biopharma Inc.) with early-stage antibacterial projects were also included. Four cases are featured for the following companies:  
Bugworks™ Research Inc.  
Cidara Therapeutic Inc.  
Entasis Therapeutics Hldg  
Qpex Biopharma Inc.

### Products

55 late-stage antibacterial projects (Phase II and onward) as reported by the WHO Antibacterial Agents in Clinical and Preclinical Development Report.  
3 late stage (Phase II and onward) antifungal projects from the 2020 Antimicrobial Resistance Benchmark.

### Expert Reviewers

Karen Gallant and Kevin Outterson (CARB-X)  
Jean-Pierre Paccaud (GARDP)  
Hatim Sati (WHO)  
Oliver Williams (Wellcome Trust)

### Sources

SME's websites, annual reports, partner websites, as well as information submitted to the Benchmark directly by the SMEs. It also draws on information available in the public domain including peer-reviewed literature, clinical databases and public health data sources.



# Biotechs are saving the world from superbugs. Can they also save themselves?

Antimicrobials are at the heart of modern medicine. They enable infection prevention and control as well as safe surgery, and make new treatments possible for diseases such as cancer, among other benefits. Yet these life-saving medicines are losing effectiveness as microbes develop resistance. Experts warn of a slow-burning pandemic from drug-resistant infections, which already cause an estimated 700,000 deaths each year.<sup>1,2</sup>

Small- and medium-sized enterprises (SMEs) drive innovation in new antimicrobials (accounting for three quarters of late-stage antibacterials in the R&D pipeline). Yet they face an uphill battle in securing the financing and resources needed to bring even the most promising products to market. Many companies go bankrupt before they can launch their products – and some fail even after reaching this milestone.

There are few new antibiotics being developed, and, once approved, even fewer that reach the people who need them. Each year globally, more than 5.7 million people die from treatable infectious diseases due to a lack of access to antibiotics. The majority of these deaths occur mainly in low- and middle-income countries (LMICs).<sup>1</sup> It is critical that companies and their partners start early on to develop plans for ensuring the people most affected by rising rates of drug resistance have access to life-saving medicines.

It is clear that the innovators of such drugs urgently need a stable economic and policy environment suitable for developing and responsibly delivering new antimicrobials. Potential solutions include cash payments to companies for successfully developing a new product in the form of a market entry reward, subscription models where governments make regular payments in return for guaranteed, on-demand supply of effective antibiotics and antifungals, and regulatory reform to harmonise effective routes to market approval.

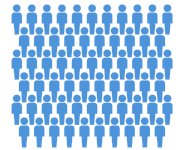
How are SMEs surviving while waiting for market and policy reforms? This paper finds that some SMEs, and their partners, are seizing opportunities to think and act globally, forging new partnerships to meet the dire need for urgent action in the countries facing the worst rates of resistance.

## SMES ARE KEY TO COMBATING AMR

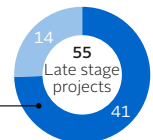
700,000 deaths from AMR



5.7 million deaths annually from lack of access to antibiotics.



75% of all projects active in late-stage antibacterial R&D today are developed by SMEs



THE STATE OF PLAY IN ANTIBIOTICS INNOVATION

## SMEs are powerhouses of innovation against superbugs

Antibacterial and antifungal R&D is risky – even compared with other areas of pharmaceutical innovation. SMEs currently shoulder most of this risk, dedicating their limited resources to the development of innovative R&D projects. Many pharmaceutical companies have exited the antibiotics field, due largely to a lack of incentives and adequate returns on investment. This has increased the world's dependency on these SMEs when it comes to turning the tide of resistance.

In antibacterial R&D, the pipeline remains alarmingly small in comparison with the scale of the threat from antimicrobial resistance (AMR). A recent report by the World Health Organization (WHO)<sup>3</sup> shows that SMEs account for the bulk of the clinical-stage antibacterial pipeline (75% of projects). The same report shows that SMEs consistently target the pathogens that pose the greatest risk from AMR (as designated by WHO and/or the US Centers for Disease Control and Prevention).

### Advance planning makes medicines accessible and protects effectiveness

Importantly, with only a limited number of antibiotics in late-stage development (currently at 55), each one must be protected from misuse and overuse from the moment of launch to ensure it keeps its effectiveness for as long as possible. With eight times more people dying due to lack of access to medicine than from drug resistance, ensuring global access must also be a priority. This requires product developers to plan, before a product hits the market, how and where to make this product accessible and how to safeguard the product's effectiveness through good stewardship.

Timely planning makes all the difference for getting treatment to those in need and keeping resistance at bay. However, SMEs funnel most of their limited funds toward the discovery and development of new products. This leaves few resources to prepare for commercialisation and distribution activities, including the planning required for stewardship and access. Only 25% (8/32) of the late-stage antibiotic projects examined in the 2020 Antimicrobial Resistance Benchmark were supported by both stewardship and access plans.<sup>4</sup>

### Is advance planning becoming a standard requirement?

Initiatives that finance antibiotic R&D are increasingly stipulating that product developers prepare stewardship and access plans. For example, the REPAIR Impact Fund requires product developers to commit to developing such plans by the time projects enter pivotal clinical trials. This is also a key milestone for the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X); its grantees are required to put plans in place within 90 days of products entering pivotal clinical trials (generally Phase III trials, or equivalent for diagnostics).

A wider systemic issue in antibacterial and antifungal R&D is that many active pharmaceutical companies, no matter their size, have limited to no experience in planning for stewardship and access, especially for LMICs. It is critical that companies and their partners start early on to develop plans for ensuring global access and appropriate use to protect their effectiveness and delay resistance.

Several non-profit R&D funding partners, including CARB-X, the Wellcome Trust, and the AMR Action Fund provide grant recipients with business, scientific and technical support in the form of tools, resources, and expertise. Guidance is now also available in a Stewardship and Access Plan Development Guide, developed by CARB-X, the Wellcome Trust, and the Access to Medicine Foundation, among others. It sets out the practical and early actions that companies and partners can take to ensure swifter access to new antibacterial products, while ensuring responsible use.

**SMEs are the engine of late-stage antibacterial R&D with<sup>3</sup>:**

**75%** of all late-stage R&D projects (41/55)

**66%** of high priority projects for AMR\* (20/30)

**73%** of projects\* that qualify as novel\*\* (11/15)

**75%** presence of the companies active in late-stage R&D

### Funding partners that stipulate advance stewardship and access planning\*\*\*

Partner	Total AMR funds
REPAIR Impact Fund	USD 165 mn
Wellcome Trust	GBP 250 mn
CARB-X	USD 480 mn
AMR Action Fund	USD 1,000 mn

\*Medicines and vaccines only, excluding projects that aim to develop 'non-traditional' products such as antibody treatments.

\*\*Meets the criteria defined by the WHO to determine whether an antibacterial medicine in the pipeline is novel.

\*\*\*As of time of writing.

