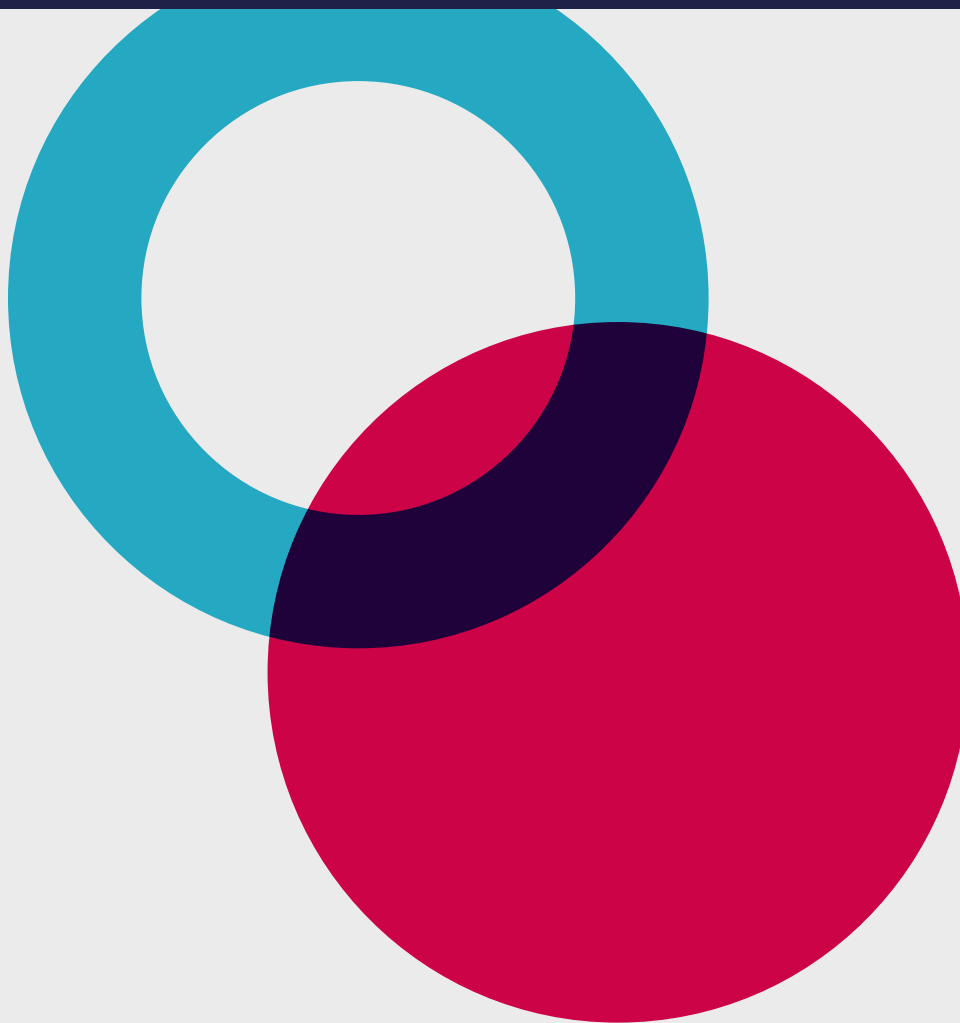


# TRACKING PROGRESS TO ADDRESS AMR

JANUARY 2018



## ABOUT THE AMR INDUSTRY ALLIANCE

The AMR Industry Alliance is a coalition of over 100 biotechnology, diagnostic, generics and research-based biopharmaceutical companies and trade associations that was formed to drive and measure industry progress to curb antimicrobial resistance. The AMR Industry Alliance will ensure that signatories collectively deliver on the specific commitments made in the Industry Declaration on AMR and the Roadmap and will measure progress made in the fight against antimicrobial resistance.

**[amrindustryalliance.org](http://amrindustryalliance.org)**

## ABOUT SUSTAINABILITY

SustainAbility is a consultancy and think tank enabling business to lead on the sustainability agenda.

**[sustainability.com](http://sustainability.com)**

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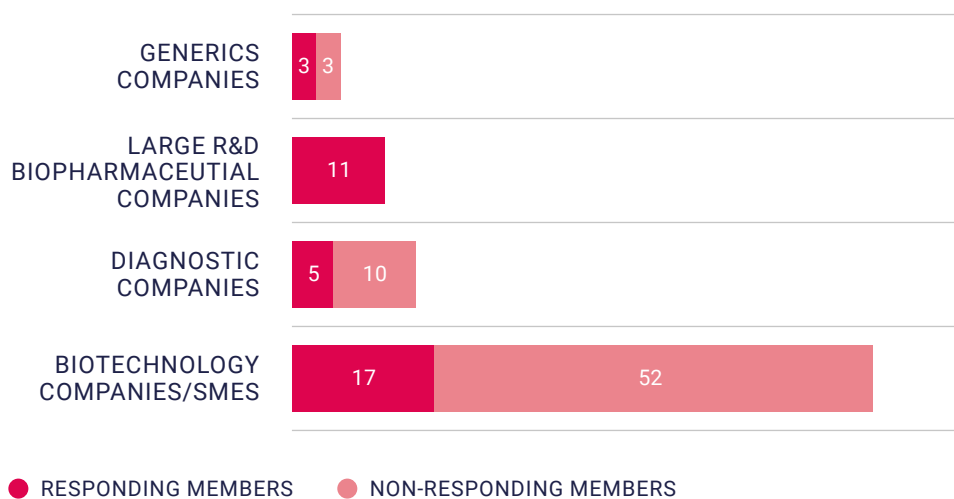
# 1

## EXECUTIVE SUMMARY

The AMR Industry Alliance is a diverse coalition of over 100 life sciences companies and associations working with stakeholders to address antimicrobial resistance (AMR). Industry has a role to play in a multi-sectoral response and is taking action against AMR, though there remain challenges to solve and gaps to close.

This is the Executive Summary of the AMR Industry Alliance's first progress report since members made commitments on AMR in the [Davos Declaration](#) in January 2016 and AMR [Industry Roadmap](#) in September 2016. The objective of the report is to identify best practice, opportunities, and gaps where further efforts may be required by industry and other stakeholders.

This report is based on analysis of the data collected from the survey responses of 36% of Alliance member companies (36 of 101) on their AMR-relevant products – therapeutic agents or technologies that have the potential to treat or prevent infectious diseases and/or combat resistance including but not limited to antibiotics, vaccines, diagnostics and novel approaches to address AMR – as well as insights from the Alliance's Working Groups and SustainAbility. This number covers all four categories of life sciences players and provides a rich source of data for analysis. However, it ultimately represents a sub-set of the total Alliance member companies, rather than Alliance members as a whole or the broader industry.



**BREAKDOWN OF ALLIANCE MEMBERS COMPANIES THAT RESPONDED TO THE AMR ALLIANCE INDUSTRY SURVEY BY SECTOR.**



Based on a rigorous analysis of the survey results, a number of observations have been made regarding the collective action the life sciences industry is taking to meet its commitments in the Davos Declaration and Roadmap to proactively address the looming public health AMR crisis. Gaps remain. The key conclusions from the report are described below.

## RESEARCH & SCIENCE

Industry is investing in AMR-relevant R&D but current activities are threatened. Urgent action is needed to address economic challenges to AMR-relevant R&D.

- Alliance members collectively invested at least USD 2 billion in 2016 in AMR-relevant R&D.\*
- Alliance members are active in early-stage research targeting bacteria that pose the greatest threats to human health as identified by public health bodies, including the World Health Organization (WHO) and U.S. Centers for Disease Control and Prevention (CDC). Two-thirds of responding companies are pursuing compounds with innovative mechanisms of action in early-stage R&D. Seven companies are working on novel, non-antibiotic approaches to address AMR.
- More than three-quarters of responding companies with R&D activity relevant to AMR have had one or more AMR-relevant products in late-stage (phase II or III) of development in the last five years.
- Responding companies report:
  - 10 antibiotics with activity against WHO priority 1 or 2 pathogens or CDC Urgent or Serious threats
  - 13 AMR-relevant vaccine candidates
  - 18 AMR-relevant diagnostic products
- Industry investment is threatened: Over 90% of responding companies viewed current progress on R&D incentives as either “promising but far to go” or “insufficient relative to the challenge”. If substantial mechanisms to support new R&D such as new pull incentives, and commercial models improve, 72% of responding companies are most likely to increase investments in this area. On the other hand, of those companies that are active in R&D, 30% said they would likely decrease investment in this area if no new incentives are established and commercial models remain as they currently are. This proportion rises to 50% if considering only large R&D biopharmaceutical companies.
- Pull incentives must be sustainable and sufficient to stimulate R&D across the full R&D lifecycle, from discovery through development, to see an impactful long-term change on the pipeline of new products.

\* This is the 2016 financial investment reported by 22 responding companies. It includes direct project and staff costs for early- and late-stage R&D on AMR-relevant products. It does not include financial investments made by other Alliance companies.

## APPROPRIATE USE

Many Alliance companies are actively engaged in activities to promote appropriate use of antibiotics, including patient and provider education, surveillance to monitor drug resistance, and a review of promotional practices. However, more can be done. Vaccines and diagnostics will be key to successfully implementing appropriate use.

- Over 80% of all responding companies are engaged in activities to support appropriate use. Nearly half of responding companies have a formal appropriate use strategy in place. These strategies cover nearly half of all antibiotics currently marketed by responding companies. While there is a strong indication of action being taken in this area, the Alliance recognizes that all antibiotics manufacturing companies should be concerned with appropriate use.
- Nearly 90% of responding companies – and 70% of those with marketed AMR-relevant products – are planning to, currently collecting or supporting the collection of surveillance data.
- More than half of responding companies – and 70% of those with marketed AMR-relevant products – are planning to or are currently engaged in stewardship education activities, directly or collaboratively.
- 70% of responding companies have examined, or are intending to examine, their promotional activities to ensure that they are consistent with the goal of advancing stewardship, which is progress towards a Roadmap commitment.
- Alliance members recognize that there is significant potential for vaccines and diagnostics. Developments in diagnostics can optimize treatment for individual patients and facilitate epidemiological surveillance. The successful development of vaccines and achieving universal vaccination for high burden diseases will be important milestones in the fight against AMR.

## ACCESS

Alliance companies are working with other stakeholders to expand appropriate access to antibiotics, though more work is needed to determine how to increase access within the context of stewardship. Alliance companies are taking action to reduce the prevalence of substandard and falsified products.

Of responding companies with marketed AMR-relevant products:

- Three-quarters have strategies, policies or plans in place that include principles or efforts to improve access to their AMR-relevant products.
- 88% are engaged in dialogues with external stakeholders on access to their products.
- Nearly half report having specific strategies in place to help reduce the prevalence of substandard and falsified products.
- Nearly two-thirds (representing large R&D biopharmaceutical and generics companies) took action to address delays or supply chain disruptions to at least one of their AMR-relevant products. In almost all cases, these companies had well-defined and robust processes in place for identifying and addressing product continuity issues – for instance, working with medical experts to identify possible medical alternatives.



## MANUFACTURING & ENVIRONMENT

Alliance companies, particularly those that made bold commitments in the Roadmap, are taking action to reduce the potential impacts of antibiotics manufacturing on AMR. There has been progress against these commitments, and more is expected in 2018.

- In 2017, many Roadmap signatories assessed the potential impact of their internal manufacturing and supply chain on AMR.
- Roadmap signatories have shared their knowledge, expertise and experience to develop a common framework for managing antibiotic discharge and have committed to start to apply it across their internal manufacturing and supply chain by the end of 2018, on track with Roadmap commitments. Additional companies have signaled they will adopt the requirements of the framework.
- Three-quarters of responding Roadmap companies anticipate beginning to implement good practice methods to reduce environmental impact of manufacturing discharge by 2018, in advance of the 2020 Roadmap commitment.
- Of responding companies that produce antibiotics, one-third have in place a current strategy, policy or plan that addresses the issue of the release of antibiotics in internal manufacturing effluents that may contribute to AMR. Two-thirds of these extend to their suppliers and supply chains.
- To address the environmental concerns related to manufacturing, all antibiotics manufacturers need to take action, and the Alliance encourages all manufacturers of antibiotics to have policies and practices in place to improve environmental management in their own manufacturing and supply chain.

## NEXT STEPS

The activities and progress reported on in this first report by the Alliance since the Davos Declaration are only a part of the global response to AMR. This report presents the initial progress in combatting AMR made by responding Alliance companies. Given that only 36% of Alliance member companies responded to our survey, further effort is needed to assess and drive progress against the commitments by all signatories of the Davos Declaration.

The Alliance will actively support member companies in filling in the gaps ahead of the next update. This will include greater outreach to non-responding companies, as well as efforts to share best practices and supporting materials. In particular, we will work with stakeholders to better understand what steps industry needs to take to impact the most critical areas.

The Alliance is committed to reporting on progress every two years. The next progress report will be published in 2020.



## CALL TO ACTION

There are gaps to close, and more can be done by Alliance members and the broader life sciences industry to address AMR. Collaboration within the industry is vital. The Alliance will reach out to all companies with AMR-relevant products that are committed to the goals of the Davos Declaration to join the initiative as it seeks to increase coverage of the market of AMR-relevant products.

Other stakeholders – including but not limited to other sectors, governments, international organizations, NGOs and academia – also have roles to play. The Alliance reinforces the call to action to governments made in the Davos Declaration to implement incentives that enable sustainable investment in AMR.

The Alliance calls on all stakeholders to move beyond statements of intent and take concrete action to address AMR. The Alliance will work with and support members and relevant stakeholders progressing on AMR.

# 2

## INTRODUCTION

### THE THREAT OF AMR

Antimicrobial resistance (AMR) occurs when a microorganism (such as bacteria, viruses, fungi and parasites) evolves to stop an antimicrobial (such as antibiotics, antivirals and antimalarials) from working against it.<sup>1</sup> While the evolution of AMR is a natural and inevitable process, the rate and spread of AMR has been accelerated by the inappropriate use of antibiotics.

AMR is a growing threat to global public health and development, with the potential to put at risk the effective treatment of a wide range of infections and jeopardize healthcare gains to society that rely on the ability to effectively treat infections. Each year at least 700,000 people die because of drug-resistant infections and 480,000 people develop multi-drug resistant tuberculosis.<sup>2</sup> Due to resistance to antibiotics, treatment for some common infections are proving ineffective in more than half of patients in many parts of the world.<sup>3</sup> AMR is present in every country around the world and infections caused by drug-resistant bacteria can cause death. This is an urgent problem that affects us all.

The nature and scale of this challenge requires collaboration across governments, the global life sciences industry, healthcare providers, civil society and patients to ensure effective and rapid action to combat AMR.

### SHARED SOLUTIONS AND INDUSTRY'S ROLE

The global life sciences industry and the members of the AMR Industry Alliance can help provide solutions to AMR. We need the capacity of business to innovate and execute, meeting patient, societal and market needs swiftly, effectively and around the world.

- Research and development for new antibiotics, vaccines, diagnostics and novel approaches
- Encouraging appropriate use, through the development and uptake of effective vaccines and diagnostic tools as well as the education of healthcare providers and the public
- Collaboration with other stakeholders to expand access
- Working to support measures to reduce environmental pollution from antibiotics manufacturing

With members from over 100 research-based pharmaceutical, generics, biotechnology and diagnostic companies and trade associations, the AMR Industry Alliance has the potential and is committed to contribute to the global response to AMR. Governments have a key role to play to slow the spread of AMR and create an environment that supports sustainable investment in AMR-relevant innovation and access. Collective action is needed to confront the global threat of AMR. Industry is ready to play its part.

# 3

## FOREWORD – AMR INDUSTRY ALLIANCE

AMR is recognized as one of the most serious health concerns worldwide. The G7, G20, WHO and many world leaders have acknowledged the growing dangers AMR presents.

AMR could force us back to a time when people feared common infections and minor surgery could prove fatal. Indeed, the WHO warned this year that this “global health emergency” threatens to undo decades of progress made by modern medicine.<sup>4</sup> Common surgical procedures such as hip replacement and treatments such as chemotherapy all require antibiotics to ward off infections.

### GROUND-BREAKING, CROSS-LIFE SCIENCES INDUSTRY ALLIANCE

A unique group of 101 companies from across the life sciences industry, the AMR Industry Alliance was established to support proactive actions taken by companies, enable coordination across the entire life sciences industry, and help hold the industry accountable to commitments it has made in the Davos Declaration and Roadmap, all towards the goal to address this challenge.

In this first report, we discuss how members of the Alliance are actively responding. We set out to collect data from all members, and intend to improve on the 36% response rate. This report presents the initial progress in combatting AMR made by responding companies from the Alliance’s biotechnology, large R&D biopharmaceutical, diagnostic and generics membership.

This effort is ground-breaking for several reasons. It is the first time that life sciences companies have joined together in working towards a common goal of tackling and contributing to overcoming AMR. Moreover, they have agreed to report jointly and share information on their progress in responding to the AMR emergency in four key areas: R&D, appropriate use, access to treatment, and reducing manufacturing’s impact on the environment. To guide us in this unique venture, the Alliance has reached out to a distinguished group of external experts on AMR from around the world to listen and learn from them.

**Thomas Cueni**, AMR Industry Alliance

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"Our ambition is to create the positive momentum that will incentivize other companies to join and become involved in global efforts and local action."

## ONE OF THE MOST CHALLENGING INNOVATION ENVIRONMENTS

Discovering new antibiotics, developing new vaccines, creating new diagnostics, making better use of existing products (including dosages, formulations and generics), ensuring access to effective treatments, and guaranteeing responsible use of existing antibiotics is not for the faint-hearted. This is one of the most challenging innovation environments that the life sciences industry knows. Even in normal circumstances, discovering and developing new drugs can take between ten to fifteen years to reach the marketplace and the risk for investors is high; each year many biotech companies go under in this protracted process. Antibiotics, however, present even greater challenges: bacteria have always been able to protect themselves from naturally-occurring antibiotics by evolving resistance. As soon as an antibiotic is used, its long-term effectiveness is limited as it also drives resistance. R&D is therefore a constant necessity.

Today, the number of antibacterials becoming obsolete due to resistance exceeds the number of new therapies being approved. We have not had a new class of antibiotics approved since the 1980s.<sup>5</sup> In addition, there is a unique market dynamic at work with antibiotics: new treatments are kept in reserve as much as possible, and this makes it hard for companies to get sufficient and predictable returns on their investments. Clinical trials face mounting recruitment and regulatory hurdles. Nevertheless, today there are around 50 new antibiotics under clinical development, but many more will be required to keep ahead of resistance.<sup>6</sup> The report shows the importance of the private sector in tackling AMR. In 2016 alone, Alliance members made investments to address the current and future medical needs that result from AMR to the tune of at least USD 2 billion. However, there is no denying that the economic environment for high risk investments in R&D to tackle AMR is fragile and there is still a long way to go. We will not be able to fully address this public health challenge without sustainable incentives to encourage more long-term investment in R&D for new medicines, vaccines and diagnostics.

## BALANCING ACCESS AND APPROPRIATE USE

While scientists seek solutions to the AMR crisis, medical practitioners and clinicians face different dilemmas. They may be unable to help a mother whose baby has an infection, either because it is multi-drug resistant or essential antibiotics are not available. The fact that many antibiotics are cheaper than diagnostics does not make the case easier. Or they may delay appropriate treatment or compound a patient's illness by over-prescribing or incorrectly prescribing antibiotics. These and other dilemmas highlight the need to strike the right balance between facilitating access while ensuring appropriate use. This report shows that Alliance companies acknowledge that appropriate use is important and are addressing it in many areas. However, here too there is a considerable way to go, particularly in fully exploring the potential of vaccines and diagnostics. There are also efforts underway to examine promotional activities to ensure that they are consistent with the goal of advancing stewardship.

## ALLIANCE UNLOCKING NEW WAYS OF THINKING

Finding creative and sustainable solutions to AMR requires thinking outside the box. By reporting on what the Alliance companies are doing in this report, we hope to inspire a new way of thinking, which is both more holistic and tailored to different country needs. The diverse Alliance membership allows us to formulate a range of such solutions. Breaking down traditional silos across the life sciences value chain is key. We need the integrated deployment of vaccines and medicines, diagnostics, antibiotics and other therapies to address the multiple challenges across the continuum of care – from prevention, monitoring and screening to treatment. We also need the right incentives – targeted, supportive of appropriate use and sustainable over the long-term – to support the R&D behind this deployment.

The light the Alliance shines on different companies' activities offers invaluable insights into the tangible



steps being taken, their successes and challenges. This transparency, we hope, encourages other companies to make proactive contributions, collaborate further and do more to address AMR. These examples illustrate how Alliance companies are collaborating with governments, academia, think tanks, patient and professional organizations, NGOs, public private partnerships, product development partnerships and foundations.

## **SPREADING THE WORD AND CALLING ON MORE COMPANIES TO JOIN THE ALLIANCE**

The AMR Industry Alliance is already a significant coalition but so far represents only a portion of the companies involved in addressing AMR. The Alliance is a heterogeneous group and its members start from different places: some have been at the forefront of the fight against AMR for several years already while others are just starting. Crucially, all partners share the same goal. Our ambition is to tackle the spread of AMR and discover and develop new vaccines and therapies for the benefit of patients, rich or poor. We want to create a positive momentum that will incentivize other companies to join and become involved in global efforts and local action to reach that goal. In a year's time, we hope to have created a domino effect – with more companies reporting positively on their efforts and achievements. We call for more life sciences companies, particularly SMEs and generics, to join the Alliance and contribute to their experience and plans.

## **SHARED GOAL AND INVITATION TO JOIN, COMMENT AND ACT**

The fight against antimicrobial resistance will take decades, and the life sciences industry is committed for the long haul. However, the full impact of industry's efforts can only be made through collaboration with governments and providers, and other public health stakeholders. We hope this report offers valuable insights to decision-makers in global health on how we can work together to defeat AMR.

**Thomas Cueni**

Chairperson, AMR Industry Alliance

# 4

## FROM THE AUTHORS: SUSTAINABILITY

SustainAbility is committed to “making the future the cause of the present.”

We also have a long history of working with the life sciences industry. We feel privileged to partner with the AMR Industry Alliance to help measure and report on the progress of biotechnology, diagnostic, generics and research-based biopharmaceutical companies and trade associations to curb AMR.

We worked closely with the AMR Industry Alliance members to develop the most relevant metrics to track their progress (see About this Report and the Appendix for further information). We recognize that this is an entirely new effort for the industry, and this first reporting exercise creates awareness, builds knowledge and lays the groundwork for greater coordination, collaboration and action in the future.

We anticipate more AMR Industry Alliance members will continue to make progress against commitments, deliver on new solutions, expand their work with other stakeholders, and report on their activities between now and the next progress report to be published in 2020. We encourage additional companies to join the AMR Industry Alliance efforts.

Our shared future, articulated in the UN Sustainable Development Goals, is threatened by AMR. Industry clearly has a role to play on AMR; no single actor can combat it alone. We believe in the potential of the AMR Industry Alliance’s work, demonstrated by transparent reporting on the right metrics and in collaboration with the efforts of other stakeholders, to be part of the solution.

**Denise Delaney**  
Director, SustainAbility

**Denise Delaney**, SustainAbility



“We believe in the potential of the AMR Industry Alliance’s work, demonstrated by transparent reporting on the right metrics and in collaboration with the efforts of other stakeholders, to help combat the threat of AMR.”

# 5

## ABOUT THIS REPORT

This is the AMR Industry Alliance's first progress report since the Davos Declaration was signed in January 2016. It identifies best practice, opportunities, and gaps where further efforts may be required. The Alliance will reflect and report on progress and changing priorities every two years.

### FROM COMMITMENTS TO METRICS

With SustainAbility, the AMR Industry Alliance translated the commitments made in the [Davos Declaration](#) and the [Industry Roadmap to Combat Antimicrobial Resistance](#) (see The Evolution of the AMR Industry Alliance and Appendix for more on these documents) into metrics across four different areas: Research and Science, Appropriate Use, Access, and Manufacturing and Environment. This was done in consultation with experts from the AMR Industry Alliance Board and working groups of representatives of member companies, including experts in the four commitment areas.