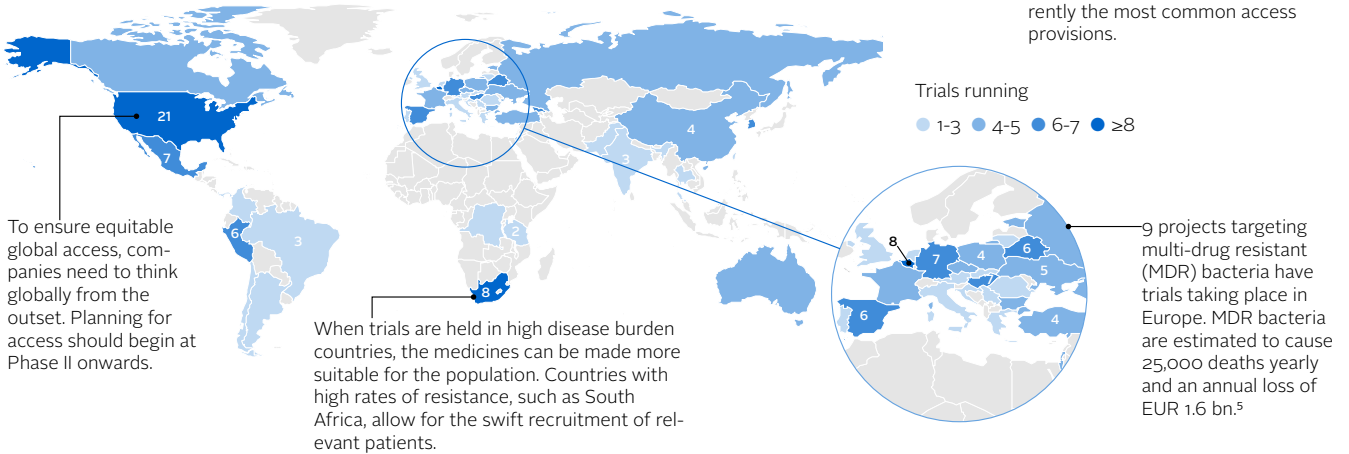
STEWARDSHIP & ACCESS PLANS

## A birds-eye view of stewardship and access planning

With only a limited number of antibiotics in late-stage development, each one must reach the people who face the highest rates of resistance, while being protected from the moment of launch to ensure it stays effective for as long as possible. Here is a look at how widespread such planning is today, supported by examples.

### 193 trials are currently running across 47 countries.

Running clinical trials locally can lead to products that are more suitable for local populations. It helps lay the groundwork for the medicine to be made available and accessible locally, if successful.



### EXAMPLES OF STEWARDSHIP AND ACCESS PLANNING PROVISIONS FOR CURRENT R&D

**Zoliflodacin** is a first-in-class oral antibiotic targeting *Neisseria gonorrhoeae*, a pathogen that is quickly becoming resistant to current treatments.<sup>6</sup> It is being developed by Entasis and the Global Antibiotic Research and Development Partnership (GARDP), a not-for-profit R&D organisation developing new treatments for priority drug-resistant infections. In Phase III, it will be a novel\* treatment for uncomplicated gonorrhoea infections. Clinical trials are being conducted in countries where prevalence is high, including South Africa, where 2 million gonorrhoea cases occur annually.<sup>7</sup> The partnership agreement follows GARDP's directive to develop strategies that take into account the local realities of the countries where the product will be deployed. GARDP retains exclusive rights to market the product in 168 countries and territories, including LMICs. Entasis retains the rights for high-income markets.<sup>8</sup>

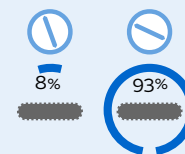
**Sulopenem** is being developed by Iteum Therapeutics with funding support from CARB-X. It is a broad-spectrum antibiotic demonstrating activity against extended-spectrum β-lactamase (ESBL)-producing cephalosporin-resistant Enterobacterales. It is in Phase III trials for the treatment of uncomplicated urinary tract infections (uUTI), complicated urinary tract infections (cUTI) and complicated intra-abdominal infections (cIAI). Resistance to the antibiotics used to treat UTI is varied and widespread. Sulopenem was initially developed by Pfizer; this was stopped despite encouraging results. Iteum acquired the licence in 2015 and restarted development. It is partnering with Eversana Life Science Services, a commercial services provider of pre-launch activities in the USA, but there is currently no information on commercialisation in other countries.<sup>10</sup> As a CARB-X awardee, they are required to develop and publish a stewardship and access plan by the point of first market approval. Iteum provides an Expanded Access Program for patients with cUTI caused by quinolone-resistant uropathogens.

**An oral antimicrobial monoclonal antibody project targeting *Campylobacter jejuni* and *E. coli* bacteria** is being developed by Lumen Bioscience with a grant from the Bill & Melinda Gates Foundation. The project aims to develop a cocktail of neutralising monoclonal antibody-like protein biologics to bind and neutralise the bacterial pathogens *C. jejuni* and enterotoxigenic *E. coli*. The bacteria targeted by the project are a major cause of diarrhoea cases and death of infants and children in LMICs. Lumen Bioscience is currently recruiting patients for its Phase II trials. The target product profile is of an edible antibody that can be easily transported and stored, including to regions which lack cold chain distribution. Lumen Bioscience states its commitment to deliver the compound to people living in LMICs regardless of their ability to pay and is working with the Bill & Melinda Gates Foundation and other global health advocates to make these products available in LMICs.

In one year, 87 million people (aged 15-49) get infected with gonorrhoea. In 2016, global prevalence was 0.9%.<sup>9</sup>



UTIs, one of the most common infections worldwide<sup>11</sup>, are more dangerous in diabetic patients and cancer patients.<sup>12,13</sup>



The rate of resistance to ciprofloxacin, used to treat UTIs, varies greatly. For *Escherichia coli* it ranges from 8.4% to 92.2%<sup>2</sup>

Diarrhoea is the 2<sup>nd</sup> biggest cause of death in children and a leading cause of malnutrition.<sup>15</sup>



\*Due to scaling, countries with trials may not be visible on the map. This figure is based on data for projects with a stewardship and/or access plan as identified by WHO (26 antibacterials projects) and the 2020 AMR Benchmark (3 antifungal projects), see Appendix I. Two additional projects were included (without a stewardship and access plan in place) on the basis that they are running in low- and middle-income country.

INCENTIVES

## Why do we need to ‘to fix the market’ for antibiotics?

Most SMEs have not yet brought products to market, and new antibiotics generally generate low revenues. As a consequence, SMEs have little room for error when it comes to commercialisation once research grants have expired. They are expected to navigate financial “valleys of death” – which starts when funding for early-stage research runs out and only ends if investors or Big Pharma start to show interest.\* At minimum, this forces SMEs to pause development while they hunt for financing. At worst, it means that promising and urgently needed candidates for new medicines, diagnostics and vaccines disappear when SMEs go bankrupt.

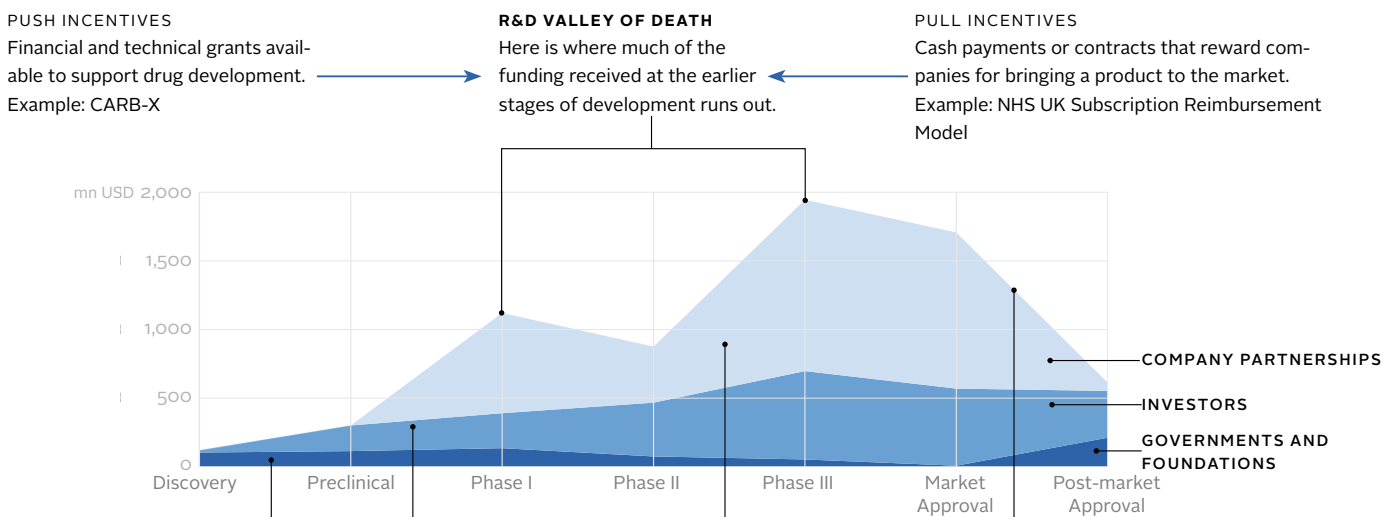
### A promising drug is not enough

For example, in 2021, the Swiss biotech company Juvabis was forced to reduce its workforce to four employees due to financing constraints.<sup>17</sup> This is despite its candidate antibiotic EBL-1003 demonstrating safety and tolerability in Phase I clinical trials and promising preclinical activity against drug-resistant pathogens, in particular *Acinetobacter baumannii*, a critical priority pathogen for antibacterial R&D according to the WHO, and *Mycobacterium abscessus*. To get to this stage, Juvabis had received extensive support from the European Gram-Negative Anti-Bacterial Engine consortium (ENABLE) and the National Institutes of Health (NIH) for pre-clinical development and completion of Phase I clinical trials.

To provide a buffer against bankruptcy – and encourage more companies to join the field – the economic and policy environment for antibiotic R&D must be reformed. This means developing the right mix of incentives to support R&D, and to reward the market entry and the sustained availability of new products, through new financing, reimbursement and regulatory tools. Currently, the majority of R&D incentives are ‘push’ incentives: financial and technical grants available to support drug development. These typically support the riskier early phases of development, which account for roughly 20% of the total costs required to bring a project to the

### How are companies plugging the funding gap?

This chart totals the support that SMEs have raised via various push and pull incentives by 24 SMEs active in late-stage antibacterial and antifungal R&D.\*\*



The discovery phase of research is considered the most risky, with many investigative leads leading to failure. At this stage, SMEs are often dependent on funding, or push incentives, from governments and philanthropic organisations.

As a project begins to move through the pipeline, venture capitalists and angel investors then select SMEs to fund. Funders mostly bank on projects with a promising return-on-investment.

To help drive a project beyond the gap and into market, SMEs mainly rely on partnerships with more resourced and experienced pharmaceutical companies.

**COMMERCIAL VALLEY OF DEATH**  
Funding for SMEs tend to dry out for a second time once the approved antibiotic hits the market. SMEs then rely on sales revenues and on any royalties and milestones from deals with other companies.

\*E.g., Pfizer recently acquired Amlyx Pharmaceuticals Inc., securing ownership of Amlyx's lead novel compound, Fosmanogepix (APX-001), under development for the treatment of invasive fungal infections as well as their early-stage pipeline of potential antiviral and antifungal therapies.

\*\* These companies are developing 28 late-stage projects, and were identified by the WHO and Antimicrobial Resistance Benchmark. Only companies with access and/or stewardship plans in place were included, see Appendix I.



market. Grants to cover the remaining 80% of costs are harder to come by, leaving a resource gap for the later phases of clinical development and post-market approval commercialisation. In total, it costs an estimated one billion USD or more to develop a new antibiotic.<sup>18</sup>

The most recent push incentive to step into this gap is the AMR Action Fund, which will support clinical-stage antibiotic research. Launched in July 2020, the Fund is an industry-led collaboration with WHO, the European Investment Bank and the Wellcome Trust. It is currently ramping up with a commitment of approximately USD 1 billion with the aim of bringing 2-4 new antibiotics to market by 2030. The AMR Action Fund will employ a set of Access & Appropriate Use Principals, as stipulated for the funding from the Wellcome Trust, and will require awardees to develop and publish stewardship and access plans. As with all R&D initiatives, advance planning for stewardship and equitable and appropriate access to all, including those vulnerable LMIC populations, must be a standard step to market and support.

**Handful of countries test new approaches for sustaining companies**

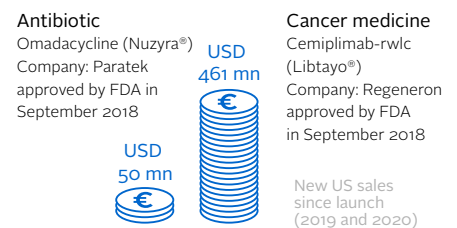
The United Kingdom, Sweden, the United States and Germany are each testing different national models that aim to reward companies for bringing products to market. They have several aims in common: to bring better outcomes for patients by incentivising new, much-needed treatment options; to bring better value for national health systems in terms of affordability and/or guaranteed supply; and at the same time to offer companies guaranteed reimbursement toward the cost of developing the product. There are, as yet, no global or regional models.

The UK's model is a unique pull incentive where sales volume is not the basis of reimbursement. Instead, companies are paid for antibiotics based primarily on the results of a health technology assessment, which evaluates the medicines' overall value to the UK's National Health Service (NHS). The Swedish Public Health Agency is piloting an agreement with four pharmaceutical companies to test if a new reimbursement model can ensure the availability of relevant antibiotics. This model offers companies an annual revenue to guarantee supply of selected antibiotics within set time-frames. In the US, two potential reforms are working their way through the legislative houses: the PASTEUR and the DISARM acts. If passed, these acts would effectively establish a subscription style model by offering upfront payments in exchange for unlimited access to new antibiotics. Both the UK and the US models stipulate stewardship provisions that should be met.