### DATA COLLECTION AND AGGREGATION

SustainAbility translated the AMR Alliance metrics into questions and developed a survey to collect data from members on their progress. All Alliance members had the opportunity to respond.

The AMR Industry Alliance members have a wide range of expertise and work in many different environments. Each commitment area has a particular scope, which impacts considerations of the results provided in this report.

The following commitment area is relevant to all responding companies that have AMR-relevant R&D activity:

- Research & Science

The following commitment areas are relevant to sub-sets of companies (e.g., those with post-marketing authorization experience and/or manufacture antibiotics):

- Access
- Appropriate Use
- Manufacturing & Environment



All data has been anonymized and aggregated, with the exception of specific examples of company activities, representing best practice and lessons learned, where explicit permission has been given.

Further information about the methodology, the assumptions underlying the metrics, and the scope, can be found in the Appendix.

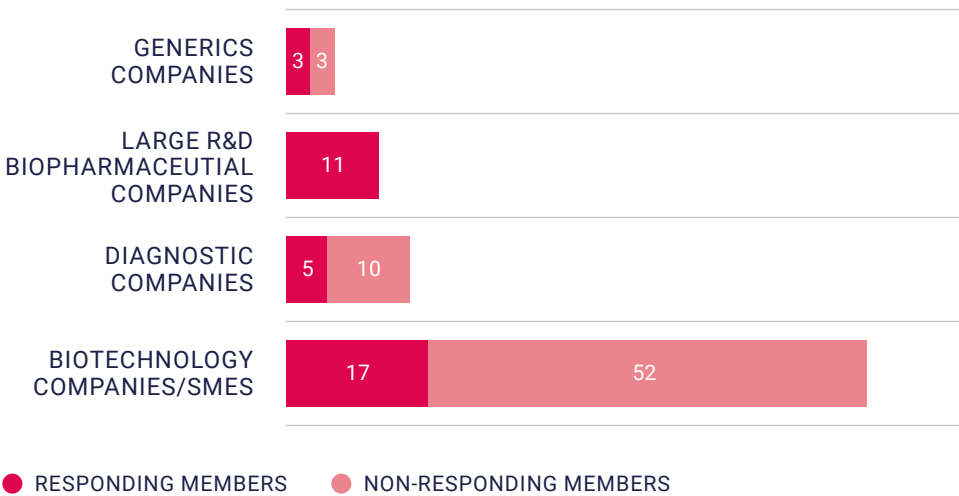
### ALLIANCE MEMBER PARTICIPATION

All Alliance members were invited to submit data through a survey tool. This report is based on analysis of the data collected from the survey responses of 36% of Alliance member companies (36 of 101) as well as insights from the Alliance’s Working Groups and SustainAbility. This number represents a sub-set of the total Alliance member companies, so it may not be representative of the Alliance or the broader industry. However, the 36 responses cover all four categories of life sciences players. All large research-based biopharmaceutical companies, about half of the generics and diagnostics companies, and a smaller proportion of biotechnology companies/SMEs responded (due to their day-to-day operational challenges), providing a rich source of data for analysis.

The varying response rate somewhat limits the conclusions that can reliably be drawn across the entire Alliance membership and the broader life sciences industry. All results documented in this report refer to the sub-set of responding companies.

All member companies are listed in the Appendix; responding companies are marked with an asterisk (\*).

The Alliance will work to increase participation in subsequent surveys. The spirit of the Alliance is one of inclusion and its diverse membership group brings together companies from different sectors. Some of those companies are small, with limited resources or staff, and with many demands on their time. These operational realities kept many biotechnology companies from participating in the AMR Industry Alliance survey. The Alliance is committed to working with all member companies to encourage participation and make progress reporting more accessible in future iterations.



**FIGURE 1: BREAKDOWN OF ALLIANCE MEMBER COMPANIES THAT RESPONDED TO THE AMR ALLIANCE INDUSTRY SURVEY BY SECTOR.**

## DEFINITIONS OF FREQUENTLY USED TERMS

### **AMR-relevant products**

Any product that has the potential to treat or prevent bacterial infections, or otherwise impact the development of resistance, including but not limited to antibiotics, vaccines, novel approaches and diagnostics.

### **Large biopharmaceutical companies**

Large research-based pharmaceutical companies.

### **Biotechnology companies and SMEs**

Small and medium-sized research-based companies.

### **Generics companies**

Manufacturers of pharmaceuticals equivalent to original reference brand-name products in dosage, strength, route of administration, quality, performance and intended use.

### **Diagnostic companies**

Companies developing and producing medical diagnostic tests and technologies.

## FREQUENTLY USED ABBREVIATIONS & ACRONYMS

**ACIP:** Advisory Committee on Immunization Practices

**AMR:** Antimicrobial resistance

**AMS:** Antimicrobial stewardship

**APIs:** Active pharmaceutical ingredients

**BARDA:** U.S. Department of Health and Human Services, Biomedical Advanced Research and Development Authority

**BEAM Alliance:** Alliance of Biopharmaceutical companies from Europe innovating in Anti-Microbial resistance research

**BIO:** Biotechnology Innovation Organization

**BMGF:** Bill and Melinda Gates Foundation

**CARB-X:** Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator

**CDC:** U.S. Centers for Disease Control and Prevention

**DNDi:** Drugs for Neglected Diseases Initiative

**EFPIA:** European Federation of Pharmaceutical Industries and Associations

**EMA:** European Medicines Agency

**EML:** Essential Medicines List (developed by the WHO)

**EU:** European Union

**FDA:** US Food and Drug Administration

**FIND:** Foundation for Innovative New Diagnostics

**GARDP:** Global Antibiotic Research and Development Partnership

**G20:** The Group of 20 (Argentina, Australia, Brazil, Canada, China, France, Germany, India, Indonesia, Italy, Japan, South Korea, Mexico, Russia, Saudi Arabia, South Africa, Turkey, United Kingdom and United States, plus the European Union)

**G7:** The Group of Seven (Canada, France, Germany, Italy, Japan, United Kingdom, and United States)

**Gavi:** The Vaccine Alliance (formerly the Global Alliance for Vaccines and Immunisation)

**HICs:** High-income countries

**ICBA:** International Council of Biotech Associations

**IDSA:** Infectious Diseases Society of America

**IFPMA:** International Federation of Pharmaceutical Manufacturers & Associations

**IMI:** Innovative Medicines Initiative

**IPC:** Infection prevention and control

**IVR:** Initiative for Vaccine Research (by WHO)

**JPIAMR:** EU Joint Programming Initiative on AMR

**LDCs:** Less Developed Countries

**LICs:** Low-Income Countries

**LMICs:** Lower and Middle-Income Countries

**MDR:** Multi-drug resistant

**ND4BB:** New Drugs for Bad Bugs

**NGO:** Non-governmental organization

**NIH:** US National Institutes of Health

**OTC:** over-the-counter

**PPL:** Priority Pathogen List (developed by the WHO)

**PMDA:** Pharmaceutical and Medical Devices Agency (Japan)

**PNEC:** Predicted-No-Effect-Concentration

**R&D:** Research and development

**SDGs:** UN Sustainable Development Goals

**SMEs:** Small and medium-sized enterprises

**TB:** Tuberculosis

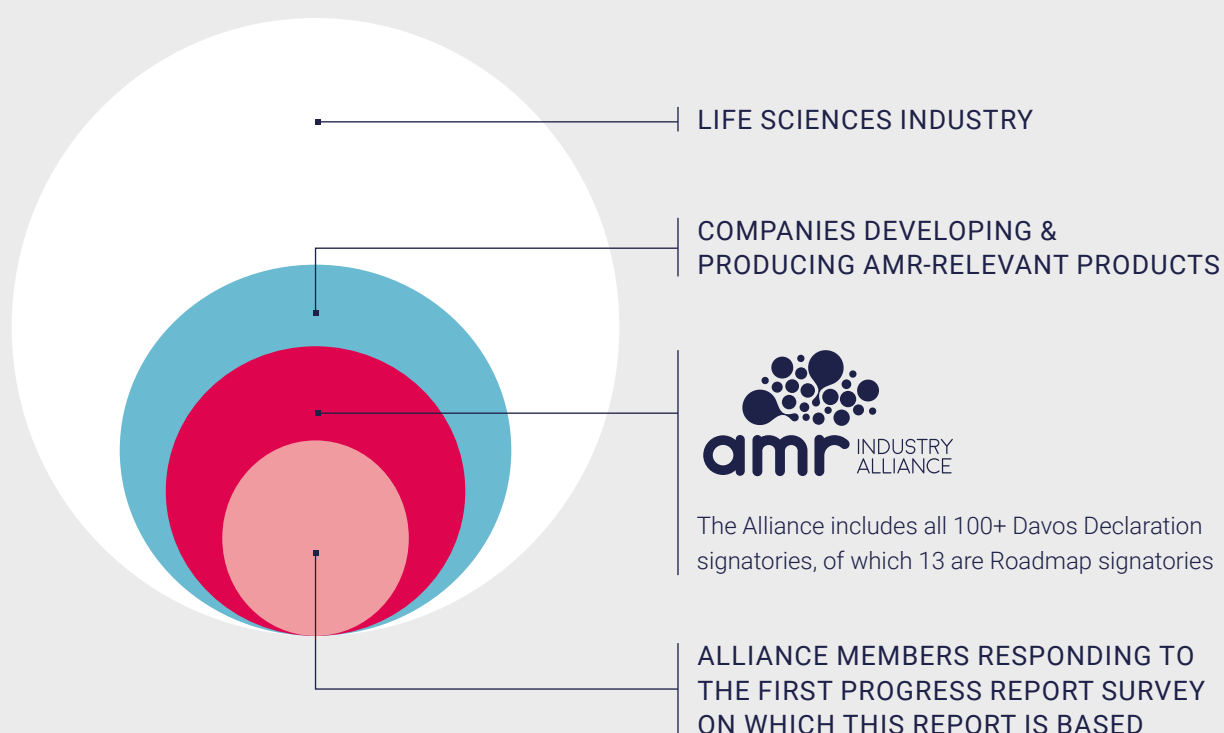
**UN:** United Nations

**USD:** US dollar

**WHO:** World Health Organization

# 6

## THE EVOLUTION OF THE AMR INDUSTRY ALLIANCE





Collective action is needed to confront the global threat of AMR. Industry is ready to play its part.

Awareness of and action against the challenge of AMR has strengthened considerably in the last decade and across many actors.<sup>7</sup>

Action by multiple stakeholders will be critical to solving this complex issue; it cannot be done by one government, company or healthcare system. Governments have a key role to play to slow the spread of AMR and create an environment that supports sustainable investment in AMR-relevant innovation and access. Collective action is needed to confront the global threat of AMR. Industry is ready to play its part.

The global life sciences industry and the members of the AMR Industry Alliance can help provide solutions to AMR. The industry has a role to play as part of broader efforts to manage the threat of AMR:

- Research and development for new classes of antibiotics and mechanisms;
- Collaboration with other stakeholders to make treatments available where access is lacking;
- Support stewardship by developing and encouraging the uptake of effective vaccines and diagnostics tools.

Recognizing their role in addressing AMR, over 100 organizations – 6 generics companies, 11 large R&D biopharmaceutical companies, 15 diagnostic companies, 15 industry associations, and 69 biotechnology companies – from more than 20 countries stepped up with a firm commitment at the World Economic Forum in Davos in January 2016

and signed the **Industry Declaration on AMR** (Davos Declaration). The Declaration sets out commitments to further action on AMR by its signatories, across three broad areas. Signatories commit to:

- Work to reduce the development of AMR;
- Invest in R&D to meet public health needs with new innovative diagnostics and treatments;
- Improve access to existing high-quality antibiotics and ensure that new ones are available to all patients, as medically appropriate.

The Davos Declaration also calls on governments to work with these organizations to develop “new and alternative market structures that provide more dependable and sustainable market models for antibiotics.” The Declaration states that new mechanisms are needed to provide appropriate incentives (coupled with safeguards to support antibiotic conservation) “for companies to invest in R&D to overcome the formidable technical and scientific challenges of antibiotic discovery and development.” These include mechanisms to ensure that, where appropriate, the valuation of antibiotics more adequately reflects the benefits they bring, and the introduction of novel payment models that reduce the link between the return on investment of an antibiotic and the volume sold.

In September 2016, at the UN High Level Meeting on AMR, 13 Alliance member companies released a set of specific commitments on AMR in the **Industry Roadmap for Progress on Combating Antimicrobial Resistance**. The Roadmap includes four areas of commitments related to: research and science, appropriate use, access, and manufacturing and the environment.

In May 2017, during the G20 Health Conference, the **AMR Industry Alliance** was formed (representing signatories of the Davos Declaration) to advise, drive and monitor industry progress and ensure collective delivery on the Davos commitments.

These areas of commitment are reflected in the metrics developed and industry's progress against these commitments in this report. It describes how industry's activities and contributions are helping to address the shared challenge of AMR and identifies gaps where more collective action is needed.



## RESEARCH & SCIENCE



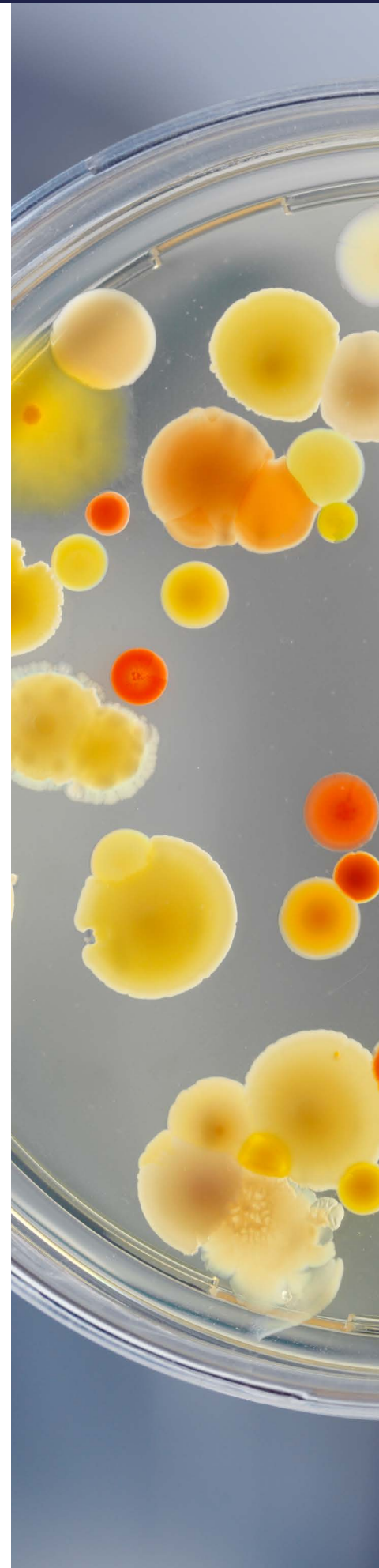
## APPROPRIATE USE



## ACCESS



## MANUFACTURING & ENVIRONMENT











# 7

## RESEARCH & SCIENCE



As resistance develops, there are fewer options to treat bacterial pathogens. Part of the solution is the development of new products. This section explores why the rate of development of new treatments has slowed, what industry is doing about it and where critical challenges remain.

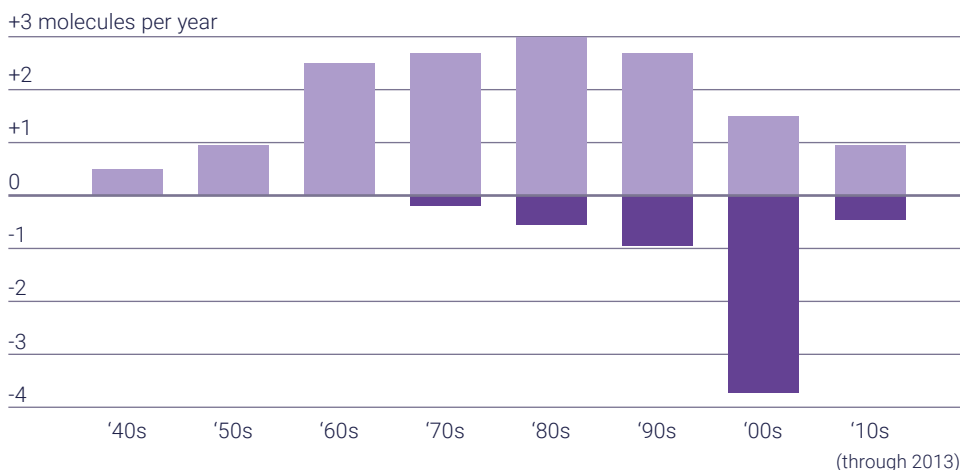
## 7.1 BACKGROUND AND CHALLENGES

There is mounting concern over the limited number of compounds in the development pipeline to address AMR. The rate at which antibiotics are becoming ineffective due to resistance exceeds the rate at which new therapies are being developed. This is leading to a shrinking pool of treatment options.<sup>8</sup>

No new classes of antibiotics have been approved since the 1980s.<sup>9</sup> Despite widespread acknowledgement by all stakeholders, including the life sciences industry, that the development pipeline is likely insufficient to meet the need for new antibiotics, the number of companies with active R&D in AMR-relevant products has declined. The WHO has identified 51 new antibiotics and biologicals in clinical development to treat priority antibiotic-resistant pathogens.<sup>10</sup> According to the WHO, this “could lead to around 10 new approvals over the next five years.” This is a fraction of approvals expected

in other areas of healthcare, such as oncology, and only partially addresses the top drug-resistant threats.

Poor discovery prospects, combined with weaker returns, means that many major drug companies have cut back or left the AMR R&D space altogether. In 1990, there were at least 18 large biopharmaceutical companies developing antibiotics<sup>11</sup>, today, there are eight. Much of the current pipeline is focused on incremental innovation based on existing classes or compounds. Some companies, particularly new biotechnology companies/SMEs, are working on new classes, mechanisms of actions, and novel approaches to address AMR. However, these products may never be developed or brought to market without additional investment from large pharmaceutical companies or private investors.



**FIGURE 2:**  
AVERAGE NEW  
ANTIBIOTIC  
MOLECULES PER  
YEAR.

● DEVELOPED  
● MADE OBSOLETE

**Source:**  
Michael S. Kinch, Denton  
Hoyer, et. al, Yale Center  
for Molecular Discovery



## DISCOVERY AND DEVELOPMENT OF PRODUCTS TO MITIGATE AMR PRESENTS SPECIFIC CHALLENGES

As with all therapeutic areas, R&D of new antimicrobial medicines and other relevant products, such as vaccines and diagnostics, is a time, resource and risk-intensive endeavor. Developers and manufacturers of antibiotics face three main types of challenges:

### SCIENTIFIC

The existence of multiple resistance mechanisms presents immense scientific challenges to the discovery of new antibiotics, particularly those that are effective but not toxic to the patient.

### REGULATORY

Placebo-controlled trials for serious bacterial infections are unethical, so novel antibiotics are approved based on non-inferiority trials (i.e. to show that a new treatment is 'not unacceptably worse' than the current standard therapy). Finding and enrolling sufficient patients with drug-resistant infections in clinical trials is difficult, so trials are usually small and expensive.

### ECONOMIC

- Novel antibiotics are generally undervalued by reimbursement systems relative to the benefits they bring society. Current Health Technology Assessments do not consider the broader benefits, such as delayed resistance or enablement of other procedures, in their value frameworks. Generic antibiotics are generally effective for patients without resistant infections. This, combined with results from smaller, non-inferiority clinical trials, makes clinical differentiation of novel antibiotics versus standard of care difficult and negatively impacts pricing and reimbursement negotiations.
- Uptake of novel antibiotics is slow, since they are usually used sparingly to preserve effectiveness when resistant infections are relatively rare and there may be limited availability of appropriate diagnostics and surveillance data.
- Reimbursement systems, including hospital bundled-payment mechanisms, can discourage use of novel antibiotics, even when they are the most appropriate treatment for a patient.



AMR-relevant vaccines face particular scientific and regulatory barriers. For instance, their target population is generally much smaller, more vulnerable and with patients more likely to possess weaker immune systems, reducing the likelihood that the vaccine is fully effective.<sup>12</sup> This central challenge, combined with the additional regulatory approvals required in some countries, creates a tough economic outlook.

The key challenges in diagnostics innovation, on the other hand, are market-based. The value that rapid diagnostics could deliver in reducing unnecessary use of antibiotics is not fully reflected in their pricing. Furthermore, demand for diagnostics is suppressed because of a combination of real and perceived issues relating to “cost-effectiveness, and a perceived mismatch between what is needed and what is on offer.”<sup>13</sup>

More R&D must be focused on preventative therapies and novel approaches.

Push and pull incentives must be sustainable and sufficient to stimulate R&D, from discovery through development, to see an impactful long-term change in the pipeline of new products.

## BEAM ALLIANCE: ASSOCIATION OF EUROPEAN-BASED SMEs ON AMR

Globally, approximately 250 biotechnology companies are focused on developing new drugs and approaches to combat AMR. SMEs are investing in a diversity of innovative R&D approaches, both antibiotic (broad spectrum, narrow spectrum, phages) and non-antibiotic (anti-virulence, anti-biofilm, vaccine and other immune-modulating approaches, decolonization/decontamination).

SMEs in the field of AMR are pioneers, operating in a financial ecosystem where funding, performing and partnering R&D is less than optimal. Initiated in 2015, the BEAM Alliance, Biotech companies from Europe innovating in AntiMicrobial resistance research (BEAM), represents over 40 SMEs supporting the AMR Industry Alliance as signatories to the Davos Declaration. Altogether, BEAM Alliance members are investing in over 120 R&D projects relevant to the treatment of resistant bacterial infections, from early stage to clinical stage development and with over 80% based on novel targets.

BEAM Alliance reports on its progress in the field of AMR to governmental, regulatory and NGO stakeholders and in early 2018 will publish an online tool showing the consolidated R&D pipeline of its members. In November 2017, BEAM published its second position paper (see BEAM position paper<sup>14</sup>).

## 7.2 AMR INDUSTRY ALLIANCE ACTION TO DATE

In the Davos Declaration, Alliance members commit to “invest in R&D to meet public health needs with new innovative diagnostics and treatments.” This could include:

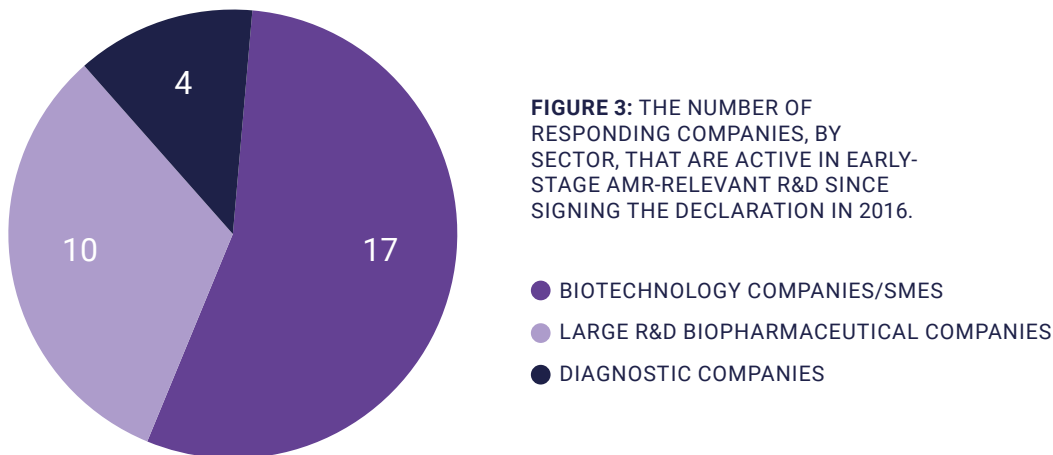
- Advancing their own pipelines
- Supporting work by others, including academia, on new and re-purposed antibiotics
- Responding to proposals for increased investment via coordinated global routes to develop diagnostics, antibiotics, vaccines, and new technologies
- Working in new ways, including open collaboration
- Working with payers and policymakers on new reimbursement and valuation mechanisms, and commercial models that specifically address the unique challenges of this market.