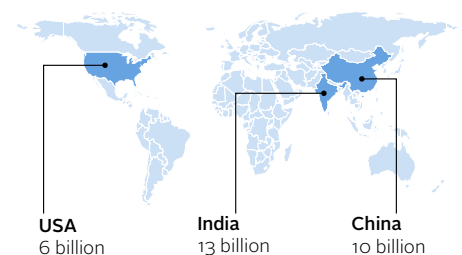
**Growth will come from emerging markets**

The antibiotics market is typically not deemed an attractive market for either pharmaceutical companies or their investors. Yet, there are clear opportunities to engage with emerging markets and neighbouring LMICs, as well as advantages. Growth (volume) in the antibiotics market in the coming years is expected to come from emerging markets, continuing a trend going back to at least 2000. In the decade to 2010, antibiotics consumption across 71 countries increased by more than a third (36%). Notably, just five countries, namely Brazil, Russia, India, China and South Africa, accounted for most of the jump (76%).<sup>19</sup> These countries have high demand for both new and old antibiotics, and account for some of the highest rates of AMR. These high rates can translate into faster enrollment of relevant patients in clinical trials, which speeds development and can ensure trial results will reflect the populations where the need is greatest. Further, engaging in emerging markets and LMICs during development opens opportunities to partner with locally based clinical trial organisations, research institutes and generic medicine manufacturers with the resources, capacity, and local regulatory and legislative expertise needed to rapidly ensure access to a new product. Plus, GARDP and WHO are spearheading the development of a new initiative called SECURE with UNICEF and CHAI, to expand access to essential antibiotics to prepare countries for the silent pandemic of drug-resistant bacterial infections.

**How do the sales of an antibiotic compare to a blockbuster medicine?<sup>20,21,22</sup>**



**Three countries consumed the most antibiotics between 2000-2010 (unit: pills/ampules)<sup>19</sup>**



## STRATEGIC PARTNERSHIPS

## Strategic partnerships drive new approaches: an SME survival tactic or new opportunities for growth?

Caught between the urgent clinical need for their R&D candidates and the lack of financing and revenue, some SMEs are carving a new path. These companies are trialling new approaches and forging innovative networks of partnerships that are enabling them to survive and expand in the medium- to long-term. These networks also put them in an improved position to enable broader access to new medicines in low- and middle-income countries (LMICs) as candidates exit the pipeline. These SMEs and their partners recognise the critical need to achieve swift global access to their new innovations. Moreover, they are facilitated by national governments including in India and China, which have invested in their domestic pharmaceutical industry including R&D and clinical trial organisation.

Two approaches are discussed here. Each enables SMEs to de-risk their operations, access additional sources of financing and revenue, and facilitate global access at scale and at an affordable price through partnerships. These partnerships can be with a range of local actors, such as local policy and decision makers, leading hospitals, clinical trial organisations, generic medicine manufacturers and suppliers of active pharmaceutical ingredients (APIs). Via these partnerships, SMEs can work toward global access to the new medicine in parallel for high-income countries and LMICs. These approaches offer SMEs a more secure route to reach those in LMICs, with companies often partnering with China-based companies.

### TWO APPROACHES FOR SMEs CARVING A NEW PATH

#### APPROACH 1

##### Expand own global footprint via local partner networks

- Maintain R&D facilities in multiple countries
- Build partnerships with local actors that can support clinical development and/or facilitate global access through commercialisation, manufacturing and distribution
- Active collaboration between the partners to accelerate development and to satisfy local regulatory criteria
- Seek agreements with generic medicine manufacturers to achieve production at scale and an affordable price
- One example discussed here: Bugworks

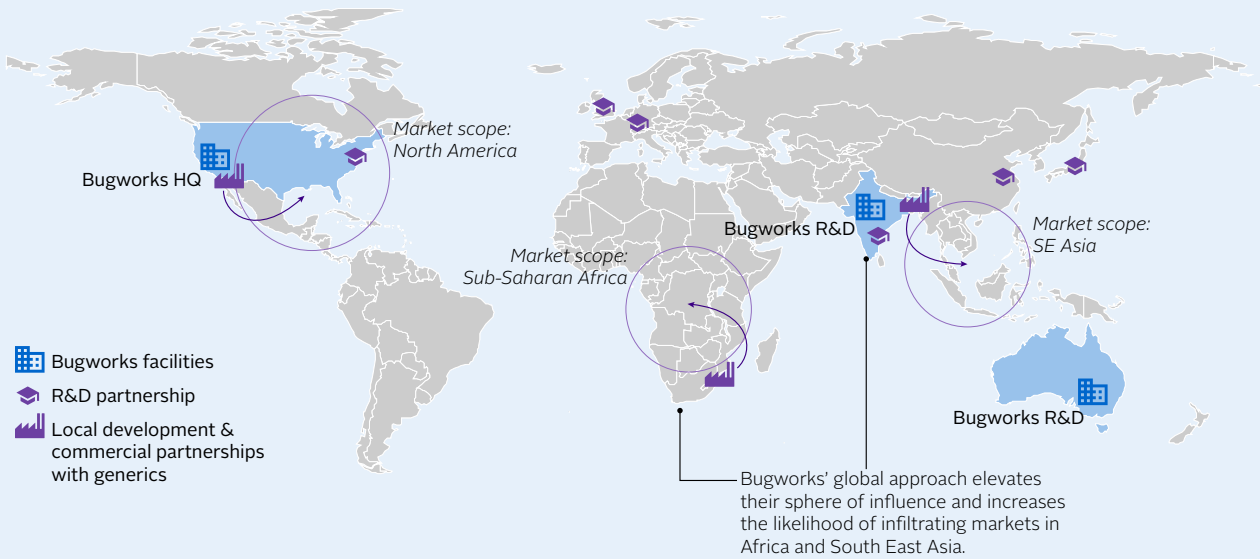
#### APPROACH 2

##### Accelerate access by licensing for entry into key emerging markets

- Maintain own facilities in a high-income country
- Enter partnership with an actor that is either based in a key emerging market, such as India or China, and/or has a footprint in strategic countries outside of the USA and Europe
- Collaboration based on licensing agreements whereby the partner takes over the last stages of development and commercialisation per country or region as a means of accelerating development and ensuring broad access to medicine beyond high-income markets.
- Three examples discussed here: Entasis, Qpex, Cidara.

## APPROACH 1

## Bugworks' global approach to R&amp;D and commercialisation



- **Bugworks headquarter:** California, USA
- **Research & Development facilities** in Australia, India and the USA
- **R&D partnerships** with clinical research organisations and academic research centers in China, the EU, Japan, India, the UK and the USA.
- **Development and commercial partnerships** with generic medicine manufacturers and local companies in India, South Africa and the USA.

In India, South Africa and the USA, Bugworks seeks and maintains strategic partnerships with local companies, organisations and generic medicine manufacturers to achieve synergies in R&D and lay the groundwork for bringing its GYROX products to the market in LMICs. This global approach expands possibilities for financing from different sources, but also ensures that innovation and testing can be done in multiple locations, making it more likely that the new medicine will be suitable and accessible for people in LMICs. Bugworks has raised USD 19 million to date from sources such as CARB-X, including USD 7.5 million from a global investment syndicate with the University of Tokyo Edge Capital, Global Brain Corporation, and Acquipharma Holdings.<sup>23</sup> Most recently, Bugworks received funding from the US Government's Defense Threat Reduction Agency (DTRA).<sup>24</sup>

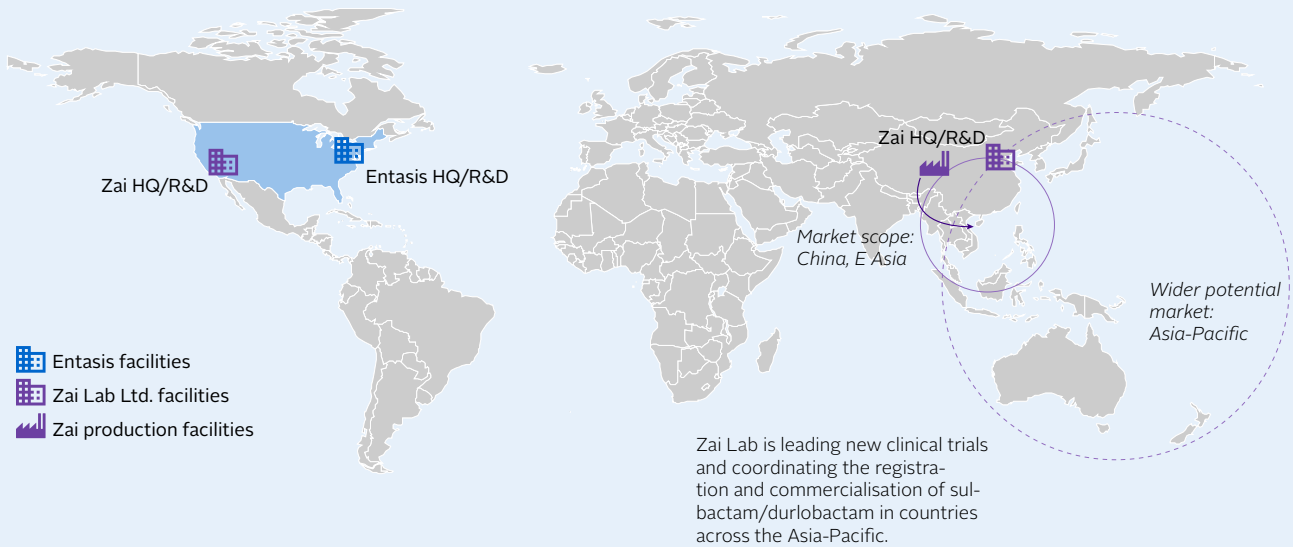
India and South Africa have high rates of AMR, which means a greater number of relevant clinical trial participants can be recruited, and clinical trials are conducted under the context where the new medicine is urgently needed, further accelerating development of effective products. If Bugworks successfully moves its products through the entire pipeline, its multi-country approach increases the potential for accessibility in countries across South East Asia and Africa.

#### R&D target: multi-drug resistant gram-negative and -positive pathogens

Bugworks is developing novel\* broad-spectrum antibiotic treatments based on the GYROX family of small molecule antibacterial agents. These have a new mechanism of action and low resistance development rate. There are three projects based on GYROX agents: one intravenous and two oral treatments that target multi-drug resistant gram-negative and -positive bacteria, including the ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter spp.*).

\*Meets the criteria defined by the WHO to determine whether an antibacterial medicine in the pipeline is novel.

**Entasis' licensing agreement opens up new financial and market opportunities in Asia-Pacific**



- **Entasis headquarter:** Massachusetts, USA.
- **Research & Development facilities** in the USA (sulbactam/durlobactam Phase III trials in 17 countries including Brazil, China, India, Mexico, Peru, Thailand).
- **R&D and commercial partner:** Zai Lab (HQ and R&D facilities in China and the USA).
- **Partnership:** Licensing and collaboration agreement covering countries in the Asia-Pacific region.

Entasis takes an international approach to managing its antibacterial pipeline. It is developing zoliflodacin (see p. 7) with GARDP, while sulbactam/durlobactam is covered by a partnership with Zai Lab that started in 2018. Zai Lab is a commercial-stage biotechnology company with headquarters in China and in the USA. Its global R&D center is in Shanghai, and it has manufacturing sites in Suzhou. Zai Lab's discovery operations are spread between Shanghai, Boston and San Francisco. Entasis' partnership with Zai Lab is based on a licensing and collaboration agreement. As part of this agreement, Zai Lab gains the exclusive license to develop, register and commercialise sulbactam/durlobactam in China, Korea, Vietnam, Thailand, Cambodia, Laos, Malaysia and Indonesia.

The agreement includes a global strategic development collaboration, wherein Zai Lab takes the operational lead to support trials and coordinate the registration and commercialisation of sulbactam/durlobactam in countries across the Asia-Pacific region. The collaboration is currently working on a Phase III clinical trial in China. The trial, called ATTACK (Acinetobacter Treatment Trial Against Colistin), is a global, two-part Phase III registrational trial enrolling approximately 300 patients with pneumonia and bloodstream infections caused by carbapenem-resistant *A. baumannii*. The data readout is expected in 2021.

Through its partnership with Zai Lab, Entasis is able to share the risk of developing and commercialising sulbactam/durlobactam across the Asia Pacific region, while securing potential future licensing revenues. In turn, this future revenue stream decreases its overall corporate risk profile and opens doors to new financing sources.

**R&D target: *A. baumannii***

Entasis is developing the combination of a  $\beta$ -lactam and  $\beta$ -lactamase inhibitor: sulbactam/durlobactam. Sulbactam is the  $\beta$ -lactam antibiotic with activity against *A. baumannii*. Durlobactam is a novel broad-spectrum IV  $\beta$ -lactamase inhibitor with broader activity against Class A, C and D  $\beta$ -lactamases. The combination is developed to treat infections caused by multidrug resistant *A. baumannii*, including carbapenem-resistant *A.baumannii-calcoaceticus* complex strains. *A. baumannii* causes a range of infections and is one of the most prevalent causes of nosocomial infections,<sup>25,26</sup> and is estimated to account for more than 200,000 cases in China each year.<sup>27</sup> With resistance on the rise, WHO and CDC have categorised it as a 'critical' and 'urgent' priority for R&D respectively.