The Industry Roadmap further emphasizes collaboration, including precompetitive collaboration, clinical trial networks and data exchange, and calls for progress on incentives for further R&D investment.

Despite economic and technical challenges, the industry is investing in R&D to meet AMR and public health needs and a multitude of approaches are being pursued.

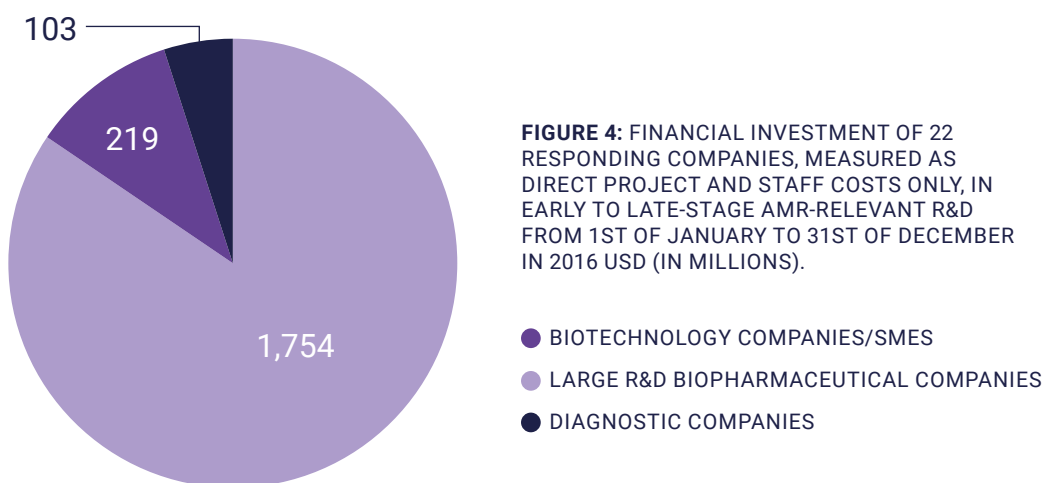
## ALLIANCE COMPANIES ARE ACTIVE IN EARLY-STAGE R&D

Of the 36 companies that responded to the AMR Industry Alliance survey, 31 are active in early-stage research and development to address AMR. The breakdown by sector is expressed below. All but one of the responding companies with relevant R&D activities in the last two years are active in early-stage research, which is defined for the purposes of this report as “basic, discovery, preclinical and phase I of research and clinical development.”



## ALLIANCE COMPANIES ARE INVESTING AT LEAST USD 2 BILLION ANNUALLY IN R&D FOR AMR-RELEVANT PRODUCTS

In 2016, 22 Alliance members invested at least USD 2 billion in research and development dedicated to AMR-relevant products (measured as direct project and staff costs only, in early to late-stage AMR-relevant R&D from 1st of January to 31st of December in 2016 USD). This is a conservative estimate of private sector investment in annual AMR R&D, since not all responding companies provided information on their R&D investments. Of the 22 responding companies, 12 were biotechnology companies/SMEs, seven were large R&D biopharmaceutical companies, and three were diagnostic companies.



## PEPTILOGICS INNOVATIVE PEPTIDE-BASED PLATFORM TO DEVELOP A NEW CLASS OF ANTIBIOTICS

Peptilogics' eCAP (engineered cationic antibiotic peptide) platform offers the prospect of a new class of antibiotics. It has demonstrated potent activity against a broad spectrum of resistant bacteria, including difficult to treat Gram-negative pathogens, in multiple non-clinical models. eCAPs possess a novel mechanism of action; pre-clinical data suggest that this novel mechanism of action impedes and delays the generation of resistance by bacteria.

### ALLIANCE COMPANIES ARE TARGETING AREAS OF HIGHEST PUBLIC HEALTH NEED

Using a variety of approaches, Alliance companies are targeting highest public health needs. They are pursuing novel compounds and approaches, including new drug classes and mechanisms of action.

The diversity of approaches reported by responding companies extends across a broad spectrum of products. Efforts encompass traditional library screening techniques to identify and exploit new intracellular targets, re-purposing or re-engineering old assets, and exploring new natural-product repositories, as well as drug-by-design techniques which use emerging new platform technologies to engineer new products.

All responding companies that are active in early-stage R&D are targeting bacteria that pose the greatest threats to human health, as identified by the WHO Priority Pathogen List (PPL) or US CDC threat list. About two-thirds are working on compounds that represent substantial changes offered over all existing options, such as new product classes, new mechanisms of action, or novel approaches.

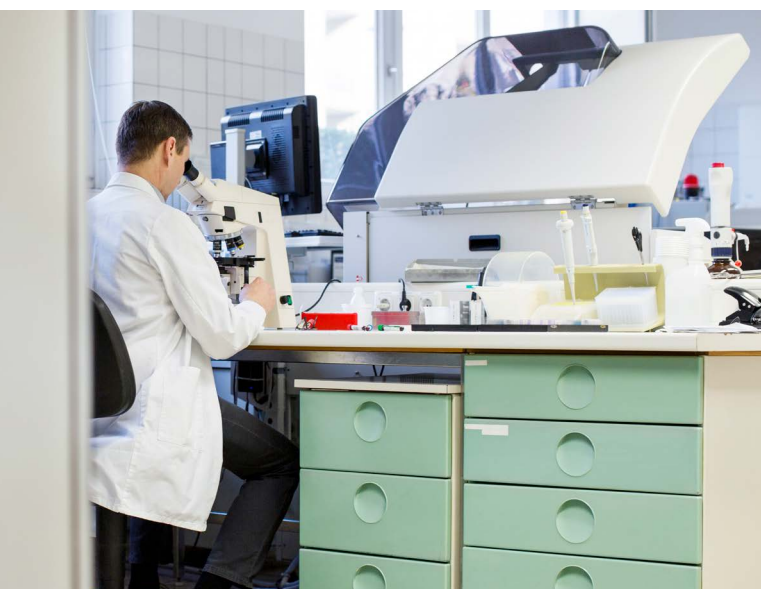
### ALLIANCE COMPANIES ARE ADVANCING A PIPELINE OF AMR-RELEVANT PRODUCTS

Over three-quarters of responding companies with R&D activity have had one or more AMR-relevant products in phase II or III of development (encompassing first dossier filing/submission) in the last five years.

Responding companies reported on their current AMR-relevant clinical development across four product types: antibiotics, vaccines, diagnostics, and non-traditional (including biologics).

The majority of responding companies' antibiotic drug products in clinical development are featured in the WHO pipeline analysis, which focused on the highest unmet medical needs.<sup>15</sup> WHO's pipeline analysis assessed the level of innovation (defined as new class, target, mechanism of action, and levels of cross resistance) and expected activity of the current clinical pipeline against pathogens on the WHO PPL.

Two novel antibiotics have been brought to market by responding companies since the Davos Declaration was signed, the period of review the Alliance is most focused on in this report. A further nine novel antibiotics have progressed in late-stage development, almost equally from large R&D biopharmaceutical and biotechnology companies.





Novel antibiotics brought to market since 2016.\*

COMPANY	ANTIBIOTIC	ACTIVITY AGAINST PRIORITY PATHOGENS	WHO PPL PRIORITY	CDC URGENT THREAT LIST
The Medicines Company	Vabomere™ (vaborbactam + meropenem)	Carbapenem-resistant <i>Enterobacteriaceae</i> (CRE)	Critical	Urgent
Melinta Therapeutics Inc.	Baxdela™ (delafloxacin)	Acute bacterial skin and skin structure infections	High and medium	Serious

**FIGURE 5: ANTIBIOTICS THAT HAVE SUCCESSFULLY ATTAINED FIRST MARKETING APPROVAL BY ALLIANCE COMPANIES SINCE SIGNING THE DECLARATION IN 2016.**

Notably, The Medicines Company's Vabomere™ (Vaborbactam + meropenem) meets the criteria of new chemical class as defined by the WHO. (Note that on 29 November 2017, The Medicines Company sold its infectious disease business to AMR Alliance member Melinta Therapeutics, Inc.<sup>16</sup>)

COMPANY	ANTIBIOTIC (DEVELOPMENT PHASE)	EXPECTED ACTIVITY AGAINST PRIORITY PATHOGENS	WHO PPL PRIORITY	CDC URGENT THREAT LIST
Achaogen	Plazomicin (PIII)	CRE	Critical	Urgent
Actelion	Cadazolid (PIII)	<i>Clostridium difficile</i>	Not included in WHO PPL	Urgent
Entasis Therapeutics	Zoliflodacin (PII)	<i>Neisseria gonorrhoeae</i>	High	Urgent
GSK	Gepotidacin (PII)	<i>Escherichia coli</i> and <i>N. gonorrhoeae</i>	Critical and high	Urgent
Merck & Co., Inc.	Imipenem/cilastatin + relebactam (PIII)	CRE and carbapenem-resistant <i>Acinetobacter baumannii</i> (CRAB)	Critical	Urgent and serious
Nabriva	Lefamulin (PIII)	Acute bacterial skin and skin-structure infections	High and medium	Serious
Pfizer, Allergan	Aztreonam + avibactam (PII)	CRE	Critical	Urgent
Shionogi	Cefiderocol (PIII)	CRE, CRAB, carbapenem-resistant <i>Pseudomonas aeruginosa</i> (CRPA)	Critical	Urgent and serious
Tetraphase Pharmaceuticals	Eravacycline (PIII)	CRE, CRAB, carbapenem-resistant <i>Pseudomonas aeruginosa</i> (CRPA)	Critical	Urgent and serious

**FIGURE 6: ANTIBIOTICS IN PHASE II OR LATER DEVELOPMENT REPORTED BY RESPONDING COMPANIES.**

\* Otsuka's Delytba™ (delaminid), Johnson and Johnson's Sirturo™ (bedaquilline), and Merck & Co., Inc.'s Zerbaxa® (ceftolozane/tazobactam) and Sivextro® (tedizolid) received first marketing authorization prior to 2016; however, PIII trials are ongoing for additional indications. PIII trials continue for Novartis' clofazimine for MDR-tuberculosis.

GSK's phase II gepotidacin met three of four innovativeness criteria as assessed by the WHO (new chemical class, new mode of action, and no cross-resistance to other antibiotic classes). Entasis' phase II oliflodacin, and Nabriva's phase III lefamulin both satisfied two of four innovativeness criteria.

Including early-stage compounds, some responding companies have multiple compounds targeting priority health needs including Entasis, GSK, Merck and Co., Inc., Otsuka and Tetraphase.

In addition to responding companies, the BEAM Alliance, BIO and ICBA associations, on behalf of their member biotechnology companies/SMEs, shared details of a number of antibiotics in phase II or later development against high or critical pathogens on the WHO PPL and serious or urgent CDC threats.

COMPANY	PROJECT/PHASE	EXPECTED ACTIVITY AGAINST PRIORITY PATHOGENS	WHO PPL PRIORITY	CDC URGENT THREAT LIST
AntibioTx	ATx201 (PII)	Methicillin-susceptible <i>staphylococcus aureus</i> (MSSA) and methicillin-resistant <i>staphylococcus aureus</i> (MRSA)	High	Serious
Debiopharm	Afabicin (Debio-1450) (PII)	MRSA	High	Serious
Destiny Pharma	XF-73 (P II)	MRSA	High	Serious
Motif Bio	Iclaprim (PIII)	MRSA	High	Serious
Polyphor	Murepavadin (PIII)	CRPA	Critical	Serious
Melinta Therapeutics, Inc.	Solithromycin (new drug application)	<i>N. gonorrhoeae</i> and causative pathogens of community acquired pneumonia (CAP) and non-gonococcal urethritis (NGU)	High	Urgent

**FIGURE 7: ADDITIONAL ANTIBIOTICS IN PHASE II OR LATER DEVELOPMENT REPORTED BY BEAM ALLIANCE, BIO AND ICBA ASSOCIATIONS.**

Including early-stage compounds, these additional companies have multiple compounds targeting priority health needs including Allecra, Polyphor, and VenatoRx Pharmaceuticals Inc.

Few generics companies provided R&D data, as most do not focus on developing new medicines.

## AMR-RELEVANT VACCINE CANDIDATES IN DEVELOPMENT

Vaccines hold significant promise in the field of AMR. Vaccines targeting bacteria directly limit infections and therefore the use of antibiotics, which would be the recommended treatment. Vaccines targeting viruses can also reduce antibiotic use, by preventing viral infections that might otherwise be inappropriately treated with antibiotics.

Six responding companies are involved in AMR-relevant vaccine R&D, with 13 candidates in active development in the last five years. Some of the relevant bacterial vaccine candidates in phase I and later of clinical development are detailed on the following page:

COMPANY	PHASE OF VACCINE CANDIDATE	EXPECTED PROTECTION AGAINST PRIORITY PATHOGENS	WHO PPL PRIORITY	CDC URGENT THREAT LIST
GSK	PII	Tuberculosis	Global priority	Serious threat
Merck & Co., Inc.	PII	<i>Streptococcus pneumoniae</i>	Medium	Serious
NovaDigm Therapeutics, Inc.	PI	<i>Staphylococcus aureas</i>	High	Serious
Pfizer	PI	<i>S. pneumoniae</i>	Medium	Serious
Pfizer	PII	<i>S. aureas</i>	High	Serious
Pfizer	PIII	<i>C. difficile</i>	Not included in WHO PPL	Urgent
Sanofi	PII	Tuberculosis	Global priority	Serious threat

**FIGURE 8: HIGHLIGHT OF VACCINES IN PHASE I OR LATER DEVELOPMENT REPORTED BY RESPONDING COMPANIES.**

The Beam Alliance reported other preventive approaches – including immunomodulating, anti-virulence and decontamination/decolonization – under development by SMEs including Antabio, Arsanis, BioVersys, BioFilmControl, Centauri Therapeutics, DaVolterra, Eligo Bioscience, Helperby, Maat Pharma, Mutabilis and Quretech.

## THE ALLIANCE IS DELIVERING AGAINST THE AMR REVIEW'S DIAGNOSTIC WISH LIST

Responding Alliance companies have brought new diagnostic capabilities to market since the Davos Declaration in January 2016, with many more in development and expected in the coming years – both for priority pathogens and for high-burden resistance strains.

Four of five responding diagnostic companies report being active in R&D over the last two years. All four, and one company classified as a large R&D biopharmaceutical company with diagnostic products, are active in both early and late-stage R&D with some activities in-house and some in collaboration. Additionally, all report their activities target priority unmet medical needs as identified by the WHO PPL or US CDC threat list.

Across these companies, 18 diagnostic AMR-relevant products were reported as having been in late-stage R&D in the last five years, many of which are now available. Many of these are new tests or assays utilizing diagnostic platforms that are already on the market.

In October 2015, the AMR Review defined four questions that the “perfect new rapid diagnostic test” would answer to address AMR. Alliance companies demonstrate advancing capabilities across all four of these questions (see Figure 9 on following page).

AMR REVIEW DIAGNOSTIC 'FOUR KEY QUESTIONS' <sup>17</sup>	EXAMPLES FROM THE ALLIANCE
<b>1</b> Is the infection causing the illness bacterial or viral?	<p>In May 2017, BD entered into collaboration with the non-profit product development partnership FIND to develop a point-of-care biomarker test to distinguish bacterial infections from other causes of fever in LMICs.<sup>18</sup></p> <p>In 2016, the FDA approved the bioMérieux VIDAS® B•R•A•H•M•S PCT™ assay as the first biomarker to be used for antibiotic stewardship; threshold levels can be used to determine when to safely withhold antibiotics in lower respiratory tract infections (LRTI) and when to safely stop antibiotics in both LRTI and sepsis.</p>
<b>2</b> If bacterial, what type of bacteria is causing the infection?	<p>A number of priority pathogens are carbapenemase-producing bacteria (<i>Enterobacteriaceae</i>, <i>P. aeruginosa</i> and <i>A. baumannii</i>) and their detection and classification have progressed due to the following: BD Phoenix™ CPO Detect, bioMérieux RAPIDEC® CARBA NP<sup>19</sup>.</p> <p>Curetis AG's Unyvero Pneumonia Application has reduced the time for identification of causative pathogens in hospital-acquired infections. Abbott's recent launch of an improved Point of Care (POC) test can measure C Reactive Protein in less than four minutes.</p> <p>bioMérieux/BioFire has launched multiplex syndromic panels which test for 20+ pathogens in 1 hour to determine the etiologic pathogen in order to withhold antibiotics (for viral infections) or choose targeted antibiotics.</p>
<b>3</b> Are the bacteria that are causing the infection resistant to available antibiotics?	<p>BD MAX™ multi-drug resistant (MDR)-TB assay, to detect rifampicin or isoniazid resistance.<sup>20</sup></p>
<b>4</b> Are the bacteria that are causing the infection susceptible to existing drugs?	<p>BD: Phoenix AST Panels, bioMérieux: VITEK® antimicrobial susceptibility testing (AST) drug rounds.</p> <p>bioMérieux has also launched CHROMID® Colistin for screening both animals and humans for colistin-resistant bacteria.</p>

**FIGURE 9:** AMR-RELEVANT DIAGNOSTICS FROM RESPONDING COMPANIES THAT CORRESPOND TO THE FOUR KEY QUESTIONS FOR THE NEXT PERFECT DIAGNOSTIC OUTLINED IN THE AMR REVIEW.

## ACTIVE EXPLORATION OF NOVEL APPROACHES TO ADDRESS AMR

In addition to the more traditional tools (small-molecule antibiotics, vaccines and diagnostics) to address resistance that companies shared, seven companies are also working on new technologies with the potential to contribute to AMR solutions. These hold great promise to address AMR alone or in combination with other antimicrobials, and have been highlighted by the UK AMR<sup>21</sup> review and others.<sup>22</sup>

## NOTABLE TECHNOLOGIES IN DEVELOPMENT

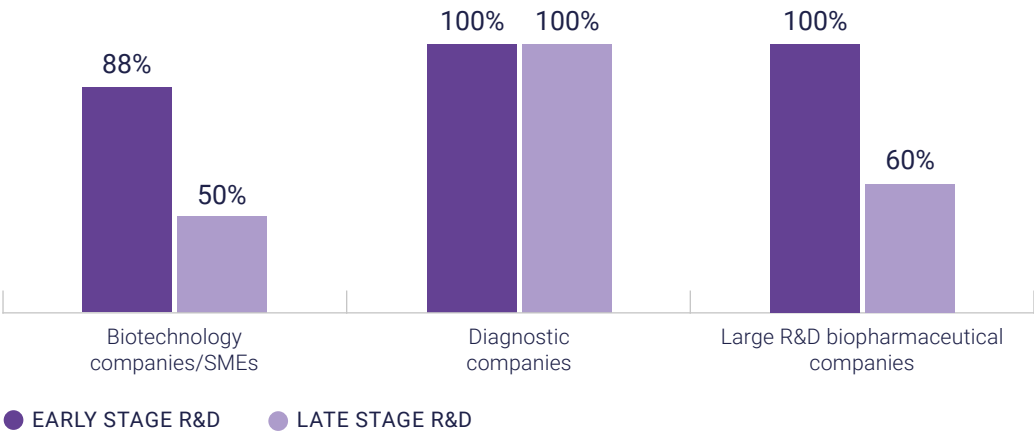
- Bacteria and fungi form biofilms – which means they adhere to surfaces, excreting a slimy, sticky ‘film’ – to shield the underlying colony from the host immune system, disinfecting biocides, vaccines, and antibiotics. The U.S. Centers for Disease Control associate biofilm with over 90% of all hospital-acquired infections. **Aequor’s** antibiotics and antibiofilm agents in development are non-toxic to plant and animal life, work alone to combat pathogens without triggering resistance, and can potentiate existing remedies so that they can work again.
- **AstraZeneca** has two biological agents (MEDI4893 and MEDI390) in phase II development which target pathogens listed on WHO’s PPL.
- **Contrafect** (CF-301, phase II) and **F. Hoffmann-La Roche AG** (DSTA-4637S, phase I) have PPL-targeting biological agents in development.
- **DaVolterra** has a product in development (DAV132) as a combination therapy, to capture residual antibiotics in the gastrointestinal tract to prevent disruption of intestinal microbiota, the reoccurrence of *C. difficile* infections and emergence of resistant bacteria. DaVolterra also have a research-stage program, DAV121, targeting the development of an oral co-treatment with advanced cephalosporins and carbapenems, to prevent multi-resistant infections in hospital-settings by preserving gut microbiota in patients treated with such antibiotics. DAV121 is partnered with the [BioAster Technology Research Institute](#).
- **iNtRON** Biotechnology has a novel bio-drug (SAL200) which is now in a phase II clinical trial targeting MRSA infections.
- **Johnson & Johnson** is addressing surgical site infections, and in the case of ETN PROtect (coated tibial nail), implant related infections.
- **Merck & Co., Inc.’s** Zinplava® (bezlotoxumab), an antitoxin to prevent recurrence *C. difficile* infections was approved in 2016.

In addition to responding companies, the BEAM Alliance, BIO and ICBA associations, on behalf of their member biotechnology companies/SMEs, shared that a number of products are in phase I or later development against high or critical pathogens on the WHO PPL and serious or urgent CDC threats.

- ASN-100 is a monoclonal antibody in development (phase II) by **Arsanis** that selectively targets *S. aureus* virulence rather than directly killing the bacteria, potentially combatting critical infections without contributing to antibiotic resistance or damaging the patient’s microbiome.
- **Combioxin’s** CAL02 is a first-in-class clinical-stage broad-spectrum anti-toxin therapy (phase I/II) that effectively neutralizes virulence factors produced by *S. aureus*, *S. pneumoniae*, *P. aeruginosa* and various other streptococcal or clostridium strains. It is active against antibiotic-resistant pathogens (e.g. MRSA) - that cause severe infections such as community- and hospital-acquired pneumonia, ventilator-associated pneumonia, other nosocomial infections and meningitis.
- **Helperby** has discovered and is developing a suite of Antibiotic Resistance Breakers (ARBs). These compounds, when combined with old antibiotics, can restore the original potency against both Gram positive and Gram negative bacteria. Helperby’s HY-004 project is in phase II trials for effectiveness against nasal MRSA decolonisation.
- **Novabiotics’s** Lynovex is a novel treatment, currently in phase II trials, for the infectious exacerbations associated with cystic fibrosis. It has a unique multi-action; breakdown of the excessive mucus produced by the lining of the airways in patients, killing of the bacteria responsible for the recurrent respiratory infections and disrupting the biofilms in which they colonise.

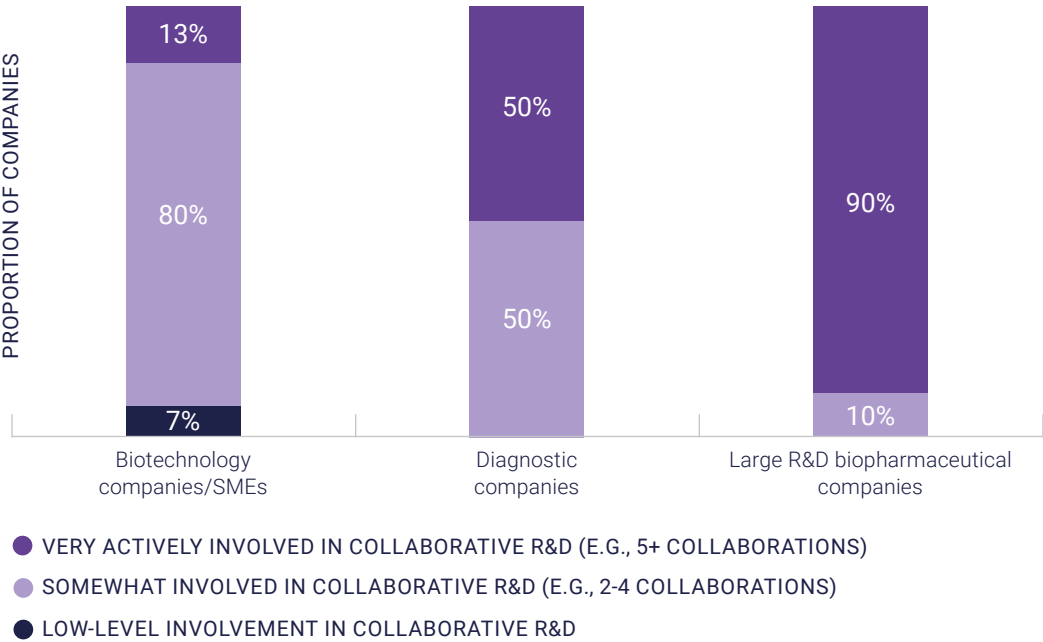
### ALLIANCE COMPANIES ARE ACTIVELY COLLABORATING ON AMR-RELEVANT R&D

Of the companies with AMR-relevant R&D, all but one were active in collaborative R&D efforts over the last two years.