## Qpex's licence brings urgent new treatment options for carbapenem-resistant pathogens to China



- **Qpex headquarter:** California, USA.
- **Research & Development facilities** in the USA (Phase I trials run in US and Australia).
- **R&D and commercial partner:** Bii Bioscience (HQ and R&D facilities in China and the USA; market presence in China).
- **Partnership:** a multi-product development, manufacturing and commercialisation collaboration in China.

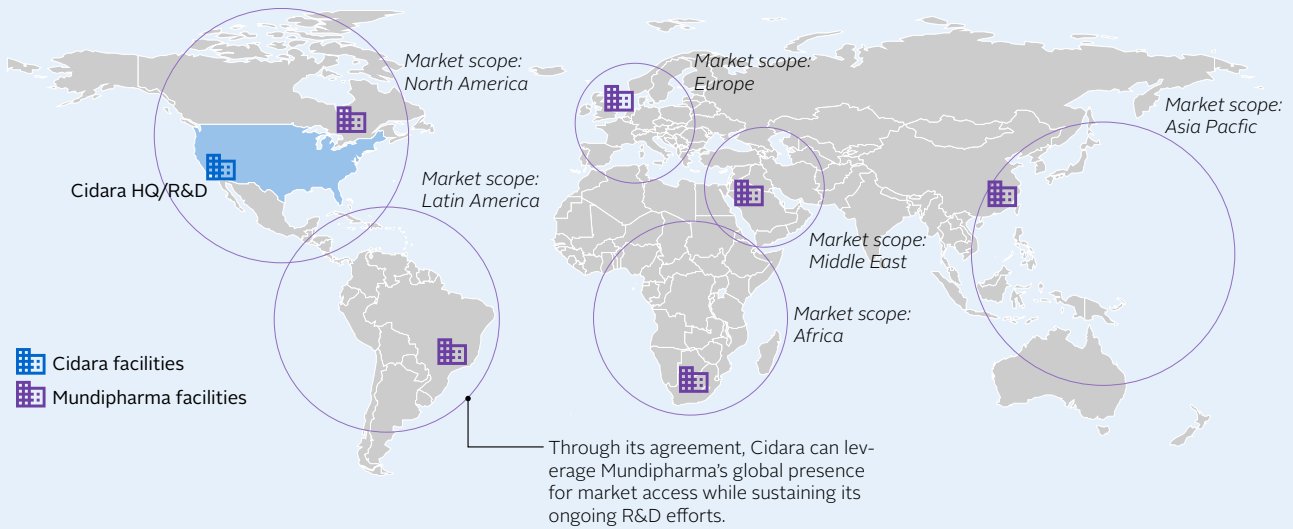
Qpex has licensed the clinical-stage company Bii Biosciences (Bii) the rights to develop, manufacture and commercialise the three products in China. In return, Qpex receives a one-off up-front payment, with further payments dependent on the achievement of specific development, regulatory and commercial milestones. Once sales of the products begin, Qpex will also receive tiered royalties. Bii will share the costs of Qpex's global development programme.

This strategy was selected for three main reasons. Firstly, Qpex's clinical products directly target the drug resistance mechanisms that are highly prevalent in clinical isolates of *A. baumannii*, *P. aeruginosa*, and *Enterobacterales* in Greater China. Secondly, Qpex's clinical products address a high unmet need in China for specific treatment options. Thirdly, China presents a profitable market in its own right, and through its partnership with Bii, developing and gaining approval for the product in Greater China, it will be easier for Qpex to bring its products to that region through its global development program. By sharing the costs and the research from the global development programme, Qpex also shares the risks while accelerating the development and commercialisation process for several areas of the world.

### R&D target: carbapenem-resistant *A. baumannii*, *P. aeruginosa*, and *Enterobacterales*.

Qpex is developing three products targeting resistant gram-negative pathogens including carbapenem-resistant *A. baumannii*, *P. aeruginosa*, and *Enterobacterales*. Carbapenem-resistant infections are associated with high morbidity and mortality due to lack of therapeutic options as high as 40%-65% and 8%-52% in children.<sup>28,29</sup> Two of these projects are based on an ultra-broad spectrum cyclic boronic acid  $\beta$ -lactamase inhibitor (QPX7728). QPX7728, has demonstrated activity in combination with several different companion  $\beta$ -lactam antibiotics against carbapenem-resistant strains of *A. baumannii* (CRAB), *P. aeruginosa*, and cephalosporin- and carbapenem-resistant *Enterobacterales* (CRE). The combination of QPX7728 and meropenem was found to be the most potent  $\beta$ -lactam/ $\beta$ -lactamase inhibitor combination tested against all groups of CRE with multiple resistance mechanisms. Both i.v. and oral forms of QPX7728 are being developed in combination with undisclosed  $\beta$ -lactam antibiotics. The third project is a next-generation polymyxin (QPX9003). In preclinical studies, QPX9003 has demonstrated activity against multi-drug resistant *A. baumannii* and *P. aeruginosa* and has a better safety profile compared to colistin and polymyxin B.

**Cidara partners with global network to sustain efforts and broaden access**



- **Cidara headquarter:** California, USA.
- **Research & Development facilities:** the USA (two rezafungin Phase III trials in 26 countries, including China, Colombia and Thailand).
- **R&D and commercial partner:** Mundipharma, a global network of associated companies (decentralised structure with operations and market presence across Africa, Asia Pacific, Canada, Europe, Latin America and the Middle East).
- **Partnership:** exclusive commercialisation rights to rezafungin outside the USA and Japan.

In 2019, Cidara granted exclusive commercialisation rights to rezafungin outside the US and Japan to Mundipharma, a global network of associated companies with research, development and manufacturing facilities and presence across Africa, Asia Pacific, Canada, Europe, Latin America and the Middle East. In exchange, Cidara received an upfront payment and equity investment, as well as near-term funding to support ongoing Phase III trials for the treatment and prevention of fungal infections. For Mundipharma, this partnership enables access to a much-needed drug for people with cancer or HIV in key markets where it has a presence. As Mundipharma further develops and commercialises rezafungin, Cidara will also receive milestone payments and royalties. Moreover, Mundipharma has assumed responsibility for approval submissions to the regulatory authorities in its territory while Cidara focuses on preparing and gaining approval from the US Food & Drug Administration (FDA).