**FIGURE 10:** PROPORTION OF RESPONDING COMPANIES (THAT ARE ACTIVE IN AMR-RELEVANT R&D) UNDERTAKING R&D COLLABORATIONS, BY DEVELOPMENT STAGE (TOTAL: 30).

While the proportions are similar across different sectors, far more large R&D biopharmaceutical companies that are collaborating (90%) describe themselves as doing so “actively” than their typically smaller peers, particularly biotechnology companies, of whom only 13% consider themselves active collaborators. This may reflect the antibiotic discovery and development chain: large biopharmaceutical companies often seek to collaborate, license, or acquire biotechnology companies/SMEs when promising compounds meet clinical development milestones.

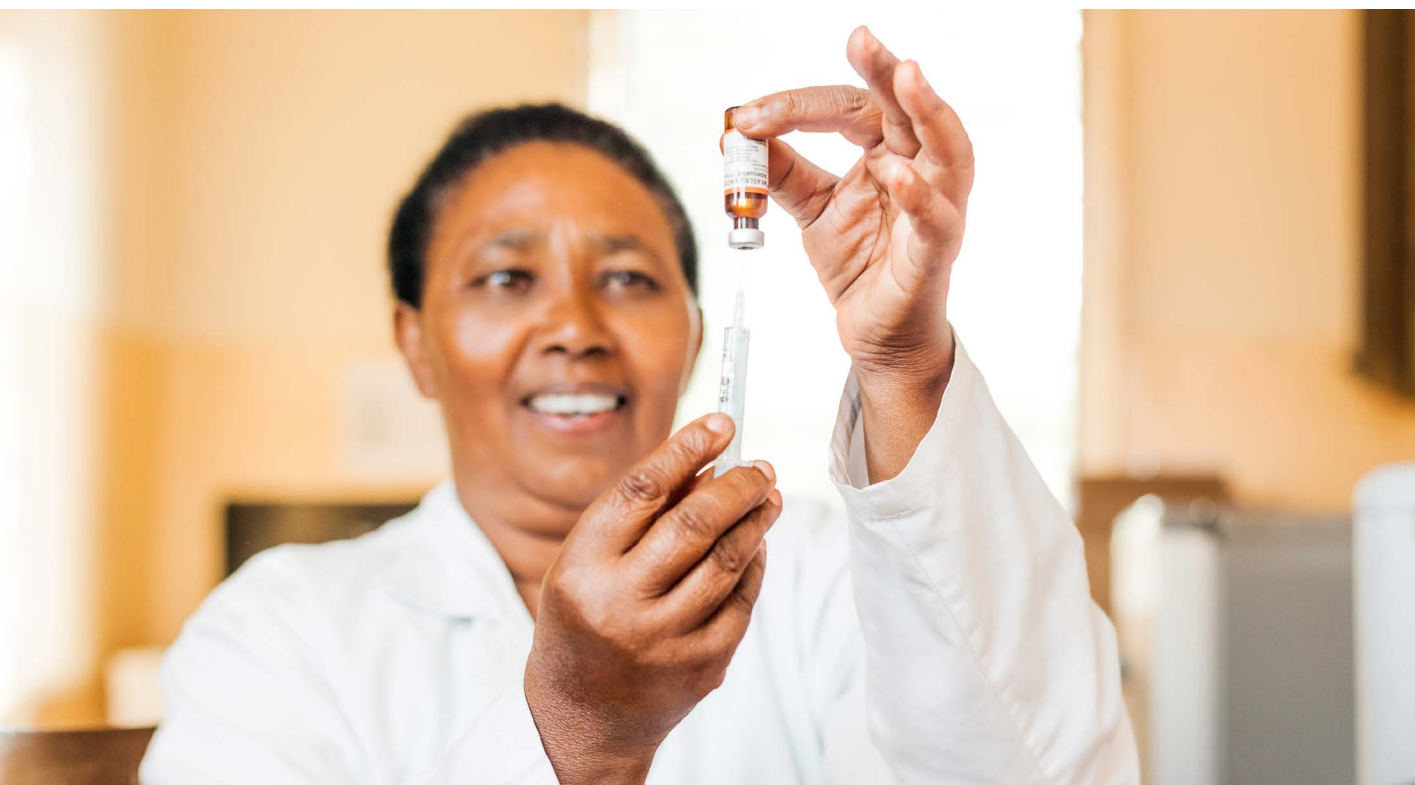


**FIGURE 11:** LEVELS OF COLLABORATION IN R&D BY RESPONDING ALLIANCE COMPANIES, BY SECTOR (TOTAL: 29).

## ALLIANCE COMPANIES ARE ENGAGED IN DIVERSE COLLABORATIONS

Recent years have seen growth in the type and nature of collaborative approaches to R&D:

- **Collaboration between large R&D biopharmaceutical and biotechnology companies:** Many of these take the form of financial support, such as AstraZeneca's retention of a financial stake in Entasis, GSK's SR One investment strategy incubating promising biotechnology companies, Merck & Co., Inc. collaborating with Discuva to access particular expertise in synthetic genomics, and Pfizer and Allergan collaborating on the development of several products.
- **Collaboration between large R&D biopharmaceutical and diagnostic companies:** Large R&D biopharmaceutical companies partner with diagnostic companies to expedite the inclusion of their products on antimicrobial susceptibility panels. These devices detect possible antibiotic resistance and enable clinicians to make appropriate prescribing decisions. Partnerships may include direct financial support as well as all required samples, bacterial isolates and data access to assist in the development of susceptibility tests.
- **Companies collaborating with academic partners:** Responding companies report frequent academic partnerships. Sanofi's partnership with Germany's Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Merck & Co., Inc.'s collaboration with scientists at Yale and other universities, and Curetis and bioMérieux highlight the value of their academic partnerships to both assist in the collection of unique/difficult/resistant strains and to help with the fundamental understanding of the genetics of antibiotic resistance to help develop rapid molecular diagnostic tests.
- **Companies collaborate with national governments:** BARDA has provided support for antibiotic development and has significant portfolio agreements with F. Hoffmann-La Roche AG, GSK, Pfizer and The Medicines Company. In lower and middle-income countries (LMICs), examples include the GSK Institute for Infectious Diseases and Public Health in China and Johnson & Johnson's partnership with the Institute of Microbial Technology (IMTECH) in India, part of the Council of Scientific and Industrial Research (CSIR) for novel TB drug discovery.





## EUROPEAN UNION'S INNOVATIVE MEDICINE INITIATIVE (IMI)

Since 2012, the EU's IMI New Drugs 4 Bad Bugs (ND4BB) program has provided a framework for a public-private collaboration between experts from small and large biopharmaceutical companies and academia. This enables project partners to share data, pool resources, and exchange expertise in an attempt to combat antibiotic resistance in Europe. To date, eight R&D projects have been financed that specifically address some of the biggest challenges in antibiotic development: Discovery, Clinical Development and Economics.

IMI PROJECT / OBJECTIVE	LARGE R&D BIOPHARMACEUTICAL	BIOTECH
<b>TRANSLOCATION:</b> Addressing the scientific challenge of penetration barriers & efflux (getting the drug into the bug).	4	0
<b>ENABLE:</b> Collaborative antibacterial drug discovery platform (from early discovery to first time in man).	3	5
<b>COMBACTE-NET</b> building strong clinical, laboratory and research networks across Europe and development of preventative and therapeutic antibacterial agents.	3	2
<b>COMBACTE-MAGNET:</b> Development of preventative and therapeutic agents for serious Gram-negative infections.	3	1
<b>COMBACTE-CARE:</b> Improve understanding of CRE infections and supporting the development of an antibiotic-inhibitor combination as a treatment option.	3	0
<b>COMBACTE-CDI:</b> Understanding of the epidemiology and clinical impact of Clostridium difficile infection.	4	2
<b>iABC:</b> Advancing the development of inhaled antibiotics for patients with cystic fibrosis and bronchiectasis.	1	1
<b>DRIVE AB:</b> Developing new economic models to incentivise antibiotic discovery and development activities while safeguarding the efficacy of antibiotics by researching and advocating their appropriate use.	6	0

The IMI is jointly funded by the EU (represented by the European Commission) and the European pharmaceutical industry (represented by EFPIA, the European Federation of Pharmaceutical Industries and Associations).

## SOME COMPANIES FACILITATE DATA EXCHANGE ON OFF-PROTECTION ANTIBIOTICS

Data exchange refers to making data (e.g., regulatory dossier or information related to dosing and manufacturing processes) on off-protection antibiotics available to external stakeholders. This exchange can be facilitated through scientific publication – for instance, companies regularly publish data in peer-reviewed journals on their products – or directly with a third-party.

Three of seven large biopharmaceutical R&D companies with late-stage AMR-relevant R&D in antibiotics in the last five years report sharing data on off-protection antibiotics. Another indicated it would consider assisting data exchange if approached to do so. Additionally, two biotechnology companies indicated that this is something they could consider in the near future (2018-2020); another biotechnology company does so on a payment basis. In addition to company-specific

examples, several Alliance members are active in the TB Drug Accelerator (TBDA), a collaboration between eight research institutions, eight biopharmaceutical companies (AbbVie, AstraZeneca, Bayer, Eisai, Eli Lilly and Company, GSK, Merck & Co., Inc., Sanofi) and a product development partnership to facilitate TB drug discovery. As part of this, Merck & Co., Inc. has completed two large in-house screening campaigns. One was a screen of over 2 million compounds, and the second was a collaborative effort with TBDA partners using its proprietary Automated Ligand Identification System (ALIS) technology. Both screens delivered “hit packages,” and intra-TBDA partnerships have sprung from this work.

#### GSK OPEN-COLLABORATION FOR TB REPURPOSING

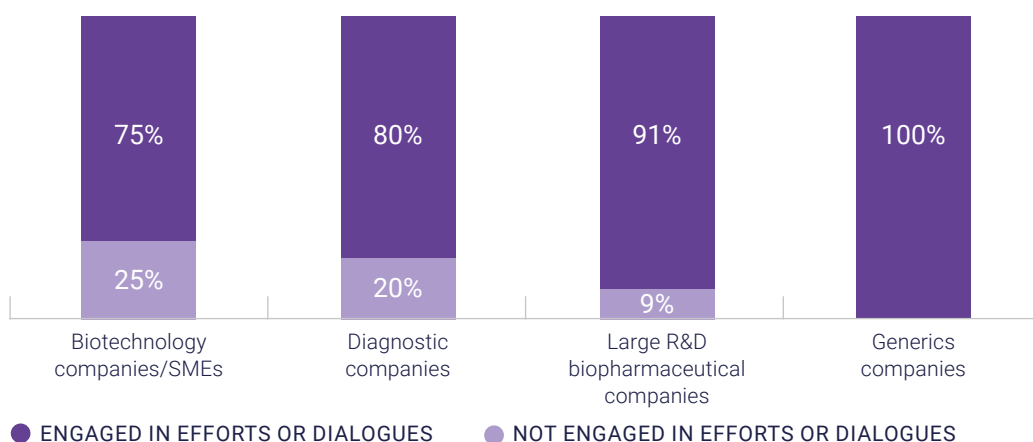
ORCHID alliance (Open Collaborative Model for Tuberculosis Lead Optimization) – a research partnership co-funded by the EU and completed in 2015. The work of this alliance included repurposing existing medicines as potential TB treatments, using the 200 hits from GSK’s compound collection to identify starting points for future drug discovery programs, and creating a portfolio of promising compounds.

#### JOHNSON & JOHNSON WORKING WITH YALE UNIVERSITY

Yale University Open Data Access (YODA) Project is empowered to make independent decisions about data release and it performs independent scientific reviews of investigator requests for Johnson & Johnson’s pharmaceutical and medical device clinical trial data, including both full Clinical Study Reports and participant-level data. Specific study information regarding LEVAQUIN® (levofloxacin) has been made available through this database.

## SIGNATORIES ARE ENGAGED TO ADDRESS MARKET CHALLENGES FOR ANTIBIOTICS, VACCINES, AND DIAGNOSTICS

The majority of responding companies (80%) – both those active in R&D and not – are involved in efforts, or national or global dialogues, seeking to address new reimbursement and valuation mechanisms, commercial models or market / regulatory barriers to development.



**FIGURE 12:** PROPORTION OF COMPANIES, BY SECTOR, THAT ARE ACTIVE IN EFFORTS TO ADDRESS THE ECONOMIC CHALLENGES IN THIS MARKET (TOTAL: 35).

Large R&D biopharmaceutical companies are much more likely to describe their involvement in these dialogues as “very active” as opposed to biotechnology or generics companies, which appear to engage through their industry groups.

## ALLIANCE COMPANIES ARE ACTIVELY COLLABORATING ON AMR-RELEVANT R&D

As part of the Davos Declaration’s call for “governments to commit funding and support the development and implementation of transformational commercial models”, responding companies provided multiple examples of the ways they are working with policymakers and proposing solutions. To date, few governments have made changes to reimbursement systems or implemented pull mechanisms to address the challenges of antibiotic R&D. Illustrative examples include:

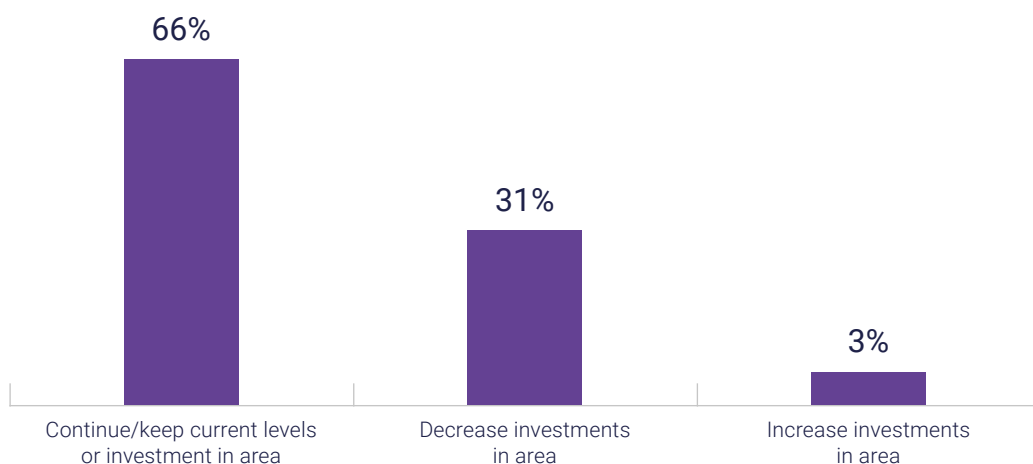
- **Contributions to high-level discussions:** On-going engagement, often at the CEO level, by companies in multilateral fora (e.g., UN High Level Meeting on AMR, UN High Level Meeting on TB, WHO, G7/G20, Organisation for Economic Co-Operation and Development, World Economic Forum, EU IMI, Asia Pacific Economic Cooperation and individual government dialogues (e.g., in UK, Sweden, Japan)).
- **Technical input to policy research:** Many responding companies report being active participants and contributors to the following initiatives (among others): The UK’s AMR (O’Neill) Review<sup>23</sup>, EU’s IMI program (including DRIVE-AB, ThinkBig, and Value-Dx), UK Royal Society, UN AMR private sector consultations, and the EU public consultation on the new EU Action Plan.
- **Dialogue and feedback to regulators:** Companies are providing input into the regulatory harmonization efforts of the Food and Drug Administration (FDA), European Medicines Agency (EMA), and Pharmaceuticals and Medical Device Agency (PMDA); WHO-led regulatory harmonization initiatives in Africa; and work to supply anti-tuberculosis medicines through the Stop TB Partnership’s Global Drug Facility (regulatory waivers)
- **Financial support to fill research gaps:** Some companies have funded policy-research, such as the Duke Margolis Centre research on antibiotic incentives for the US market<sup>24</sup>, Office of Health Economics work on value assessments for novel antibiotics, and Global Expert Meetings on AMR at the Center for Strategic and International Studies/Global Health Policy Institute.
- **Development of industry-wide positions/papers/dialogue:** Notably, many – particularly smaller companies – work through the 14 industry associations that are also signatories to the Davos Declaration, including putting forward workable incentive mechanism proposals. To date, trade associations have prepared policy positions or put forward concrete proposals to create an environment that is supportive of sustainable investment in antibiotic R&D (see [BEAM Alliance](#); [BIO](#); [IFPMA](#); and a [joint statement](#) by ABPI, EFPIA and IFPMA).

## INCENTIVES ARE CRITICAL TO SUSTAINED R&D

Over 90% of responding companies viewed current progress on R&D incentives as either “promising but far to go” or “insufficient relative to the challenge.”

Across all sectors, only one-quarter of responding companies reported that existing or implemented incentives, such as additional push incentives and/or regulatory changes, had positively influenced investment decisions. For the remaining three-quarters, these incentives had not positively impacted investment decisions within their companies.

If valuation mechanisms and commercial models improve, 72% of responding companies active in R&D stated they would likely increase investments in this area. On the other hand, of those companies that are active in R&D, 31% of all respondents (and 50% of large R&D biopharmaceutical companies) said they would likely decrease investment in this area if valuation mechanisms and commercial models remain as they currently are.



**FIGURE 13: HOW PROPORTIONS OF RESPONDING COMPANIES WITH AMR-RELEVANT R&D WILL RESPOND IF VALUATION MECHANISMS AND COMMERCIAL MODELS REMAIN AS THEY ARE (TOTAL: 29).**

## ALLIANCE MEMBERS SUPPORT PUSH INCENTIVES

Responding companies welcomed the progress so far in implementing push incentives, yet see these efforts as fragmented and short-term. They cited the EU's IMI program, CARB-X, and funding available through US agencies such as the NIH and BARDA. Responding companies also report examples of private and philanthropic financing such as from the Bill and Melinda Gates Foundation (BMGF) and Wellcome Trust. Specific examples of ways in which Alliance members have benefited are detailed below:

US agencies such as NIH have supported Otsuka (MDR-TB exposure prevention), Tetrphase (TP-271) and NovaDigm Therapeutics, Inc. (*S. aureus* vaccine). BARDA has also supported Tetrphase (eravacycline) and Discuva in the development of candidates.

BMGF supports the Group B Streptococcus (GBS) Assay Standardization Consortium, which was formed to develop standardized assays to support the development of sero-correlates of protection for invasive GBS disease that could be used as the basis for vaccine licensure. The consortium includes GSK and Pfizer, as well as SMEs and public partners. Additionally, the Global Health Innovative Technology Fund created by the Japanese government, BMGF and Japanese pharmaceutical companies (including Shionogi & Co. Ltd.) funds infectious disease R&D.

## SUPPORTING EARLY-STAGE ANTIBIOTIC R&D THROUGH THE CARB-X<sup>25</sup>

CARB-X is the world's largest public-private partnership devoted to antibacterial preclinical R&D, leveraging USD 455 million in BARDA and Wellcome Trust funds with matching funds from Wellcome Trust. It provides financial and scientific support to accelerate the most promising drug-resistant bacterial infection research projects from around the world through the early-stages of product development so they can attract additional private or public investment for clinical-stage development. CARB-X funding targets the most urgent drug-resistant gram-negative bacteria, as prioritized by the CDC and the WHO.

In 2016-2017, the CARB-X funded 18 projects awarded USD 41.6 million with up to USD 52.6 million more in milestone-based options. Importantly those projects will be eligible to receive scientific support. Of those companies receiving CARB-X support, nine are members of the Alliance – all from the biotechnology sector. Four of these companies responded to the AMR Industry Alliance Survey.

**TETRAPHASE:** Advancement of TP-6076, a phase I antibiotic for the treatment of serious and life-threatening bacterial infections, including those caused by pathogens otherwise resistant to current treatment options including carbapenem-resistant *A. baumannii* and *Enterobacteriaceae*.

**ENTASIS:** Development of a novel oral agent to treat multi-drug resistant bacterial infections, including those caused by CRE as well as a novel antibiotic class that has demonstrated potent antibacterial activity against some of the toughest to treat pathogens, including MDR *P. aeruginosa*, CRE, and MDR *A. baumannii*.

**CONTRAFECT:** Development of a recombinant lysin protein as a potential treatment for invasive infections caused by *P. aeruginosa*.

**ACHAOGEN:** Development of their LpxC Inhibitor Antibiotic showing potent activity against *P. aeruginosa*.

## ALLIANCE MEMBERS SEE LITTLE PROGRESS ON PULL INCENTIVES

Pull incentives – such as market entry rewards, transferable exclusivity and improved post-market valuation – as well as reimbursement reform were seen by nearly all responding companies as critical to meaningfully and sustainably address the economic challenges of the market. There was near-total consensus that progress on pull incentives is needed to change internal investment decisions. Many responding companies expressed frustration with the lack of concrete action in this area despite years of discussion and effort. Pull incentives must be sustainable and sufficient to stimulate R&D across the full R&D lifecycle, from discovery through development, to see an impactful long-term change on the pipeline of new products. Some generics and diagnostic companies felt these discussions were too narrowly focused on bringing innovative new medicines to market. Incentives should also respond to the challenges of other health technologies, support the continued availability and access to older antibiotics, and facilitate stewardship.

Responding companies clearly articulated their current views of incentives, citing new and substantial pull incentives as the greatest need. In the words of one responding company, echoed by many others, "Now is the time to drive theoretical discussions to action."



Now is the time to drive theoretical  
discussions to action.

”



## 7.3 GAPS AND EMERGING SOLUTIONS

Alliance companies represent a cross-section of the total life sciences industry working to develop new technologies to address AMR.

Collectively, Alliance companies are investing significant resources into the discovery and development of AMR-relevant products. However, this investment is threatened and action by other stakeholders is urgently needed to strengthen the AMR-relevant pipeline.

Responding companies indicate that diverse discovery and development approaches are being pursued. They also acknowledge the role that additional upfront funding and financing streams (in the form of push incentives) and facilitated regulatory requirements have played in maintaining these current early-stage efforts.

However, these efforts alone will not be sufficient to address AMR. A suite of incentives, including push incentives, novel pull mechanisms, and reimbursement and valuation reform will be required. Without changes to reimbursement, valuation mechanisms and ultimately commercial models, nearly one-third of all responding companies, including half of all large R&D biopharmaceutical companies, report that they will likely decrease their investments in antimicrobial R&D. Without pull incentives to complement push incentives, we may see more companies accepting push funding to develop antibiotics and subsequently exiting the space once products are approved.<sup>26</sup> The lack of pull incentives puts public investment in push incentives at risk.

Private investment in AMR is precarious: some biotechnology companies and SMEs, including Alliance members, have gone out of business or exited the AMR market since the launch of the Davos Declaration in

January 2016. Governments must be more willing to implement reimbursement reform and pull incentives that address the economic challenges of antibiotic R&D – particularly as products begin to enter the more expensive later stages of development. If not, private investment in addressing AMR, is at risk.

Collaboration is essential: companies should continue to seek out new collaborations, explore opportunities to engage in open-innovation initiatives, and revisit old assets in partnership with other stakeholders.