**R&D target: candidemia**

Cidara is developing rezafungin, an echinocandin currently in Phase III trials for the treatment of candidemia (blood stream infection) and invasive candidiasis (infections caused by *Candida spp.* that can affect the blood, heart, brain and eyes, among other parts of the body) and for the prevention of invasive fungal disease caused by *Candida*, *Aspergillus*, and *Pneumocystis* species in the recipients of blood and marrow transplantation. This new medicine is designed to provide several advantages over existing treatments, including a simpler dosing regimen (one IV dose administered per week) and better efficacy against some drug-resistant *Candida* species. Invasive candidiasis is a devastating infection in immunocompromised or critically ill, hospitalised patients, such as those with cancer with an associated mortality rate of up to 50%.<sup>30</sup> Invasive candidiasis is also the most frequent fungal infection in HIV positive patients.<sup>31</sup> The incidence of candidemia has increased five-fold in the last 10 years globally. The increase is most evident in LMICs, where the rates are 4 to 15 times higher than in high-income countries.<sup>32</sup>

## CASE STUDY

## China is a prominent market for antibiotic development partnerships

SMEs often work with partners in China when seeking antibiotic development and commercialisation partners, as indicated by our review of partnership announcements issued by companies developing late-stage antibacterials and antifungals. Will developments in China provide a gateway for ensuring access to successful new medicines in low- and middle-income countries (LMICs)? There are compelling signs that China will become a global hub for the development, manufacturing and commercialisation of antibiotics and antifungals with several partners from China partnering with SMEs from around the world in the near to medium term. If so, what happens in these relationships and how access is brought to populations within China will be key for achieving good stewardship and global access to these life-saving medicines.

### China is the largest producer and user of antibiotics

The business case for partnering with companies and organisations in China is strong. China is one of the largest producer and user of antibiotics in the world.<sup>33</sup> Per its National AMR Action Plan (2016-2020), China committed to increasing its investments in antibiotic R&D, aiming to launch 1–2 new antibacterial agents and 5–10 new diagnostic tools.<sup>34</sup> Developing and gaining approval for new products in China can open opportunities to bring new antibiotics to other markets in Asia.

China ranks among the countries with the highest incidence of AMR. For example, infections of *A. baumannii* in China account for approximately 11% of all Gram-negative infections worldwide. The resistance of *A. baumannii* to the carbapenem class of antibiotics in China has increased significantly in recent years. Estimated at 60% in 2016, rates in some provinces are now as high as 70-80%.<sup>35</sup> A study cited by WHO estimated that, by 2050, antibiotic resistance could result in 1 million premature deaths annually in China at a cost of USD 20 trillion.<sup>36</sup> As part of its National Campaign for Rational Antibiotic Use, China will require all hospitals to educate staff, implement antibiotic prescription guidelines, conduct prescription reviews and feedback, and adopt a web-based prescribing system.<sup>34</sup>

This level of prioritisation, alongside rising rates of AMR, means that doctors in China need faster, affordable access to old and new therapies. It has the public health infrastructure and advanced digital and data technologies to enable that access at scale.<sup>37</sup> China employs a technology-based distribution system integrated with a centralised system for tracking prescriptions and personal health information, which provides opportunities to ensure good stewardship. All product developers seeking to bring antibiotics to market, whether in China or elsewhere, have the responsibility to build stewardship and access provisions into their partnership agreements, so that the most vulnerable populations can benefit from appropriate access to the new medicines.

### China: A gateway for access to markets in Asia?



China ranks among the countries with the **highest incidence** of AMR.

**By 2050**, antibiotic resistance could result in 1 million pre-mature deaths in China at a cost of 20 trillion USD.

**10 SMEs** are reaching into China markets via **licensing agreements**. One SME, Aridis, established a joint venture with Shenzhen Hepalink, a pharmaceutical company based in Shenzhen for the development and commercialisation of two projects targeting *P. aeruginosa* and methicillin-resistant *S. aureus* (MRSA).

Per its National AMR Action Plan, China is committed to **increasing investments** in antibiotic R&D.

Gaining market approval in China can open **opportunities** to bring new antibiotics to other markets in Asia.

## CONCLUSION

# SMEs are opening gateways for new drugs to reach new markets. With better incentives, this could lead to global access.

Each year, 5.7 million people die from treatable infectious diseases – most live in low- and middle-income countries (LMICs) – and 700,000 people die each year from drug-resistant infections. New antibiotics and antifungals are urgently needed to replace the ones losing their effectiveness. Even though small- and medium-sized companies (SMEs) are developing the bulk of the late-stage antibacterial and antifungal pipeline, they struggle to secure resources and face bankruptcy as a result. When SMEs fail, their pipelines are frozen, leaving new drugs stranded on the lab bench. If the loss of such promising products continues, the pandemic of drug-resistant infections will pose a bigger global health emergency than COVID-19. This paper shows that SMEs are finding new ways of navigating the broken antibiotic market.

### **People in LMICs are being left last in line for new antibiotics.**

A stable economic and policy environment is urgently needed for developing and responsibly delivering new antimicrobials. SMEs now play a prominent role in antimicrobial R&D following the departure of many pharmaceutical companies and investors from this space. While the current mix of R&D incentives is valuable, it will not be enough to prevent the slow-burning pandemic of drug-resistant infections. People living in LMICs will be left last in line for new products unless the policy and regulatory environment is explicitly re-designed, including through the use of market entry rewards and subscription models, to enable and incentivise global access to antibiotics and antifungals.

### **All companies – large and small – are competing for a small pool of R&D lifelines.**

Many companies active in antimicrobial R&D appear to be waiting for a concrete system of pull incentives to be implemented. While waiting for incentives to ramp up, companies compete for a mosaic of funding and revenue sources, such as the subscription models being piloted by the UK and Swedish governments, and grants e.g., from the AMR Action Fund, BARDA, CARB-X and Wellcome Trust.

### **Out-of-the-box thinking can pair effective new products with hospital-based opportunities**

Some SMEs and their partners are bringing their products into specialised situations in hospitals and healthcare settings, such as to support cancer treatment, or for intravenous use. SMEs thereby meet a critical need in a system that is at least somewhat prepared to pay for delivery. They are using partnerships in countries such as China, India and South Africa to accelerate development and secure prospective revenue streams. They and others like them aim to survive and expand by making new medicines accessible in emerging markets and neighbouring LMICs at the same time as in high-income markets. Most efforts center on emerging markets and hospital settings. Community-based infections must also be prioritised in order to achieve health for all as promised in Sustainable Development Goal 3.

### **China is developing into a hub for antibacterial development and commercialisation**

A review of the partnerships announced by SMEs with projects in late-stage development indicates that they focus on China when seeking antibiotic development and commercialisation partners. This is likely due to high demand for antibiotics, the government's prioritisation of R&D and stewardship, and a mature network of partners that can share risks and offer financing and revenues. This trend raises the possibility of China being a future gateway for ensuring equitable and responsible access to successful new antibiotics and antifungals for people living in other LMICs.

### **Antibiotics are not reaching the people who need them. Advance planning for access and stewardship must become standard.**

There are few new antibiotics being developed, and, even fewer that reach the people who need them once approved. Eight times as many people currently die from lack of access to medicine than from drug-resistant infections. Further, each antibiotic must be used responsibly to ensure it stays effective for as long as possible. This will only happen when SMEs and their product development partners, supported by investors and donors, are able to make stewardship and access planning a standard step, from Phase II. Then equitable and appropriate access to antibiotics can become the norm, not the exception.



## APPENDIX I.

Breakdown of the access and stewardship plans being carried out by SMEs. This chart shows the SMEs with a least one stewardship and/or access plan in a place for a late-stage antibacterial and/or antifungal project as identified by the AMR Benchmark and WHO.