While promising work has already been done to help prioritize antibiotic needs, other areas, such as vaccines and diagnostics, lack consensus priority lists to signal unmet needs to companies. It is hoped that WHO's Initiative for Vaccine Research<sup>27</sup> can help to determine vaccine priorities globally. Additional efforts can help focus company resources where they are needed most.

The life sciences industry is one part of the puzzle, as the AMR Review highlighted: opening up the playing field, bringing down barriers to entry into research, and rewarding success – wherever it comes from – are also crucial.<sup>28</sup> Action is needed by all stakeholders to address the scientific, regulatory, and economic barriers to antimicrobial R&D. If an environment that enables sustainable private investment can be created, the life sciences industry can be a valuable partner to discover and develop new products, promote appropriate use, and expand access.





# 8

## APPROPRIATE USE



While the evolution of resistance is a natural and inevitable process, the inappropriate use of antimicrobials in both people and animals accelerates the process. This section describes what role the life sciences industry can play to support appropriate use of antimicrobials.

## 8.1 BACKGROUND AND CHALLENGES

Antimicrobial resistant-microbes are found in people, animals, food, and the environment (in water, soil and air). They can spread person-to-person, and between humans and animals, including from food of animal origin. Poor infection control, inadequate sanitary conditions and inappropriate food-handling can spread AMR.<sup>29</sup> Other challenges include a lack of surveillance data and uncontrolled use, such as through internet and over the counter (OTC) sales.<sup>30</sup> This report and the Alliance's work to date has focused on human health.

There are many drivers of antibiotic use and the choice of antibiotics, including policies, availability and use of diagnostic tools, pricing and education, among others. This means that many stakeholders including developers, governments, regulators, insurers, pharmaceutical buying consortia, distributors, pharmacists, healthcare professionals and patients themselves can influence how antibiotics are used. Each actor has its own role and responsibilities in promoting appropriate use of antibiotics.

The role of the life sciences industry is, first and foremost, to develop, manufacture and support access to antibiotics, vaccines, diagnostics (particularly rapid point of care diagnostics) and novel approaches to prevent and treat AMR. The industry also carries out educational and promotional activities in line with country laws and regulations for products including marketing materials, packaging and labelling. These can support and promote appropriate use. Many pharmaceutical and diagnostic companies also have their own surveillance programs.

There are many factors impacting appropriate use that

are beyond the reach of the pharmaceutical industry. For example, sanitation continues to be a key challenge globally and is at the root of many bacterial infections. Estimates indicate that the number and cases of water and sanitation-related diarrhoea could be reduced by 60% by introducing sanitation infrastructure.<sup>31</sup> Further, there are many factors impacting healthcare provider behaviors and prescribing practices: availability and use of diagnostics, availability of different treatment options, awareness and education, protocols and guidelines, and policies and behavioral interventions. Consumer preferences also influence antibiotic use. Regulators and policymakers can also influence appropriate use. For instance, antibacterials may be accessed in some countries directly from local pharmacies without a prescription.

The Alliance is committed to promote patient-centered antimicrobial stewardship to slow the emergence of resistance, prolong the activity of antimicrobials and improve patient outcomes and population health. The Alliance has adopted the following definition for appropriate use of antimicrobials: "the right patient receiving the right drug at the right dose in the right formulation at the right time for the right duration for the right pathogen and site of infection" (see Appendix for Alliance's full definition of appropriate use in humans). This is consistent with the definition used by other key stakeholders such as CDC, IDSA and WHO. The appropriate prescription of antimicrobials is included in this definition, and antibiotic therapy must be limited to appropriate use only to treat bacterial infection. The Alliance notes that patients should be educated in how to manage symptoms of non-bacterial infections and not to self-prescribe antibiotic therapy.



## APPROPRIATE USE DEFINED:

“The *right* patient receiving the *right* drug at the *right* dose in the *right* formulation at the *right* time for the *right* duration for the *right* pathogen and site of infection.”

- AMR Industry Alliance

## 8.2 AMR INDUSTRY ALLIANCE ACTION TO DATE

One of the key commitments of the Davos Declaration was to reduce the development of AMR by promoting use of antibiotics only for patients who need them.

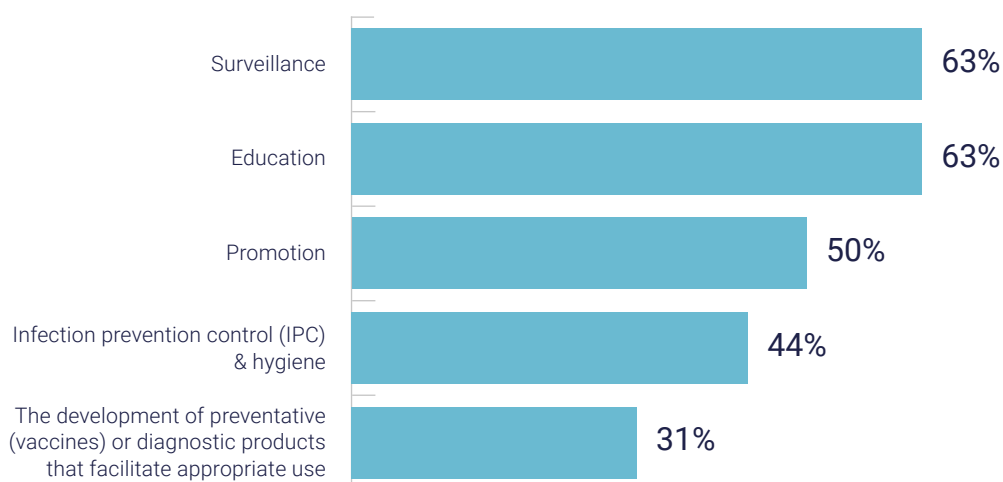
The following section on industry activity corresponds to data submitted by 35 companies that responded to the appropriate use-related aspects of the survey; of these, 17 were found to already have AMR-relevant products on the market.

### MANY ALLIANCE MEMBERS HAVE PUT IN PLACE STRATEGIES, POLICIES AND PLANS TO SUPPORT APPROPRIATE USE

Nearly half of all responding companies have a strategy, policy or plan in place to ensure appropriate use of their products. Half of these companies – or a quarter of all responding companies – have relevant marketed products and a strategy, policy or plan.

Of the companies with relevant marketed products but without a current strategy, policy or plan in place, almost one-third are still active in this area, and a few are currently developing strategies. Half of generics companies report being active on appropriate use despite having no formal strategy in place.

The appropriate use strategies companies have in place or in development take a multi-faceted approach and cover many aspects of appropriate use. Of the 16 appropriate use strategies, policies, or plans reported, the following aspects were addressed:



**FIGURE 14: PROPORTION OF RESPONDING COMPANY APPROPRIATE USE STRATEGIES, POLICIES OR PLANS ADDRESSING THESE ASPECTS OF APPROPRIATE USE (TOTAL: 16).**

The Alliance is also committed to collaborate with governments, relevant agencies and other stakeholders to reduce uncontrolled antibiotic purchase, such as via over-the-counter (OTC) and non-prescription internet sales. These aspects featured less in appropriate use strategies (in 13%), potentially due to the nature of the portfolios of responding companies. For example, OTC or internet sales may be less of an issue for intravenous antibiotics, vaccines, and advanced diagnostics that require skilled healthcare professionals. Three companies report strategies addressing appropriate use through improvements to packaging and brochures.

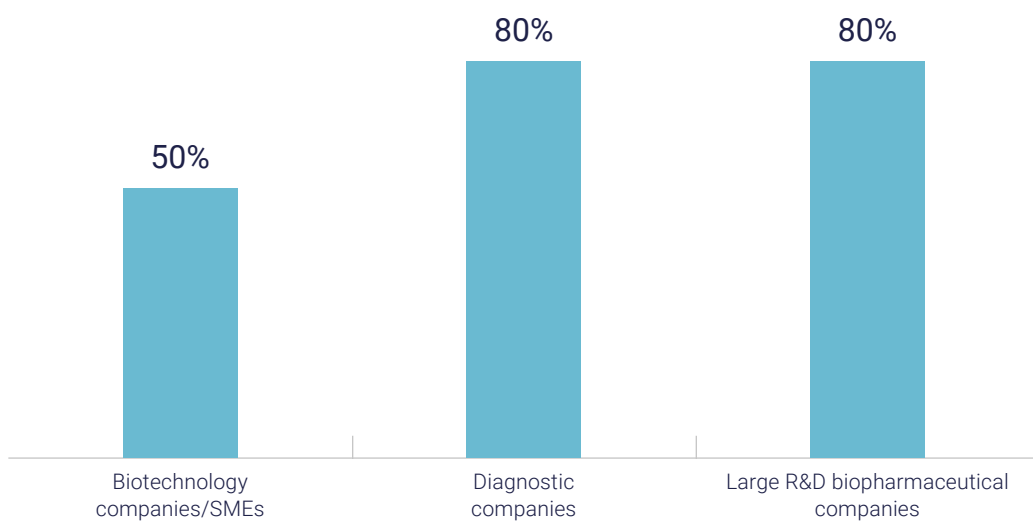
## SURVEILLANCE IS A KEY CONTRIBUTION FROM INDUSTRY ALLIANCE MEMBERS

In the Davos Declaration, Alliance members commit to “continue to share the surveillance data we generate with public health bodies and healthcare professionals, and work with them to improve understanding of resistance trends, inform appropriate antibiotic and vaccine use and, over time, thereby help increase surveillance capabilities globally.”

Surveillance is an important activity. In addition to being a regulatory requirement in some cases, it allows for the assessment of incidence rates of resistance to various antibiotics globally, regionally, by country, and at the hospital-level. For drug and diagnostic developers, surveillance data can provide early indicators of future unmet medical needs and guide research efforts to develop new products to address growing resistance.

The majority of responding companies are planning to, currently collecting or supporting the collection of some form of surveillance data (89%) to support products in development and/or marketed products. This includes 70% of those responding companies with products already on the market. Data is collected through various means: company sponsored, supporting independent sponsored, and through supporting public health partners/programs.

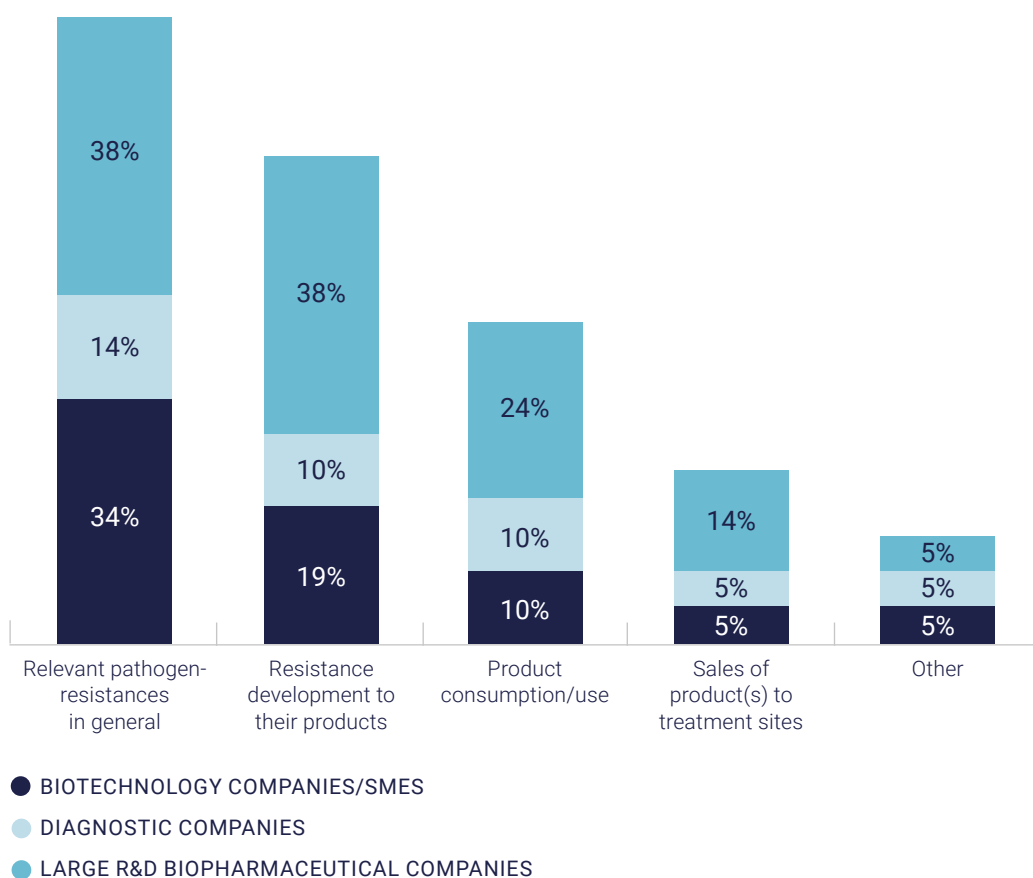




**FIGURE 15:** PROPORTION OF COMPANIES, BY SECTOR, CURRENTLY COLLECTING OR SUPPORTING THE COLLECTION OF SURVEILLANCE DATA (TOTAL: 35).



The type of data collected by companies varies.



**FIGURE 16:** TYPE OF SURVEILLANCE DATA COLLECTED BY RESPONDING COMPANIES (TOTAL: 21).

Most responding companies currently, or plan to, openly share their surveillance data externally (60%). Greater availability of data may support appropriate use by informing decisions on patient treatment and strategies to address AMR. While there is value in the current surveillance systems that are managed by individual companies.

Separate, company-driven surveillance systems are a necessary step in supporting successful registration of new antibiotics and are important commitments to continue the collection of data to aid our understanding of resistance over time. Companies share surveillance data by many different routes, from scientific publications to web- and app-based systems. Additional benefits may come from data standardization, pooling, and sharing. Next steps to create an even greater awareness and understanding could include a register of historical and current surveillance programmes with a description of data available with the aim of helping increase surveillance capabilities globally.

## INDUSTRY ACTION ON SURVEILLANCE

Surveillance studies can yield important information for the identification of trends in pathogen incidence and AMR, and provide early indicators of the emergence of resistant strains. This is fundamental for establishing effective strategies for limiting the spread and defining the appropriate treatment of resistant infections. Below are just a few examples of industry's surveillance activity.

### **Survey of Antibiotic Resistance, GSK**

With a long history in antibiotic surveillance, in 2002 GSK began the Survey of Antibiotic Resistance (SOAR) as a response to serious clinical concerns that emerging resistance was complicating empirical therapy of community-acquired respiratory tract infections. GSK leads the study, analyzes data, develops study reports and publications, and runs training, webcasts and lecture series. Study management is run by a third party, with external investigators for collecting and identifying isolates and testing antibiotics. GSK collects and identifies the most common community-acquired respiratory tract infections-related pathogens (e.g., *Streptococcus pneumoniae* and *Haemophilus influenzae*) and tests them against a wide range of antibiotics (GSK's and others). GSK proactively shares the data and trains healthcare professionals and GSK's staff on the importance of antibiotic surveillance and how this data can be used to help the development of local antibiotic prescribing guidelines to ensure appropriate use.

### **Study for Monitoring Antimicrobial Resistance Trends, Merck & Co., Inc.**

The Study for Monitoring Antimicrobial Resistance Trends (SMART), initiated by Merck & Co., Inc. in 2002, is one of the world's largest surveillance studies monitoring antibiotic activity against Gram-negative bacteria. It has strong longitudinal data, with many of its 192 sites worldwide (with plans to expand to 217 sites in 63 countries in 2018) part of SMART since its inception. Isolates have been collected from patients with community-acquired intra-abdominal infections since 2002, from patients with complicated urinary tract infections since 2010, and from patients with reproductive tract infections since 2015. In 2016, Merck & Co., Inc. announced its collaboration providing OpGen with access to the SMART database of over 200,000 bacterial pathogens gathered over the last 15 years to accelerate development efforts in validating their rapid diagnostic tools to enable prompt and informed antibiotic prescribing to improve patient outcomes.

### **Antimicrobial Testing Leadership and Surveillance Program, Pfizer, Inc.**

Pfizer launched the Antimicrobial Testing Leadership and Surveillance (ATLAS) program in 2017. ATLAS represents the integration of three global surveillance programs (TEST, AWARE, INFORM), and collectively has generated 14 years of continuous global bacterial susceptibility data versus a panel of antibiotics. It includes source information from more than 760 sites across 73 countries and over 200 hospitals, with data encompassing more than 556,000 isolates. Since 2004, publicly reported findings from these surveillance programs have been made available through over 50 published journal articles and over 750 medical congress presentations. Pfizer also provides access to cumulative ATLAS data through a public [website](#) with an interactive platform enabling physicians to analyze and export data with parameters such as organism, region, specimen source and in vitro susceptibility data. Pfizer also offers ATLAS as a mobile application to enable rapid access. Both the website and app are regularly updated with new and emerging data.

### **Global Point Prevalence Survey, a collaboration between Antwerp University & bioMérieux**

Global Point Prevalence Survey (Global-PPS), managed by the University of Antwerp and supported by bioMérieux, supports hospitals and country coordinators to monitor rates of antimicrobial prescribing and resistance in infections in hospitalised patients. In 2017, Global-PPS focused on LMICs where high antimicrobial prescription rates and resistance levels have been reported. Participants were aided in the interpretation of surveillance results as well as communication of those results at local and international level. The survey was launched together with a series of educational tools to support LMICs and to help hospitals to develop and implement customized action plans.

## ALLIANCE MEMBERS ARE MAKING DIVERSE CONTRIBUTIONS TO SUPPORT EDUCATION ON AMR AND STEWARDSHIP

In the Davos Declaration, Alliance members commit to “support governments and public health work to educate healthcare professionals and patients on the value and importance of appropriately using antibiotics, and the value of vaccination as a cost-effective intervention that complements antibiotic stewardship.”

In this context, education refers to product-independent materials and activities which aim to increase knowledge relevant to AMR, including around appropriate use. While direct healthcare and patient communication by industry is governed by many codes and rules, companies can still serve as valuable resources on the appropriate use of antibiotics. For instance, several companies are active in continuing medical education, activities that help to maintain or increase the knowledge and skills of healthcare professionals. Doing so in collaboration, or together with independent accredited providers, can help minimize potential conflicts of interest.

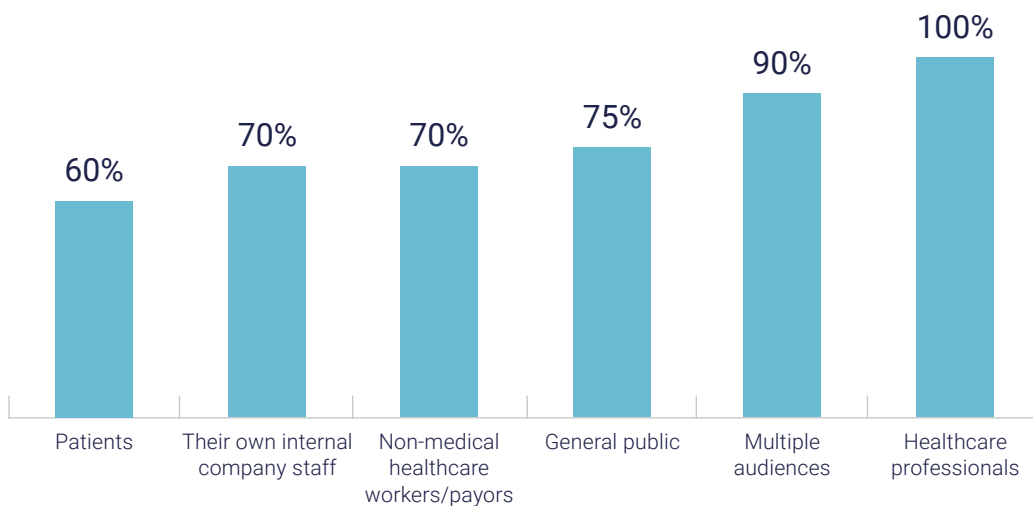
### “RESISTANCE FIGHTER” AWARENESS AND MOBILIZATION CAMPAIGN, BECTON, DICKINSON AND COMPANY (BD)

BD established a campaign in 2017 to raise awareness of AMR and the importance of proper diagnosis and prescribing practices across infectious disease specialists, primary care physicians, pharmacists, microbiologists, infection control practitioners, and patients. The campaign can be “branded” by any organization that signs up to be “a resistance fighter”. Messaging is being deployed through multiple channels including digital and print media and professional meetings. The campaign was introduced at the US Congressional AMR Awareness fair in November 2017. BD engaged an agency to develop the campaign and partnered with a broad coalition of key opinion leaders, patient groups, individuals and other organizations dedicated to utilizing their personal and organizational capabilities to combat AMR.

Overall, more activity – and collaborative efforts – are welcome. While most sectors and many responding companies are undertaking AMR-relevant educational activities, these appear relatively nascent. It is interesting to note that these are not confined only to companies with products on the market.

More than half of responding companies are planning to or are currently engaged in education activities around stewardship either directly or collaboratively. For companies with an AMR-relevant product on the market, this increases to 70%. Nearly all large R&D biopharmaceutical companies are planning to or are currently engaged in stewardship education activities (80%), whereas this is closer to half of responding biotechnology companies. This likely reflects that many of these companies’ R&D programs have not progressed far enough to inform their stewardship activities. Some are planning to engage in educational activities within the next five years. Therefore, we expect to see more activity in future years.

Responding companies' educational efforts engage a variety of stakeholders:



**FIGURE 17: PROPORTION OF RESPONDING COMPANIES ENGAGING ON EDUCATION WITH EXTERNAL STAKEHOLDERS (TOTAL: 20).**

Educational and stewardship activities cover a range of topics, including the benefits of vaccines in preventing infections, broad awareness of AMR, the risks of inappropriate use, and the environmental impact from the production of antibiotics.

The means by which companies educate and communicate is also diverse, including: brochures, social networks and webinars done alone or in partnership with patient organizations, universities and foundations through to formal trainings in-country.



## WORLD ANTIBIOTIC AWARENESS WEEK

World Antibiotic Awareness Week (WAAW) aims to increase awareness of AMR globally and to encourage best practices among the general public, health workers and policy-makers to avoid the further emergence and spread of resistance. The overall theme of the campaign, Antibiotics: Handle with Care, reflects the message that antibiotics are a precious resource to be preserved, used to treat bacterial infections (only when prescribed by a certified health professional), never shared, and courses of treatment always completed. The UN General Assembly urges countries to take part in WAAW, as the resistance of microbes to antibiotics knows no borders.

A number of Alliance members – companies as well as associations – support WAAW each year with public health campaigns, conferences, events and other activities. During Antibiotic Awareness Week in the US this year, AdvaMedDx, BD and IDSA organized an AMR Awareness Fair on Capitol Hill partnering with 20 stakeholder organizations to educate Capitol Hill staff on the impact of AMR.

## ANTIMICROBIAL STEWARDSHIP ACTIVITIES, MERCK & CO., INC.

Merck & Co., Inc. is involved in several initiatives to increase awareness on the importance of appropriate use and AMR amongst a variety of stakeholders:

- Collaboration with the Global Chief Medical Officer Network to take steps to improve awareness of AMR amongst the approximate 9 million employees of the 55 participating companies globally.
- In Latin America, Merck & Co., Inc. has partnered with CIDEIM, an independent, non-profit microbiology/ infectious disease research institute to serve as an Antimicrobial Stewardship (AMS) Center of Excellence, providing training, guidance and support to hospitals across the region.
- Since 2008, Merck & Co., Inc. has worked with more than 900 hospitals in 27 countries to develop and implement stewardship programs. More than 10,000 healthcare providers have been trained and more than 500 locally tailored treatment pathways have been implemented.
- In 2009, Merck & Co., Inc. launched its first stewardship program in India, which enables local customization of globally accepted stewardship strategies and is also expanding its user-friendly eAMS mobile platform, which assists physicians in making empirical antimicrobial therapy decisions.
- Independent grant to the Center for Infectious Diseases Research and Policy to develop a web-based, dynamic, up-to-date resource on antimicrobial resistance and stewardship, including issues related to clinical practice, research, infection prevention, and policy, and across both human and animal health.
- Independent grant to the Society for Healthcare Epidemiology of America to develop and convene an annual conference on teaching sound research methodology for stewardship and sharing best practices regarding demonstrating and disseminating the impact of stewardship.
- Independent grant to the Antibiotic Resistance Action Center at George Washington University to work with the Urgent Care Association of America to develop and implement an educational campaign to improve health literacy about resistance and stewardship.

## ALLIANCE COMPANIES ARE WORKING TO ENSURE PROMOTIONAL ACTIVITIES ARE ADVANCING STEWARDSHIP

In the industry Roadmap, signatory companies committed to “examine our promotional activities to ensure they align with the goal of advancing stewardship and eliminate those that do not, to protect the utility of antibiotics by encouraging their correct use.”

Pharmaceutical promotion provides valuable information to providers, but should be done in a way that supports appropriate use and reduces inappropriate use. Antibiotics are unique as a treatment that needs to be preserved for when they are most needed. Promotional activities can be an area of concern for potential conflict of interest for the industry; therefore, stakeholders are interested in how companies are adapting their practices for these specific products.

Most responding companies have examined, or are intending to examine, their promotional activities to ensure that they are consistent with the goal of advancing stewardship (70%). Of these, large R&D biopharmaceutical and diagnostic companies perform well, with 90% and 80% respectively active in this area.

For those responding companies that have examined their promotional activities to ensure they support stewardship, half have modified product-specific promotional activities or sales and marketing incentives. Responding companies have altered their promotional activities in various ways:

- Repositioning advertising material to explain how some products advance antibiotic stewardship programs in hospitals.
- Adapting and introducing new mechanisms and promotional brochures explaining responsible antibiotics use.
- Removing sales-based incentives.

The responding companies not currently examining their promotional activities for consistency with appropriate use efforts are planning to do so within the next two years, in line with the industry Roadmap commitment. The companies that have already taken this step are encouraged to share their lessons with others.



Pharmaceutical promotion provides valuable information to providers, but should be done in a way that supports appropriate use and reduces inappropriate use.

## INFECTION PREVENTION AND CONTROL, HYGIENE & OTHER MEASURES: EMERGING AREAS FOR INDUSTRY

Prevention is a common catch-all for measures which may stop new or repeat infections. This includes infection prevention and control (IPC) measures, hygiene considerations such as water and sanitation, and vaccination (covered later). Industry has a less direct role in IPC and hygiene efforts, so these areas were not the focus of the current survey. However, some companies shared their contributions to IPC, hygiene and other measures.

## INFECTION PREVENTION AND CONTROL: GSK COMMUNITY-BASED PROJECTS

GSK is involved in many community-based projects contributing to the prevention and control of infections. It re-invests 20% of profits made in less developed countries (LDCs) back into improving the healthcare infrastructure and educating communities in those countries to recognize diseases and refer to health services. Since 2009, GSK has invested in 35 LDCs, helping support the training of 40,000 frontline health workers and reaching 11 million people. GSK also invests in Personal Hygiene and Sanitation Education (PHASE) for children in the world's poorest countries and, through partnership with Save the Children, it has developed an antiseptic gel to prevent umbilical cord infections in new born infants.

Given the unique role that vaccines and diagnostic tests have to play regarding this aspect of appropriate use, we focus on these manufacturers below.

### DIAGNOSTICS

Diagnostics tests are crucial in the fight against AMR. They help ensure that the right patients receive the right treatment based on the pathogen and infection. In addition to the vital role of ongoing product innovation (see Research and Science section) for treatment optimization for individual patients, diagnostic tests can facilitate epidemiological surveillance. This includes the early identification of emerging resistant infections and transmission, which represents a key step in broader AMR efforts. Responding companies reported a number of activities in this regard.

## DIAGNOSTICS DEVELOPMENTS

- **Peptilogics Inc.** is exploring the feasibility of implementing and using rapid diagnostics to restrict the use of product under development so that it is only used with the appropriate patient populations.
- **bioMérieux** routinely monitors emerging resistance and the performance of current antibiotics to determine if they need to be redeveloped to better detect resistance in the field. bioMérieux works with the CDC, the Clinical & Laboratory Standards Institute, the EU's European Committee on Antimicrobial Susceptibility Testing, and other public health and/or academic organizations to establish breakpoints, exchange scientific information and understand the most "problematic" strains and use these as a challenge set to ensure a high level of performance for current/difficult strains.
- **Ares Genetics (Curetis AG)** has the GEAR Database, which currently comprises the full genome sequences of 11,000 clinical isolates collected globally over three decades as well as deep phenotyping data on their sensitivity to the 21 most commonly used antibiotics. The database enables deeper insight into the genetics of antibiotic resistance and can be leveraged for improved rapid diagnostic tests for antibiotic resistance as well as support pharmaceutical manufacturers in understanding mechanisms of action, lead prioritization and clinical development.



## ADVAMEDDX SUPPORTING DIAGNOSTIC COMPANIES

AdvaMedDx, the US national association focused on policy opportunities and challenges facing companies that discover, develop and manufacture diagnostic technologies. It is committed to collaborating with key global health stakeholders to optimize the use of diagnostic tests in the fight against AMR. It educates patients, providers and policymakers on the critical role they play in helping to curb this public health crisis.

In January 2017, AdvaMedDx announced a global stakeholder initiative to optimize the use of diagnostic tests. The initiative is based on a stakeholder statement of commitment that serves as a framework for collaborative action, outlining specific goals for leveraging existing diagnostic solutions and investing in improvements and access. In addition to outlining future goals, the commitment highlights the immediate benefits of leveraging existing diagnostic tests.

AdvaMedDx has also developed materials to help educate both the general public and healthcare professionals about the prudent use of antibiotics and how diagnostics can serve as an important tool in identifying the cause of an infection and, in turn, help improve prescribing decisions and better inform care. AdvaMedDx has also organized a number of events in the US and Geneva focused on raising the visibility of the role of diagnostics in fighting AMR.

## TEST TARGET TREAT™ INITIATIVE, ABBOTT

The Test Target Treat™ initiative, implemented with the Alliance for the Prudent Use of Antibiotics, empowers healthcare professionals to make targeted treatment decisions sooner with rapid diagnostics, reducing inappropriate antimicrobial use and the spread of resistance. Test Target Treat has over 60,000 visitors each year from all regions of the world with free access to case studies, webinars by experts in the field of AMR and educational materials on Antimicrobial Stewardship. It also supports and helps develop educational materials in the field of AMS and appropriate use of antibiotics on an ongoing basis. It has provided an unrestricted grant to support the creation and operation of the free online Massive Open Online Course on Antimicrobial Stewardship. Developed by the British Society for Antimicrobial Chemotherapy and the University of Dundee, this landmark course is the first free, global online course available to all learners across the globe. Designed for healthcare professionals, this six-week course informs healthcare professional about – and empowers them to provide – safe, high-quality antibiotic use. The course was launched in September 2015; in the first 12 months, over 30,000 people registered. It has recently been translated into Mandarin.

## VACCINES

Vaccines hold considerable promise in the field of AMR – not only to pre-emptively reduce the burden of infectious diseases but to reduce the prevalence of resistance by reducing the need for antibiotics to which we may become resistant.<sup>32</sup>

The impact of a vaccine is likely to be highest for diseases with a high burden, where antibiotics are the primary treatment and where resistance is high and increasing, such as TB or typhoid. However, at the moment, vaccines are only available to prevent a small proportion of infectious diseases caused by bacterial pathogens. The successful development of vaccines and universal vaccination will be important milestones in the fight against AMR.



## ANIMAL HEALTH

The Alliance recognizes the importance of improving antibiotic use in animals. However, the Health for Animals member company have made their own set of commitments. Only one Alliance member develops and produces vaccines and antibiotics for animals.

## HEALTH FOR ANIMALS: GLOBAL ANIMAL MEDICINES ASSOCIATION

Health for Animals promotes health for animals worldwide, protecting animals and – as a consequence – humans from disease. As an organization it acts as a unified global industry voice drawing its membership from across both the world and the animal health sector (producers of animal health products and their associations; one member of the AMR Industry Alliance is also a member of Health for Animals). Health for Animals works across a multitude of themes and issues and has recently released a declaration on the animal health's sector response to the antimicrobial resistance crisis. Members commit to five principles and practical actions:

- Protect animal health and welfare in a unified One Health approach
- Use antibiotics judiciously and responsibly
- Invest in development of products for prevention and treatment
- Promote disease prevention and increased access to products/expertise
- Increase knowledge, transparency and communications

## 8.3 GAPS AND EMERGING SOLUTIONS

Improving appropriate use of antibiotics requires actions from many different stakeholders, including industry.

More can be done by industry to:

- Develop and implement appropriate use strategies, policies and plans to ensure prescribers and patients access and use products effectively
- Harmonize surveillance approaches to facilitate greater data accessibility, collaboration and analysis across the datasets
- Support public awareness campaigns on AMR and appropriate use
- Promote wider use of vaccines that can prevent infections
- Partner with other health actors to address OTC and non-prescription internet sales
- Work to reduce the inappropriate use of antibiotics in humans and animals.

Other players, particularly policymakers, can support these actions, as well:

- Implement patient-centered antimicrobial stewardship programs that support appropriate use of antibiotics
- Set system-wide policies and take actions to reduce infections and the need for antibiotics
- Improve the provision of clean water and sanitation services – as well as access to symptom-relieving or hygiene OTC products to prevent infections
- Support the development of a solid evidence base for implementation of strategies to increase appropriate use of antibiotics.





9

ACCESS



Effective solutions to combat the rise of AMR must also address the challenges of access to antibiotics, diagnostics and vaccines, particularly – but not only – in LMICs. Action to address AMR should balance appropriate use of antibiotics with the need to improve access where it is lacking – ensuring access without excess.

## 9.1 BACKGROUND AND CHALLENGES

While the CDC estimates that one in three<sup>33</sup> antibiotic prescriptions in the US is unnecessary, almost 6 million people die each year around the world from infections because they lack access to antibiotics.<sup>34</sup> Enhanced access to antibiotics – aligned with antimicrobial stewardship – will save lives and slow the spread of AMR.

But enhancing access to antibiotics, particularly in LMICs, is challenging. Countries with high burdens of infectious diseases and weak health systems often struggle to provide basic access to healthcare, including generic antibiotics. And access is not just a developing world issue; high-income countries (HICs) are increasingly experiencing access problems for some antibiotics due to supply chain issues, ineffective procurement, products being discontinued in certain markets, and the challenges of maintaining supply of existing older antibiotics.<sup>35</sup> There are also access issues associated with the reimbursement systems in high-income markets, including hospital bundled-payment mechanisms that can discourage use of novel antibiotics, even when they are the most appropriate treatment for a patient.

Affordability can be one barrier to access for patients. Developers have traditionally recouped their investment in R&D on novel antibiotics through higher prices while these products are patent protected. On the other hand, low prices can jeopardize quality, sustainable production and are a disincentive to the use of diagnostics.

Regulation that makes antibiotics available exclusively through prescription, while an effective and valuable means to improve appropriate use in some countries, may have the unintended consequence of cutting off access altogether for parts of the population, particularly in poor and resource constrained areas.<sup>36</sup>

Ensuring supply chains are continuous, sustainable and secure is key to improving antibiotic access in all countries. Antibiotics are one of the therapeutic groups most affected by supply chain disruption resulting from production challenges. Additionally, challenges in demand forecasting and distribution can lead to stock-outs of essential medicines and antibiotics.<sup>37</sup> This in turn can drive the circulation of substandard or falsified antibiotics. A recent WHO report found that one in 10 medical products in LMICs is substandard or falsified,<sup>38</sup> and of these antimalarials and antibiotics are the most commonly reported. This may cause harm to their users and contribute to AMR in every region of the world by increasing the possibility of sub-therapeutic doses of active ingredients in people who use them.<sup>39</sup>

Despite growing multi-sector attention, there is a lack of consensus on how best to expand appropriate access to antibiotics (both novel and generic), vaccines and diagnostics globally. Industry has a role, but expanding appropriate access will require effort from many stakeholders. There is no one-size-fits-all solution to access challenges; tailored approaches will be required to ensure market sustainability.



## WHO'S ESSENTIAL MEDICINES LIST (EML)

The WHO EML, updated every two years since 1977, contains medications considered to be most effective and safe to meet the most important needs in a health system, including antibacterials. The most recent review saw 10 additions made to the main list and 12 additions made to the children-specific list. The EML provides a framework that can inform industry's approach to enhancing access to different types of antibiotics. A new categorization for antibacterials was also proposed:

- **Access:** First and second choice antibiotics for the most common infectious syndromes
- **Watch:** Antibiotics with higher resistance potential whose use should be limited
- **Reserve:** Antibiotics to be used mainly as “last resort” treatment options

## 9.2 AMR INDUSTRY ALLIANCE ACTION TO DATE

In the Davos Declaration, Alliance companies commit to “improve access to high quality antibiotics and ensure that new ones are available to all.” Roadmap signatories also “support mechanisms to facilitate affordable access to high quality new and existing antibiotics, diagnostics and vaccines to the patients who need them, in all parts of the world and at all levels of income.” The Alliance calls for collaborative efforts – recognizing the success of initiatives to improve global access to drugs in HIV, TB and malaria – to address issues of access to antibiotics.

The Roadmap specifically commits signatories to work with other parties to: identify and address specific access, market sustainability and supply bottlenecks for existing antibiotics, vaccines, and diagnostics; to improve access to new antibiotics, vaccines, and diagnostics; and seek to reduce the prevalence of substandard/counterfeit antibiotics in high risk markets.

Of the responding companies, half have approved AMR-relevant products on the market. Other companies, mostly biotechnology companies and SMEs, do not have any approved products. The following sections focus on how companies with approved products are approaching the access-excess tension.



## ALLIANCE COMPANIES HAVE DEVELOPED STRATEGIES, POLICIES AND PLANS FOR ACCESS

Enhancing access to AMR-relevant products is clearly a focus for many Alliance members: more than three-quarters with AMR-relevant products on the market have a formal access strategy, policy or plan in place covering some or all of their products. Approximately half of companies with relevant R&D activity in the last two years have some kind of access strategy, policy or plan – slightly more when considering those with clinical stage R&D only. It is encouraging that despite only a few of the biotechnology companies having products available on the market, 38% have an access strategy, policy or plan in place. For patented antibiotics, over 70% of launch plans were tailored for access prior to launch.

**75%+**

OF RESPONDING COMPANIES WITH AMR-RELEVANT PRODUCTS ON THE MARKET HAVE A **FORMAL ACCESS STRATEGY, POLICY OR PLAN IN PLACE COVERING SOME OR ALL PRODUCTS**

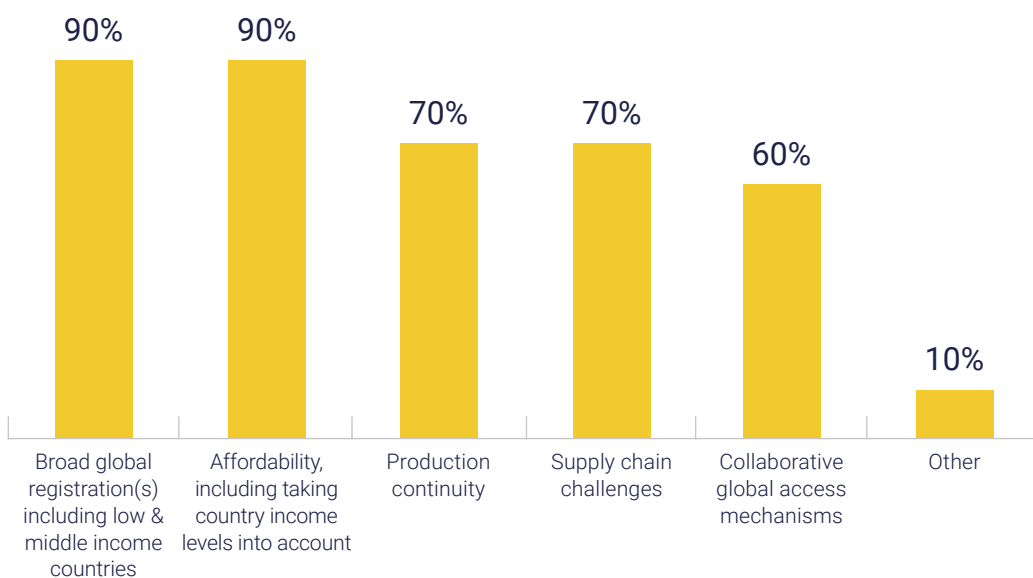
**90%+**

ACCESS PLANS DEVELOPED FOR GENERIC AND INNOVATIVE ANTIBIOTICS FEATURED: **BROAD GLOBAL REGISTRATION (INCLUDING LMICs) AND AFFORDABILITY**

Two of the most important access determinants within the control of companies, broad global registration (including in LMICs) and affordability, feature most often in companies' access plans – for instance, in more than 90% of access plans developed for generic and innovative antibiotics.

Two of the three responding generics companies have access plans – one covering the entire portfolio, the other broadly encompassing broad global registration and affordability.

While responding large R&D biopharmaceutical companies lead on transparency in this area with two-thirds of access plans publicly available, the majority of responding companies with access plans (78%) have not published these, indicating an area where steps could be taken in coming years. Stakeholder scrutiny is important and making more of these plans publicly available by all sectors is an important area for improvement.



**FIGURE 18:** PROPORTION OF RESPONDING COMPANIES' ACCESS PLANS, STRATEGIES OR POLICIES FOR PATENTED ANTIBIOTICS FEATURING THESE ASPECTS (TOTAL: 10).



## PROVIDING ACCESS TO VACCINES, ANTIBIOTICS, DIAGNOSTICS & TREATMENT FOR INFECTIONS, PFIZER

Trachoma is a preventable eye disease, caused by the bacterium *Chlamydia trachomatis*, that can lead to blindness. Millions of people in 41 countries are at risk of developing trachoma despite it being treatable and preventable. Pfizer has been working with the International Trachoma Initiative, a part of the Alliance for the Global Elimination of Trachoma by 2020, to provide access to antibiotics that treat trachoma. The initiative brings together 100 governments, NGOs and private sector partners and implements the SAFE (surgery, antibiotics, facial cleanliness and environmental improvements) strategy to address trachoma. Pfizer has donated 500 million doses of antibiotic azithromycin for those in need.

Pfizer is also helping to address two other treatable infections: cryptococcal meningitis and esophageal candidiasis. Pfizer works to improve access to diagnostics and treatment as part of the Diflucan Partnership Program. The partnerships provide face-to-face training, distributes program materials to healthcare professionals to help improve patient management and medicine distribution, and develops online training modules to support the diagnosis. Since 2000, the program has donated over 106 million fluconazole treatments with a total value of more than USD 1.8 billion to more than 6,000 sites in 63 countries across Africa, Asia, the Caribbean, and Latin America.

Pfizer also participates in Gavi, which funds immunization programs for some of the world's poorest countries. It has committed 740 million doses of vaccine Prevenar® 13 as part of the Advanced Market Commitment. Since 2010, more than 45 low-income countries (LICs) have launched pneumococcal immunization programs with the vaccine.

## EXTENSIVE PRODUCT REGISTRATION STRATEGY FOR ACCESS, MERCK & CO., INC.

Merck & Co., Inc. has an extensive product registration strategy and wide registration footprint. For example, as of September 2017, Merck & Co., Inc.'s most recently approved antibiotic Zerbaxa® (ceftolozane/tazobactam; approved in the US in December 2014) had been registered in over 50 countries, with over 20 further submissions pending. For older antimicrobials like Tienam® (imipenem/cilastatin), Merck & Co., Inc. holds marketing authorizations in over 100 countries, including some LICs. Merck & Co., Inc. has also created early access programs (in line with relevant laws and policies) to partner with governments and Ministries of Health to make products available for urgent cases prior to registration.

## AN EQUITABLE PRICING STRATEGY & IP PROTECTION FOR IMPROVING ACCESS, GSK

GSK is working to implement an equitable pricing strategy. It applies tiered pricing based on a country's wealth and ability to pay, capping the prices of medicines in LDCs at no more than 25% of prices charged in developed countries. GSK takes a flexible and multi-faceted approach to intellectual property (IP) protection, expanding its graduated approach to filing and enforcing patents so that IP protection reflects a country's economic maturity. GSK does not file for patent protection in LDCs and LICs. In LMICs it grants licences to generic manufacturers to supply versions of GSK medicines.

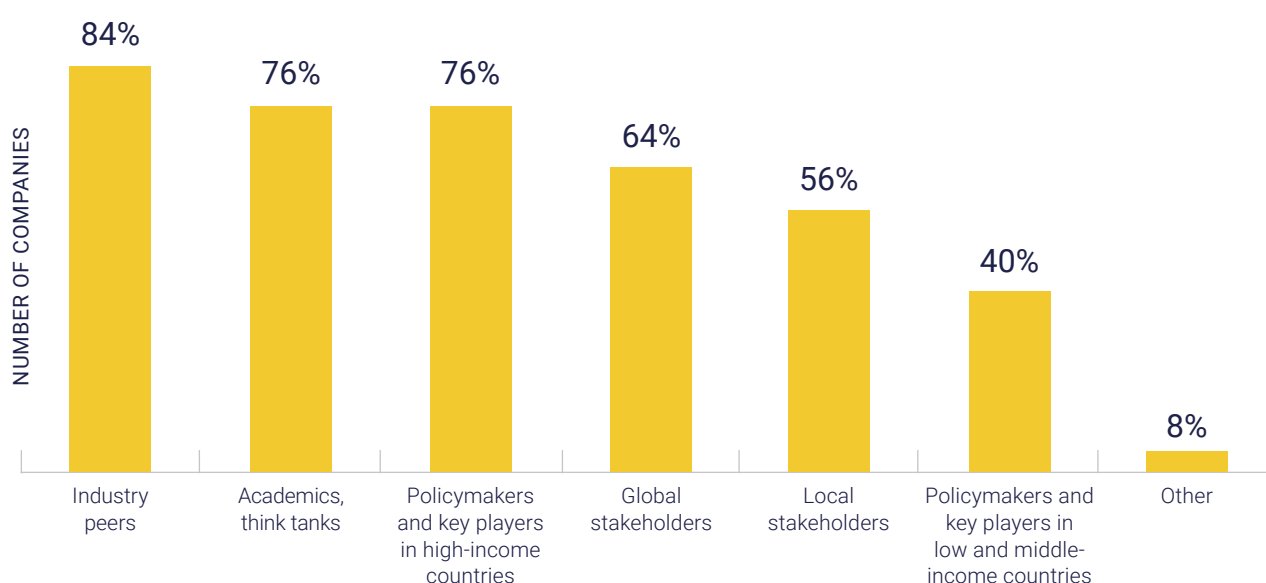
To improve access to vaccines, GSK partners with Gavi, which funds immunization programs for some of the world's poorest countries. Eligible countries get GSK's lowest prices, which can be as little as one-tenth of those for developed nations. GSK has also committed to freeze vaccine prices for graduating countries for 10 years, and will provide Gavi with more than 850 million vaccine doses at reduced prices to help protect 300 million children in the developing world by 2024.

## BROAD STAKEHOLDER ENGAGEMENT ON ACCESS

Due to the multi-stakeholder nature of access challenges, there is broad recognition of the importance of collaborative efforts, with over 70% of responding companies engaging in dialogues with external stakeholders regarding the subject of access to their AMR-relevant products. These discussions take place across a broad range of stakeholders: three-quarters engage with academics and think tanks as well as policymakers and key players in HICs. About two-thirds engage with global stakeholders such as WHO and international NGOs.

Across the board, responding biotechnology companies have not engaged directly with policymakers in LMICs. This follows from their core focus on R&D and limited commercial development and reach, given only a fraction intend to market compounds themselves.

Many responding companies - including biotechnology, diagnostic and generics companies - often engage indirectly on access principles through their associations.