- Covers LMICs
- No information available
- No stewardship plan

Company/Developer	Project name	Development Phase	Access Plan Detail	Stewardship Plan Detail	LMICs Reach
Allegra Therapeutics GmbH	Cefepime/enmetazobactam	Phase III	Licensing Agreement (Exclusive), Shanghai Haini Pharmaceutical Co. Ltd. (CHINA)	Surveillance programmes (Susceptibility Test)	●
Amplyx Pharmaceuticals Inc	Fosmangofepix (antifungal)	Phase II	Expanded Access Program	Davos Declaration 2016, Commitment	●
Aridis Pharmaceuticals Inc	AR-101 mAb (Aerumab™)	Phase II (completed)	Licensing Agreement (Exclusive), Serum Institute of India Ltd. (INDIA) Licensing Agreement (Exclusive), Shenzhen Hepalink Pharmaceutical Group Co. Ltd. (CHINA)	●	●
Aridis Pharmaceuticals Inc	AR-301 mAb (Salvecin®)	Phase III	Licensing Agreement (Exclusive), Serum Institute of India Ltd. (INDIA) Licensing Agreement (Exclusive), Shenzhen Hepalink Pharmaceutical Group Co. Ltd. (CHINA)	●	●
Aridis Pharmaceuticals Inc	AR-105 (Aerucin®)	Phase II	Licensing Agreement (Exclusive), Serum Institute of India Ltd. (INDIA)	●	●
Cidara Therapeutics Inc	Rezafungin (anitfungal)	Phase III	Licensing Agreement (Exclusive), Mundipharma International Ltd. (UK) Expanded Access Program	○	●
Entasis Therapeutics Holdings Inc	Sulbactam/durlobactam	Phase III	Licensing Agreement (Exclusive), Zai Lab Ltd (CHINA) Equitable Pricing Strategy Expanded Access Program (US)	Surveillance; Avoid expansion of use in unnecessary indications	●
Entasis Therapeutics Holdings Inc	Zoliflodacin	Phase III	Equitable Pricing Commitment (Tiered Pricing), GARDP	Stewardship and Responsible Use Commitment, GARDP; Surveillance Studies; Developed for treatment of one indication, gonorrhoea.	●
ImmuniMed Inc	IM-01 (Antibody-Vaccine Therapy)	Phase II	Humanitarian commitment to provide access in developing countries.	●	●
iNTRON Biotechnology Inc	Tonabacase (N-Rephasin® SAL200)	Phase II	Licensing Agreement, Roviand Sciences Inc (SWITZERLAND)	●	●
Iteum Therapeutics Plc	Sulopenem, Sulopenem etzadroxil/probenecid	Phase III NDA submitted in Nov 2020 (US)	CARB-X Graduate: CARB-X awardees are required to develop a stewardship and access plan at the point of first market approval. Commercialisation Agreement, Eversana™	Yes (CARB-X Requirement)	●
LegoChem Biosciences Inc	Delpazolid (LCB01-0371)	Phase II	Licensing Agreement, HaiHe Biopharma Co. Ltd. (CHINA) Working Group on New TB Drugs (Stop TB Partnership)	Working Group on New TB Drugs (Stop TB Partnership)	●
Lumen Bioscience Inc	LMN-101	Phase II	Commitment to provide access in developing countries, and Bill & Melinda Gates Foundation Funding.	Yes (Bill & Melinda Gates Foundation Requirement)	●
Melinta Therapeutics Inc	Delafloxacin (Baxdela®)	Marketed	Licensing Agreement (Exclusive), Menarini Group (Italy) Licensing Agreement, Eurofarma Laboratories Co Ltd (BRAZIL)	●	●
Melinta Therapeutics Inc	Meropenem/vaborbactam (Vabomere®)	Marketed	Licensing Agreement (Exclusive), Menarini Group (Italy) Licensing Agreement (Exclusive), Hikma Pharmaceuticals Plc	●	●
MicRx Pharmaceuticals Inc (CHINA)	Contezolid (MRX-1)	Phase III NDA submitted in Dec 2020 (China)	Registration Filing (CHINA) Working Group on New TB Drugs (Stop TB Partnership)	Working Group on New TB Drugs (Stop TB Partnership)	●
Nabriva Therapeutics Plc	Lefamulin (Xenleta™)	Marketed	Licensing Agreement (Exclusive), Sinovant Sciences Ltd/Sumitomo Pharmaceutical Suzhou Co Ltd (CHINA) Named Patient Program (NPP), WEP Clinical (UK)	●	●
Paratek Pharmaceuticals Inc	Omadacycline (Nuzyra®)	Marketed	Licensing Agreement (Exclusive), Zai Lab Ltd (CHINA)	●	●
Qurient Co., Ltd	Telacebec (Q-203)	Phase II	Working Group on New TB Drugs (Stop TB Partnership)	Working Group on New TB Drugs (Stop TB Partnership)	●
Scynexis Inc	Ibrexafungerp (antifungal)	Phase III NDA submitted in Oct 2020 (US)	Compassionate Use Program Licensing Agreement (Exclusive) Hansoh Pharmaceutical Group Co. Ltd (CHINA) Commercialisation Agreement US only, Amplitude Health (US)	●	●
Sequella Inc.	Sutezolid	Phase II	The Global Alliance for TB Drug Development, STOP TB Partnership and WORKING GROUP on new TB DRUGS	The Global Alliance for TB Drug Development	●
Spero Therapeutics Inc	SPR-720	Phase II	Licensing Agreement (Exclusive), Bill & Melinda Gates Medical Research Institute	Yes (Bill & Melinda Gates Foundation Requirement)	●
Summit Therapeutics Inc	Ridinilazole	Phase III	Licensing Agreement (Exclusive), Eurofarma Laboratories Co Ltd (BRAZIL)	●	●
TenNor Therapeutics Ltd (CHINA)	TNP-2092	Phase II	No information available	●	●
La Jolla Pharmaceutical Co	Eravacycline (Xerava™)	Marketed	Licensing Agreement (Regional), Everest Medicine Ltd (CHINA)	Surveillance (Global In Vitro)	●
Vedanta Biosciences Inc	VE303	Phase II	CARB-X Graduate: CARB-X awardees are required to develop a stewardship and access plan at the point of first market approval. Bill & Melinda Gates Foundation Funding.	Yes (CARB-X Requirement)	●
Venatorx Pharmaceuticals Inc	Taniborbactam/Cefepime	Phase III	Licensing Agreement (Exclusive), GARDP Licensing Agreement (Exclusive), Everest Medicine Ltd (CHINA)	Stewardship and Responsible Use Commitment, GARDP	●
Wockhardt Ltd (INDIA)	Levonadifloxacin (Emrok) Alalevonadifloxacin (Emrok-O)	Marketed	Registration Filing (India)	●	●
Wockhardt Ltd (INDIA)	Nafithromycin (WCK-4873)	Phase III	Registration Filing (India)	●	●

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