**FIGURE 19: PROPORTION OF RESPONDING COMPANIES ENGAGING WITH DIFFERENT STAKEHOLDER GROUPS REGARDING ACCESS TO THEIR AMR-RELEVANT PRODUCTS (TOTAL: 25).**

About half of responding large R&D biopharmaceutical companies, on the other hand, were engaged in discussions with these key players and policymakers in LMICs, compared with 72% in HICs (high income countries). See below some highlights from their areas of engagement:

- Two-thirds of overall engagement activity focused on collaborative global access mechanisms and broad global registration.
- Affordability featured in less than half of responding companies' areas of engagement, but nearly all large R&D biopharmaceutical companies cover it.
- Production continuity and supply chain challenges featured in 40% of engagements, which may reflect the high proportion of companies that do not yet have a marketed product.

Only 20% of responding companies that have engaged with external stakeholders report that initiatives, such as company-NGO partnerships, had been launched as a result.

## ENABLING ACCESS TO NEW TREATMENT FOR MULTI-DRUG RESISTANT TB

Each year, there are roughly half a million new cases of multi-drug resistant TB (MDR-TB), many of them transmissible. Only a quarter of these patients start treatment, and only half of those are successfully treated. The standard of care for MDR-TB treatment until recently has required approximately 14,000 pills and injections taken over the course of 24 months, with only moderate success and many side effects.

**Johnson & Johnson:** Sirturo® (bedaquiline), as part of combination therapy, received accelerated approval by the US FDA at the end of 2012 and conditional approval in the EU in 2014 for the treatment of MDR-TB. It represented the first new drug for TB treatment in more than 40 years. The discovery, research and clinical development program of this product, with a new mechanism of action, spanned nearly two decades and involved 15 clinical trials.

Many steps were taken to promote broad, equitable access to bedaquiline: a global distribution agreement through the Stop TB Partnership® Global Drug Facility, targeted access programs in key high-burden countries, a safety net donation program of 30,000 regimens through USAID, equity based tiered pricing in key markets, and a manufacturing partnership with Pharmstandard to promote access in Russia and the Commonwealth of Independent States. Johnson & Johnson's Global Public Health group and Janssen have been working with a variety of local, national and global stakeholders. This includes providing healthcare provider training and undertaking appropriate pharmacovigilance and surveillance activities to monitor resistance to bedaquiline and other companion treatments within the same regimen.

To date, more than 30,000 patients have been put on bedaquiline in more than 80 countries. The most significant rollout to date has occurred in South Africa through a dedicated national program. Rollout is expanding in other key high-burden markets, including India, Russia, and China where controlled access programs are in place.

Janssen and the non-profit organization FIND are also providing increased access to molecular diagnostic tools for TB case detection and MDR-TB diagnosis, and on ensuring accelerated access to effective treatments.

**Otsuka:** In 2002, Otsuka discovered Deltyba™ (delamanid), which received regulatory approval from the European Medicines Agency, as well as Japan, in 2014 as an oral treatment against adult pulmonary MDR-TB and in further countries in 2015 and 2016. In 2015, it was added to the WHO's EML.

Otsuka launched the FighTBack initiative with the aim to expand access to and ensure responsible use of delamanid, as well as to continue R&D efforts into novel MDR-TB treatment options, including diagnostic and treatment monitoring tools. The aim is that at least 20% of diagnosed and treated MDR-TB patients have delamanid as part of their treatment regimen through high quality programs by 2020. A key component of the initiative is also Otsuka's partnership with Stop TB Partnership® Global Drug Facility from 2016, which enables about 100 eligible LMICs to procure delamanid.

Otsuka also participates in a number of collaborative studies. One of them is the endTB project led by Médecins Sans Frontières (MSF), Partners in Health, and Interactive Research & Development. The endTB project will evaluate new regimens for the treatment of MDR-TB and reduce existing country-level barriers to the uptake of new TB drugs. Another study is called "MDR-END" led by the Seoul National University Hospital, looking at regimens that could shorten MDR-TB treatment. In December 2015, Otsuka provided a one-time donation of 400 treatment courses of delamanid to MSF for the endTB project in order to provide rapid access to patients in urgent need.

Otsuka and **Mylan**, both Alliance members, also agreed on a license for access to delamanid in LMICs.

*The **Global Drug Facility** is the largest procurer of quality-assured TB medicines and provides TB drug management technical assistance in an effort to promote equitable access to TB medicines and diagnostics.*



## MANAGING PRODUCT SUPPLY DISRUPTIONS

Nearly two-thirds of responding large R&D biopharmaceutical and generics companies with AMR-relevant products on the market were aware of delays or supply chain disruptions to at least one of their AMR-relevant products in the last two years. Such disruptions may have impacted downstream markets, causing stock-outs and resulting in restricted access to antibiotics and other medicines. Global supply chains are complex and there is insufficient clarity on the underlying drivers. Common reasons cited for product supply disruptions include:

- Unanticipated delays to regulatory approvals related to change control.
- External supply chain equipment failures and adverse quality inspection outcomes.
- Environmental monitoring investigations related to sterile products.

In almost all cases, companies that reported supply chain disruptions had well-defined and robust processes in place for identifying and addressing product continuity issues – for instance, in some cases, working with medical experts to identify possible medical alternatives. One responding company noted that insufficient supply chain transparency has led to a lack of awareness of this issue, resulting in unwanted and unsustainable developments that affect both originator-type products as well as older generic antibiotics in both emerging and developed countries.

In order to stabilize supply interruptions, two-thirds of these companies have implemented some kind of integrated risk management process to anticipate potential failures. A sub-set of this group is going further, moving to ensure a duality of sources of supply when sourcing drug product and/or components from high risk geographies.

## REDUCING THE PREVALENCE OF SUBSTANDARD/FALSIFIED AMR-RELEVANT PRODUCTS

Antibiotics are some of the most reported substandard and falsified medical products. This contributes to the problem of resistance by exposing patients to sub-optimal doses.<sup>40</sup>

The trade in illegal medicines is a global issue that requires global solutions, including strong partnerships and education. A number of responding companies have policies in place requiring employees to report substandard or falsified medicines that come to their attention as well as receiving reports from patients, healthcare professionals and law enforcement and regulators. For example, companies may gather evidence for a prosecution (according to globally acceptable standards) for relevant local law enforcement agencies, report appropriate cases to health authorities and may take in-market action alerting doctors, pharmacists or wholesalers.

- Of responding companies with AMR-relevant products on the market, nearly half report having specific strategies in place to help reduce the prevalence of substandard and falsified products.
- Serialization, or “track and trace,” is favored by the majority of companies with strategies (88%), and the same proportion have detection and reporting systems in place to capture and report incidents of substandard/falsified AMR-relevant products.
- All responding companies share information with relevant national authorities as relevant, 57% share information from their detection systems with business partners, and 43% share information on detected counterfeits with end customers and the WHO Rapid Alert System.

## 9.3 GAPS AND EMERGING SOLUTIONS

Industry efforts to expand access to medicines in LMICs have involved a number of strategies and approaches, including:

- Tiered pricing strategies (both within and between countries)
- Increased product registration in priority countries
- Non-exclusive voluntary licensing approaches
- Product donations

While some of these strategies may be relevant for antibiotics, there are specific challenges to this therapeutic area.





In addition to these industry-initiated mechanisms, responding companies indicate they are increasingly partnering with global organizations such as Gavi, a public-private global health partnership that is increasing access to immunization in poor countries and has helped avert an estimated four million deaths by providing vaccines to 296 million children from 2010 to 2015.<sup>41</sup>

Despite efforts by many responding companies, often in partnership with the public sector and global stakeholders, the analysis suggests that there is a lack of tangible antibiotic-specific action and reporting from any sector to identify and overcome the considerable barriers that prevent people from accessing antibiotics.

While most companies have broad access strategies or principles in place, few of these cover entire AMR-relevant portfolios or address challenges specific to this therapeutic area; only two companies have made their AMR-relevant strategies public. With a small number of concrete examples of improved access to AMR-relevant products, or publicly-available policies and plans for scrutiny, it is difficult to see how responding Alliance members are progressing substantially in this area. The additional challenge of aiming for wide access, without triggering uncontrolled excess use of antibiotics means that specific approaches are needed, but cannot be delivered solely by companies.

Generics companies are very often pivotal to making off-patent medicines and antibiotics, rapidly, widely and affordably available throughout the world but especially so in LMICs. While their core business model aligns with this goal, greater transparency would help external stakeholders acknowledge and understand the approaches this sector is taking to balance their access efforts with excess (i.e. appropriate use) considerations. The Alliance represents a sub-set of the global

pharmaceutical market, and uptake for this reporting exercise included three generics companies.

Despite the shortcomings, there are strong signals from responding companies that partnerships are being forged and dialogues had across the AMR community with 70% engaging with external stakeholders, with good representation across the industry and across the spectrum of policymakers, academics, and global and local stakeholders.

Access will remain a challenge – both in LMICs with weak health systems and HICs where reimbursement models may not always incentivize appropriate use or provide a sustainable marketplace. As the developers and manufacturers of AMR-relevant products, industry has an important role to play. Others must play their part, too. There exist today no access funding or global procurement mechanisms for industry to collaborate with, and beyond the WHO's EML<sup>42</sup>, there is limited guidance for companies on how to expand access. A lack of common language to talk about barriers limits the broad and open discussions that are needed on this subject at multiple levels of the AMR community.

Through the examples that have been highlighted in this report, where there are donors, mechanisms or national programs, industry has participated and delivered results. For instance, industry welcomes further harmonization of regulatory procedures and the reduction of regulatory barriers in LMICs, which can improve access (in addition to reducing costs). Partnerships between industry and national authorities, global multilateral organizations, non-governmental and not-for-profit organizations are fundamental to increasing access to antibiotics and other AMR-relevant technologies while conserving their effectiveness through appropriate use.



Access will remain a challenge – both in LMICs with weak health systems and HICs where reimbursement models may not always incentivize appropriate use.



Throat Lozenges

1100

25

0

Each capsule contains  
400 mg gabapentin  
Elke kapsule bevat  
400 mg gabapentin

gabapentin 400 mg  
capsules  
gabapentin 400 mg  
capsules

# 10

## MANUFACTURING & ENVIRONMENT



The manufacturing of antibiotics may increase the risk of AMR if factories do not carefully manage their manufacturing discharges. In this section, we explore this link, what industry is doing about it and where there are outstanding challenges.

## 10.1 BACKGROUND AND CHALLENGES

Antimicrobials are present in the environment – from natural and man-made causes. Bacteria exposed to these environmental antimicrobials can develop resistance. Sources of environmental antimicrobials can include the food chain, water supply, run-off from farms, sewage, as well as human and animal use and excretion (understood to be the primary sources), and antibiotics from manufacturing waste. Academic, media and other reports suggest elevated levels of antimicrobials are present in some environmental samples. Many stakeholders, including industry, recognize this is a concern.

The supply chain for producing antibiotics is global, with companies own manufacturing facilities as well as their suppliers based in countries around the world. Production facilities are expected to operate in compliance with local environmental regulations as well as, in the case of global pharmaceutical companies, specific corporate environmental requirements.

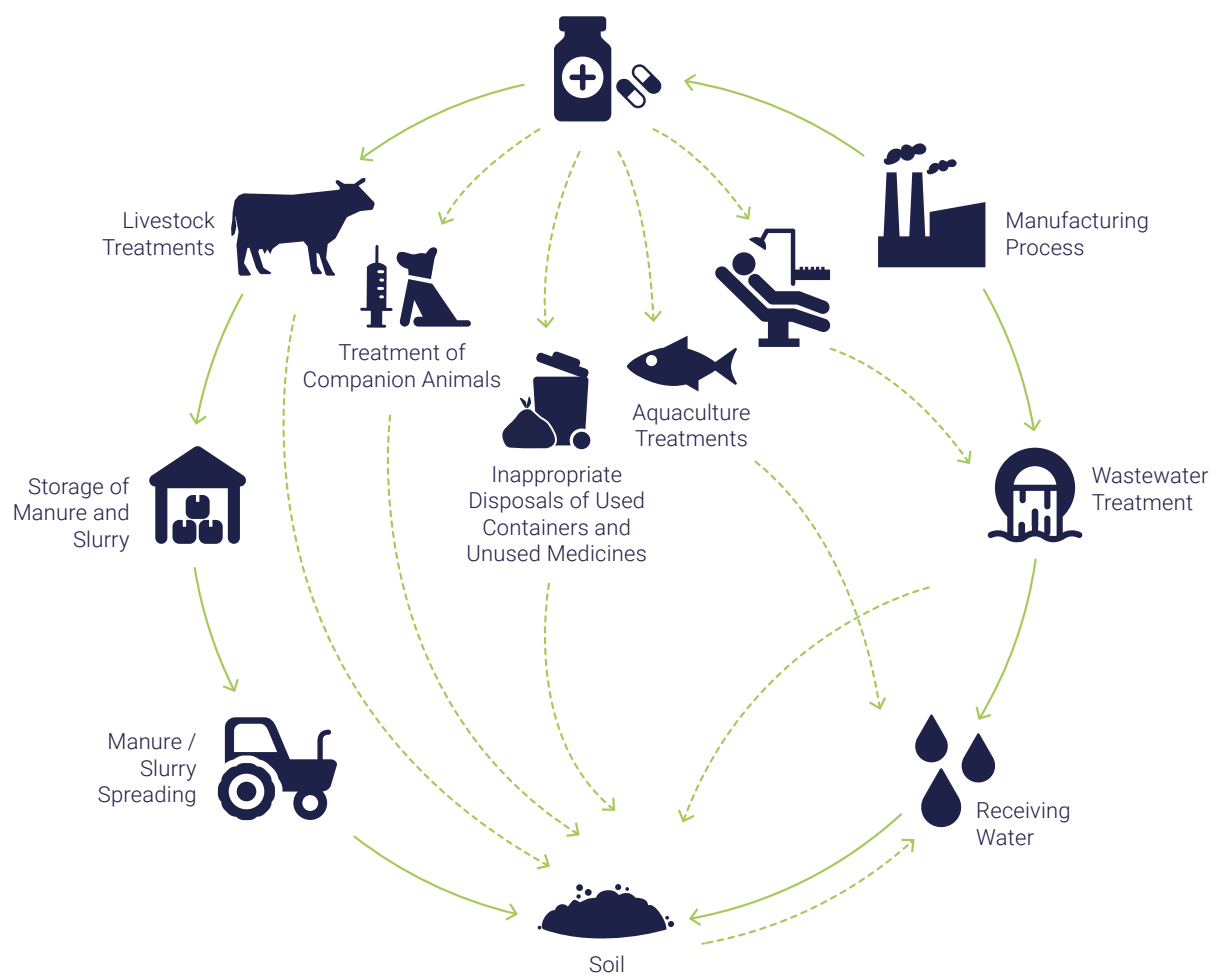
The Alliance seeks to ensure common, protective, environmental expectations are established and adhered to across the antibiotic supply chain.

Challenges in manufacturing and the environment are diverse and include:

- Need for a clear understanding of the pathway for antibiotics reaching the environment, the contribution of antibiotic residue in the environment to bacteria developing resistance, and how resistant bacteria spread to humans

- Inconsistency in regulatory inspection, oversight and enforcement of existing regulations of current practices
- Lack of common or recognized standards, nationally or internationally, for acceptable environmental control of API in antibiotic manufacturing operations
- Lack of agreed scientific methods and environmental impact data for products to determine environmentally safe discharge levels of residual antibiotics in manufacturing wastewater
- Broader waste management, infrastructure and pollution concerns in some countries as it correlates to potentially poor environmental management and performance in the supply chain, including inconsistency in regulatory inspection or oversight
- Challenges with available technology that limit scalability and affordability for implementation in all countries

As all concerned stakeholders advance their understanding of this topic, industry is taking actions to minimize the presence of antibiotics in the manufacturing waste discharges. The Alliance recognizes its leadership role to advance responsible manufacturing across industry, including and beyond the Alliance and Roadmap companies.



**FIGURE 20:** SOURCES OF ANTIMICROBIALS IN THE ENVIRONMENT. AS BASED ON THE ORIGINAL FROM BOXALL, ALISTAIR A. B., 'THE ENVIRONMENTAL SIDE EFFECTS OF MEDICATION', EUROPEAN MOLECULAR BIOLOGY ORGANIZATION REPORTS, VOL. 5, NO. 12, 2004.



## 10.2 AMR INDUSTRY ALLIANCE ACTION TO DATE

In the Davos Declaration, Alliance members commit to work to support measures to reduce environmental pollution from antibiotics. The Roadmap introduces more specific commitments related to the production of antibiotics and the environment:

- Assess good practice in controlling releases of antibiotics into the environment
- Establish a common framework for managing antibiotic discharge and start to implement in 2018
- Develop a mechanism to transparently demonstrate that supply chains meet the standards in the framework
- Establish science-driven, risk-based targets for discharge concentrations for antibiotics and good practice methods to reduce environmental impact of manufacturing discharges by 2020.

Twenty-six companies provided data relating to some survey questions on manufacturing and the environment. This includes 10 signatories of the industry Roadmap and 16 additional companies, some with launched products and others interested in evolving their thinking on the potential environmental impacts of their companies in future.

Alliance members' environmental practices regarding antibiotics were surveyed. This primarily encompasses companies producing antibiotics but could include those using antibiotics in-house – for research and development, for instance.

### CURRENT SIGNATORIES OF THE ROADMAP:

- 1 Allergan
- 2 AstraZeneca
- 3 Cipla
- 4 DSM Sinochem Pharmaceuticals
- 5 F. Hoffman-La Roche Ltd.
- 6 GSK
- 7 Johnson & Johnson
- 8 Merck and Co., Inc, Kenilworth, NJ, USA
- 9 Novartis
- 10 Pfizer
- 11 Sanofi
- 12 Shionogi & Co., Ltd.
- 13 Wockhardt



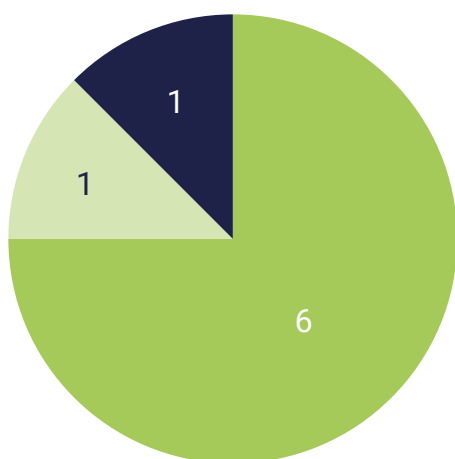
## SIGNATORY COMMITMENTS: STATUS

A number of companies have sound environmental management practices at their own facilities and have established environmental management expectations of suppliers. In 2017, many Roadmap signatories audited suppliers against expectations. Roadmap companies have shared their knowledge, expertise and experience to develop a common framework for managing antibiotic discharge (see Appendix). Finalized in late 2017 and made public for the first time in this report, they plan to start to apply it across their internal manufacturing and supply chain by the end of 2018, on track with Roadmap commitments. Going forward, additional companies have signalled they will adopt the requirements of the framework.

Furthermore, Roadmap companies plan to implement science-based discharge limits once they establish a method for determining resistance based limits (estimated 2020) and will adopt good practice methods to reduce the potential impact of manufacturing discharge. In the meantime, Roadmap signatories are developing interim guidance based on literature and pooled company ecotoxicology data to most effectively manage manufacturing waste water.

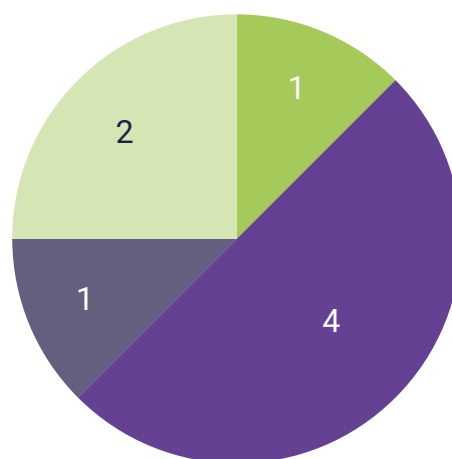
Three-quarters of responding companies anticipate beginning to implement good practice methods to reduce environmental impact of manufacturing discharge by 2018, in advance of the 2020 Roadmap commitment.

Responding companies aim to establish science-driven, risk-based targets for discharge concentrations for antibiotics. Half anticipate committing to discharge concentration targets within three years (by 2020), in line with the Roadmap commitment.



● BY 2018 ● BY 2019 ● BY 2025

**FIGURE 21:** PROPORTION OF RESPONDING COMPANIES (TOTAL: 8) THAT PLAN TO IMPLEMENT GOOD PRACTICE METHODS TO REDUCE THE ENVIRONMENTAL IMPACT OF MANUFACTURING DISCHARGE BY 2018, 2019, AND 2025.



● BY 2018 ● BY 2020 ● BY 2022 ● BY 2025

**FIGURE 22:** PROPORTION OF RESPONDING COMPANIES (TOTAL: 8) THAT ANTICIPATE COMMITTING TO DISCHARGE CONCENTRATION TARGETS 2018, 2019, 2022 AND 2025.



Plans are varied with regard to transparently demonstrating that their supply chains meet the standards in the Roadmap framework. One-quarter of responding companies anticipate doing so by 2018, with some expecting this to take until 2025.

Encouragingly, one-third of responding Alliance members who are not currently party to the Roadmap are considering signing up. Two-thirds of the Alliance is comprised of biotechnology companies, which may be too far from manufacturing and commercializing their products for the Roadmap to be immediately relevant.

## ALLIANCE COMPANIES ARE TAKING ACTION TO REDUCE THE POTENTIAL IMPACTS OF ANTIBIOTIC MANUFACTURING ON AMR

One-third of responding companies that produce antibiotics have in place a current strategy, policy or plan that addresses the release of antibiotics in internal manufacturing effluents that may contribute to AMR.

Of these, most (three-quarters) are taking specific actions to address the release of antibiotics in internal manufacturing effluents that may contribute to AMR:

- All include the implementation of procedures and measures to determine discharge concentrations (e.g., through mass balance, or, in some instances and where warranted, measurement).
- The majority also cover the identification of environmental risks as well as the determination of discharge concentrations and procedures.
- Approximately half externally disclose reporting of strategy, policy or plan, including breaches.
- Approximately one-quarter have internal compliance and/or external oversight procedures related to manufacturing discharges.
- In addition, individual companies report advocacy activity with external stakeholders for the establishment of science-driven and risk-based standards for active antibiotic compounds in pharmaceutical effluent and publishing Predicted-No-Effect-Concentration (PNEC) information.

## INDUSTRY ENGAGEMENT: ECO-PHARMACO-STEWARDSHIP (EPS) CONCEPT

The European pharmaceutical industry, represented by the Association of the European Self-Medication Industry (AESGP), the European Federation of Pharmaceutical Industries (EFPIA), and Medicines for Europe, recognizes and understands the concerns raised by stakeholders regarding the presence of pharmaceuticals in the environment. They have come together to develop the Eco-Pharmaco-Stewardship (EPS) concept, a proposal that strives to protect patients' access to medicines while appropriately considering environmental aspects. It takes a life-cycle approach to focus on areas where it believes industry can most effectively reduce the potential environmental risks that might result from industry activities. One of the initiative's pillars concerns managing pharmaceutical site effluent effectively, including antibiotics. The EPS initiative was launched in 2014 and is continuously growing and improving the knowledge of members.<sup>43</sup>

## SUSTAINABLY PRODUCED ANTIBIOTICS, DSM SINOCEM PHARMACEUTICALS (DSP)

As part of DSP's commitment to fight AMR through minimizing the environmental impact from antibiotics manufacturing, DSP is actively seeking to promote green, enzymatic routes for production of amoxicillin and other antibiotics, utilizing patented technology. Pharmaceutical manufacturing requires a large volume of solvents, produces considerable CO<sub>2</sub> emissions and contributes to the growing threat of AMR through the release of active pharmaceutical ingredients (APIs).

In 2000, DSP built a new plant for the production of antibiotics intermediates in Delft, the Netherlands, which was designed to be the most efficient of its kind in the world. It applied a number of technological innovations, such as DSP's unique, patented fermentative and enzymatic process. This approach, which has no need for chemical solvents, is more environmentally sustainable and has a much smaller carbon footprint than production methods used elsewhere. By 2011, the enzymatic production of APIs had been rolled out globally to DSP's manufacturing sites for beta-lactam antibiotics in China, India, Spain and Mexico.

Beyond eliminating solvents and improving energy efficiency, the company is committed to minimizing the release of antimicrobial active ingredients into the environment. The concept of dedicated wastewater treatment was extended to all other antibiotic production sites globally.

In 2015, DSP developed its own test to measure concentrations of antibiotic activity in effluent as a first step in defining the actual efficacy of its wastewater treatment. This test was rolled out to all its manufacturing sites in 2016.

## ALLIANCE COMPANIES ARE ASSESSING THE POTENTIAL IMPACTS OF THEIR SUPPLY CHAIN ON AMR

Approximately two-thirds of companies with antibiotic manufacturing operations have a strategy, policy or plan addressing the environmental impact of their business operations on AMR that extends to suppliers and supply chains.

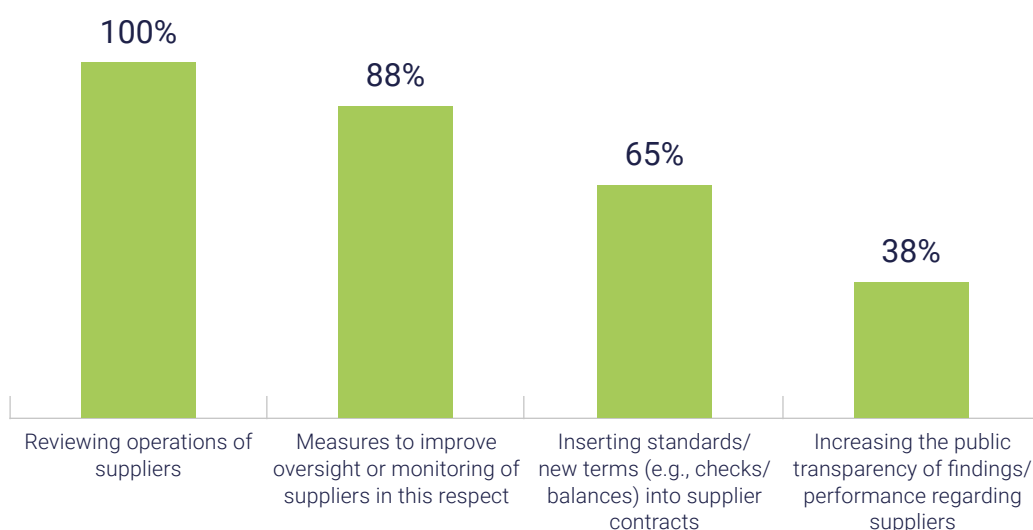
## ROADMAP IMPLEMENTATION IN ACTION

Roadmap signatories are committed to reviewing their manufacturing and supply chains; establishing a common framework for managing antibiotic discharge and working with stakeholders to develop a practical mechanism for demonstrating supply chains meet these standards; and establishing science-driven, risk-based targets for discharge concentrations and good practice methods to reduce environmental impact of manufacturing discharges by 2020.

Roadmap companies carried out tailored audits of their antibiotics manufacturing and supply chains in 2017. These audits range from a few manufacturing operations in the case of companies with a small number of antibiotic products, to over a hundred manufacturing and supplier sites in the case of companies with significant antibiotic portfolios.

These audits and future engagements with suppliers, including audits undertaken in accordance with the Roadmap's "common antibiotic manufacturing framework", will help ensure suppliers have sound environment practices in place, including adherence to applicable environmental regulations and good practices minimizing the concentration of antibiotic residues in manufacturing waste streams and appropriate treatment prior to discharge to the environment.

Many stakeholders believe that Alliance companies, including Roadmap signatories, are in an influential position, through their own sites and by encouraging their suppliers to effect change throughout the product supply chain. Of those companies taking action, two-thirds are reviewing the operations of suppliers. Just under two-thirds are increasing the public transparency of findings regarding suppliers. Almost half are inserting standards/new terms (e.g., checks/balances) into supplier contracts. One-quarter are active in other measures that address the environmental impact on AMR of their suppliers' operations. Leveraging the leadership represented by the Alliance will be important to advance responsible production by all manufacturers.



**FIGURE 23: PROPORTION OF RESPONDING COMPANIES (TOTAL: 8) IMPLEMENTING SPECIFIC ACTIVITIES RELATING TO REDUCING THE ENVIRONMENTAL IMPACT FROM PRODUCTION OF ANTIBIOTICS.**

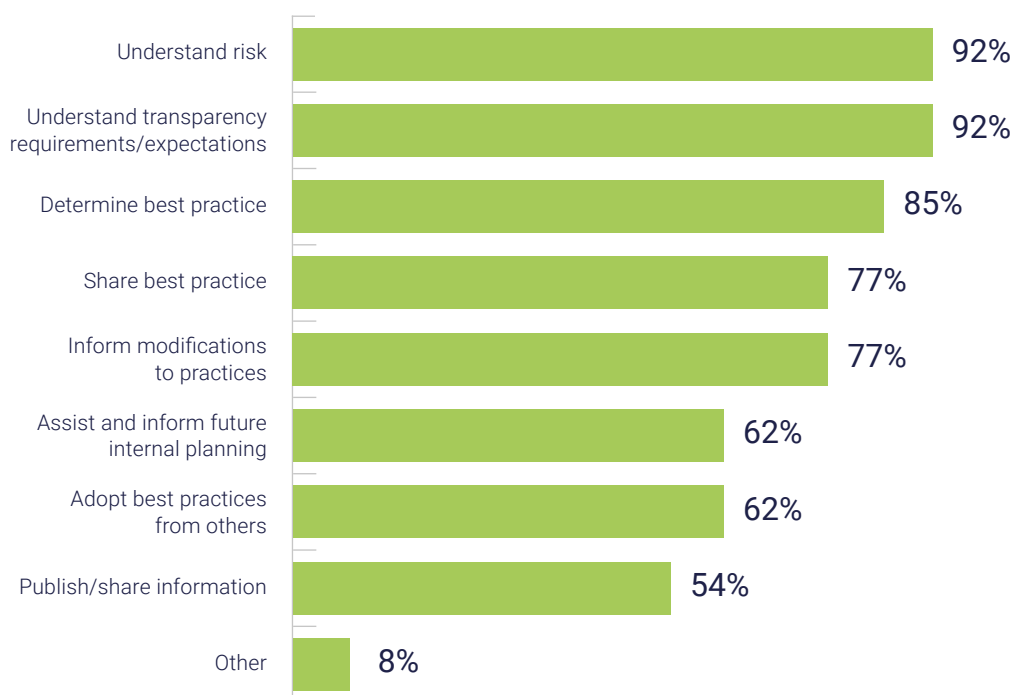
## EMERGING STAKEHOLDER ENGAGEMENT ON MANUFACTURING & THE ENVIRONMENT

Approximately half of the responding companies are engaged in discussions on the environmental impact of business operations on AMR with industry and/or other external stakeholders, such as governments, international and multilateral organizations, academic institutions, etc.

The specific objectives of engagement in this area vary (see Figure 24).

Engagement on manufacturing and the environment was seen as premature by a number of companies with R&D activities but no products yet on the market.

Some companies are looking forward to becoming more engaged in stakeholder discussions on this topic as it evolves, particularly over the next five years. Roadmap signatories, specifically, are committed to working with relevant stakeholders to develop science-driven, risk-based targets for discharge concentrations. More generally they are looking to help advance the understanding of manufacturing environmental management and relevant science through collaboration with stakeholders and participation in key national and international meetings, such as those organized through the UN Foundation, the US National Academies of Science and other similar bodies.



**FIGURE 24: ENGAGEMENT OBJECTIVES OF RESPONDING COMPANIES IN DISCUSSIONS WITH EXTERNAL STAKEHOLDERS ON THE ENVIRONMENTAL IMPACT OF THEIR BUSINESS OPERATIONS (TOTAL: 13).**

## INTEGRATING HUMAN AND ENVIRONMENTAL HEALTH IN ANTIBIOTIC RISK ASSESSMENT, ASTRAZENECA

Effective environmental risk assessment regulatory guidance should be informed by science-based protection goals for antibiotic manufacturing discharges.

AstraZeneca established a program to help identify environmental protection goals that could be applied to antibiotic production facilities as part of their UN AMR Roadmap Commitments. It has fully funded (USD 140,000) a four-year PhD student with the University of Exeter to analyze all existing public environmental and clinical data assessing the impact of antibiotics. AstraZeneca is using the results to help inform its strategies to fill existing antibiotic data gaps and refine the way that antibiotics environmental risks are currently assessed. So far, this work has highlighted the need for:

- Inclusion of a larger selection of bacterial species for testing to account for the variability in sensitivity between species and for greater confidence in the protection of bacterial communities and the ecosystem services they provide.
- Test systems to determine PNEC or Minimum Selective Concentrations for AMR development for clinical and environmental species.
- In the absence of sufficient reliable clinical and environmental data, methodologies and empirical data to draw firmer conclusions on discharge limits.

## 10.3 GAPS AND EMERGING SOLUTIONS

The next few years will be a period of crucial learning for all stakeholders on antibiotics and the environment as companies advance in this area and implement the Roadmap commitments. Industry is invested in supplying needed antibiotics and using its knowledge and expertise to improve manufacturing and supply chain environmental management.

The Alliance provides a forum for companies committed to reducing the risk of AMR to work together to identify and advance solutions. Further, the Alliance recognizes that the Roadmap signatories represent a minority of current antibiotics manufacturing capacity and encourages all manufacturers of antibiotics to have policies and practices in place to improve environmental management in their own manufacturing and supply chains.



The next few years will be a period of crucial learning for all stakeholders on antibiotics and the environment.

### IMPLEMENTING 'ZERO LIQUID DISCHARGE' AT MANUFACTURING FACILITIES IN INDIA, MYLAN

Many of India's common, or public, effluent treatment plants, including those serving some of Mylan's facilities, have faced technological and operational challenges over the years in ensuring proper treatment of wastewater. The nation's environmental authorities have been focused on redoubling their efforts to address the situation.

A more practical approach to keeping antimicrobial compounds out of the environment is to prevent them from being discharged at all. Mylan began installing zero-liquid-discharge, or ZLD, equipment in 2009 to meet strict regulatory requirements, minimize wastewater contaminants, recycle wastewater for use in boilers and cooling towers, and reduce their impact on the surrounding communities. Today, all of Mylan's manufacturing plants in Hyderabad feature it.

Effluent from Mylan's ZLD facilities is recycled and reused in non-potable applications; there is no discharge to the environment or to common effluent treatment plants. All solid wastes generated go to authorized disposal sites. Further, many of Mylan's facilities are ISO 14001 certified and go through regular audits from certifying agencies.

These plants are operated 24 hours a day, seven days a week by qualified individuals and have been visited by various regulatory and environmental authorities, including the State Pollution Control Board, which often showcases Mylan's facilities to third parties as best-in-class ZLD units. The plants also have been audited by the multinational companies to which Mylan supplies APIs.

Mylan's use of ZLD technology helps eliminate the discharge of antibiotics and keep other APIs and AMR-contributing compounds out of the environment. Further, Mylan continues to invest in and expand the technology to other facilities throughout India, which lacks sophisticated water-treatment infrastructure and is home to approximately half of Mylan's production sites around the world.







# 11

## WHAT'S NEXT

### NEXT STEPS FOR THE ALLIANCE

This report is the first review of the AMR Industry Alliance's activity and progress on commitments made in the Davos Declaration and Industry Roadmap.

The Alliance will review and report on progress and changing priorities every two years; the next report is to be published in 2020. We hope to see the following progress and next steps:

#### RESEARCH & SCIENCE

- More investment in AMR-relevant R&D, particularly that which targets new mechanisms of action or novel approaches
- More concrete action to address market challenges for antibiotics, vaccines, and diagnostics, especially in the area of pull incentives
- New collaborations, opportunities to engage in open-innovation initiatives
- Increased data exchange on off-protection antibiotics
- Progress towards developing consensus priority lists to signal unmet needs to vaccine and diagnostics developers

#### APPROPRIATE USE

- Further development and implementation of appropriate use strategies, policies and plans to ensure prescribers and patients access and use products effectively
- Harmonizing surveillance approaches to facilitate greater accessibility, collaboration and analysis across the datasets
- Increased public awareness campaigns on AMR and appropriate use
- Promotion of wider use of vaccines that can prevent infections
- Partnership with other health actors to address OTC and non-prescription internet sales
- Work to reduce the inappropriate use of antibiotics in humans and animals



## ACCESS

- Tangible antibiotic-specific action to identify the considerable barriers to appropriate access to antibiotics
- Increased dialogue on mechanisms to facilitate access to high-quality new and existing antibiotics, diagnostics, and vaccines
- Transparent access strategies, particularly from generics companies, to better understand progress and learning
- Common language to bring greater precision to discussions and more guidance from others on how to expand access would create a stronger basis for collaboration

## MANUFACTURING & ENVIRONMENT

- Implementation of the common framework for managing antibiotic discharge
- More companies assessing good practice in controlling releases of antibiotics into the environment
- Establishing science-driven, risk-based targets for discharge concentrations for antibiotics and good practice methods to reduce environmental impact of manufacturing discharges
- A mechanism to transparently demonstrate that supply chains meet standards agreed in the framework
- Greater engagement with diverse stakeholders on this issue
- More companies to sign up to the Roadmap

## THE ALLIANCE WILL GROW

The Alliance welcomes more life sciences companies involved in developing and producing AMR-relevant products to commit to the Davos Declaration and Roadmap, particularly SMEs and generics, and share their experience and plans.

## MORE ALLIANCE MEMBERS WILL CONTRIBUTE DATA

The Alliance will continue to aim for a response rate of 100% of members for more complete reporting.

The Davos Declaration will be monitored by the AMR Industry Alliance with the support of an external advisory group comprised of experts and stakeholders from diverse backgrounds. The group's objectives are to help the Alliance:

- Identify and share best practices and remaining barriers.
- Understand better where the industry could add value in the fight against AMR.
- Identify where improvements will be closely dependent on potential collaborations with external stakeholders, in particular governments.

Experts will be invited to provide suggestions on how the reporting mechanism and future progress targets for the AMR industry Alliance can be improved.

## CALL TO ACTION

There are gaps to close.

The AMR Industry Alliance represents a sub-set of the life sciences industry, but needs to expand to increase its impact. Collaboration within the industry is vital.

Other stakeholders – including but not limited to other sectors, governments, international organizations, NGOs and academia – also have essential roles to play. The Alliance reiterates the call to action to governments made in the Davos Declaration to implement new and alternative market structures that provide more dependable and sustainable market models for antibiotics. Companies need appropriate incentives to continue to invest in R&D to overcome the challenges of discovery and development.

All stakeholders must go beyond existing statements of intent and take concrete action.



## CONTACT US

The AMR Industry Alliance invites your support, comment and challenge:

**[amrindustryalliance.org](https://amrindustryalliance.org)**

**[info@amrindustryalliance.org](mailto:info@amrindustryalliance.org)**

 **[@AMRAlliance](https://twitter.com/AMRAlliance)**

 **[LinkedIn](https://www.linkedin.com/company/amrindustryalliance)**

# 12

## APPENDIX

This appendix contains information on the AMR Industry Alliance members, commitments, contributors to this report and the methodology used. The Common Antibiotic Manufacturing Framework and Appropriate Use in Humans definition are also included for reference.

### 12.1 AMR INDUSTRY ALLIANCE MEMBERS

As of December 2017, the following organizations are members of the AMR Industry Alliance. Those marked with an asterisk (\*) responded to part or all of the first AMR Industry Alliance survey on progress in 2017.

#### Biotechnology companies/SMEs

- ABAC Therapeutics, Spain
- Abgentis Ltd., United Kingdom
- Absynth Biologics, Ltd., United Kingdom
- \* Achaogen Inc., United States
- \* Actelion Ltd., Switzerland
- \* Aequor Inc., United States
- \* AiCuris Anti-infective Cures GmbH, Germany
- \* Alaxia Pharma, France
- Allegra Therapeutics, Germany
- Allergan plc, Ireland
- Antabio, France
- AntibioTx ApS, Denmark
- Arsanis, Austria
- \* Auspherix, Ltd., United Kingdom
- BioFilm Control, France
- BioVersys AG, Switzerland
- Biovertis AG, Austria
- Blueberry Therapeutics Ltd., United Kingdom
- Cantab Anti-infectives Ltd., United Kingdom
- Chemical Biology Ventures Ltd., United Kingdom
- \* Contrafect, United States
- \* Da Volterra, France
- Deinobiotics, France
- Destiny Pharma Ltd., United Kingdom
- \* Discuva Ltd., United Kingdom
- Eligo Bioscience, France
- \* Entasis Therapeutics, United States
- Evotec, Germany
- Fedora Pharmaceuticals Inc., Canada
- Helperby Therapeutics plc, United Kingdom
- IMMT, Slovenia
- \* iNtRON Biotechnology, Inc., Korea
- Lamellar Biomedical Ltd., United Kingdom
- MaaT Pharma, France
- Macrolide Pharmaceuticals Inc., United States
- Meiji Seika Pharma Co., Ltd., Japan
- Melinta Therapeutics, Inc., United States
- MGB Biopharma Ltd., United Kingdom
- Microbion Corporation, United States
- MicRx Pharmaceuticals Inc., China and United States
- Motif Bio, United States
- Mutabilis, France
- \* Nabriva Therapeutics AG, Austria
- NAICONS, Italy
- Nexgen Bio, United States
- Northern Antibiotics Ltd., Finland
- \* Nosopharm, France
- NovaBiotics, United Kingdom
- \* NovaDigm Therapeutics, Inc., United States
- OJBio Ltd., United Kingdom
- OLMIX Group, France
- \* Peptilogics Inc., United States

PHARMA VAM Ltd., Russia  
Pherecydes Pharma, France  
Phico Therapeutics Ltd., United Kingdom  
Polyphor AG, Switzerland  
Redx Pharma plc, United Kingdom  
SetLance, Italy  
Setubio S.A., France  
Spero Therapeutics, LLC, United States  
Synamp Pharmaceuticals B.V., The Netherlands

Synthetic Genomics, United States  
TechnoPhage, Portugal  
\* Tetraphase Pharmaceuticals, United States  
\* The Medicines Company, United States  
VenatoRx Pharmaceuticals Inc., United States  
VibioSphen, France  
Vitas Pharma Ltd., India  
Xellia Pharmaceuticals, Denmark

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### Large research-based biopharmaceutical companies

* AstraZeneca plc, United Kingdom	* Novartis AG, Switzerland
* F. Hoffmann-La Roche AG., Switzerland	* Otsuka, Japan
* GlaxoSmithKline plc, United Kingdom	* Pfizer Inc., United States
* Johnson & Johnson, United States	* Sanofi S.A., France
* Merck & Co., Inc., Kenilworth, New Jersey, United States	* Shionogi & Co. Ltd., Japan
* Merck, Germany	

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### Generics companies

Cipla Ltd., India  
\* DSM Sinochem Pharmaceuticals, Netherlands  
Laboratorios Cinfa, Spain  
\* Mylan, United States  
\* Teva Pharmaceuticals, Ltd., Israel  
Wockhardt Ltd., India

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### Diagnostics companies

* Abbott (formerly Alere), United States	* LabCorp, United States
* Becton, Dickinson and Company (BD), United States	Luminex B.V., The Netherlands
* bioMérieux, France	Mobidiag Oy Ltd., Finland
Cepheid, United States	Momentum Bioscience Ltd., United Kingdom
* Curetis AG, Germany	QuantuMDx Ltd., United Kingdom
HemoCue AB, Sweden	Spectromics, United Kingdom
Hyrax Biosciences (Pty) Ltd., South Africa	Thermo Fisher Scientific, United States
QIAGEN, Germany	

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### Industry Associations

AdvaMedDx  
Alliance of Biopharmaceutical companies from Europe innovating in Anti-Microbial resistance research (BEAM Alliance)  
Antimicrobial Innovation Alliance (AIA)  
Association Innovative Medicines, The Netherlands  
Association of the British Pharmaceutical Industry (ABPI)  
Biotechnology Innovation Organization (BIO)  
British Generic Manufacturers Association (BGMA)  
British In Vitro Diagnostics Association (BIVDA)  
European Federation of Pharmaceutical Industries and Associations (EFPIA)  
German Association of Research-Based Pharmaceutical Companies (VFA)  
International Council of Biotech Associations (ICBA)  
International Federation of Pharmaceutical Manufacturers & Association (IFPMA)  
Japan Pharmaceutical Manufacturers Association (JPMA)  
Medicines for Europe  
UK BioIndustry Association (BIA)



## 12.2 COMMITMENTS

The Davos Declaration and Roadmap together comprise the AMR Industry Alliance's commitments.

### 12.2.1 DAVOS DECLARATION


In January 2016, leading international pharmaceutical, generics, diagnostics and biotechnology companies, as well as key industry bodies, came together to call on governments and industry to work together in taking collective action against drug-resistant infections, with a joint Declaration launched at the World Economic Forum in Davos, Switzerland (read the press release [here](#)). The Davos Declaration sets out a common set of principles for global action to support antibiotic conservation and the development of new drugs, diagnostics and vaccines. The declaration is composed of two parts:

#### 1) A call to action for governments

In the Davos Declaration, signatories call on governments to work with them to develop new and alternative market structures that provide more dependable and sustainable market models for antibiotics. These mechanisms are needed to provide appropriate incentives (coupled with safeguards to support antibiotic conservation) for companies to invest in R&D to overcome the formidable technical and scientific challenges of antibiotic discovery and development. These include mechanisms to ensure that, where appropriate, the pricing of antibiotics more adequately reflects the benefits they bring; and novel payment models that reduce the link between the profitability of an antibiotic and the volume sold.

#### 2) A series of commitments from the signatory companies

The Davos Declaration also sets out commitments to further action on drug resistance by its signatories, across three broad areas. They commit to:

 <b>Work to reduce the development of antimicrobial resistance</b>	 <b>Invest in R&amp;D that meets global public health needs with new innovative diagnostics and treatments</b>	 <b>Improve access to high-quality antibiotics and ensuring that new ones are available to all</b>
 Support appropriate use and improved stewardship	 Invest in innovative antibiotics, vaccines, alternative technologies, and diagnostics	 Ensure affordable access to new and existing antibiotics
 Encourage infection control	 Support research in academia and Small and Medium Enterprises on new and re-purposed antibiotics	 Support programs to improve global access
 Support the one health approach and responsible use	 Support open collaboration between industry and public researchers	
	 Develop new valuation mechanisms and commercial models with payers and policy makers	

## 12.2.2 INDUSTRY ROADMAP

Ahead of the United Nations General Assembly (UNGA) High-Level Meeting on Antimicrobial Resistance (AMR) in September 2016, 13 leading pharmaceutical companies – all signatories to the Davos Declaration and AMR Industry Alliance members – presented a new Industry Roadmap for Progress on Combating AMR that lays out four key commitments they will deliver by 2020 to reduce AMR. The commitments follow the principles identified and agreed upon in the Davos Declaration. The Roadmap includes commitments relating to manufacturing and the environment and is reflected in the metrics developed and progress reported in this report.

## 12.3 METHODOLOGY

This section details the scope and metrics of the AMR Industry Alliance survey.

### 12.3.1 SCOPE

**Company scope:** All signatories to the Davos Declaration (as of September 2017), which includes research-based and generic pharmaceutical companies, vaccine and diagnostic manufacturers, developers of novel approaches to address AMR, and small and medium enterprises (including but not limited to biotechnology companies). This also includes signatories of the Roadmap.

**Disease scope:** All infectious diseases caused by bacterial pathogens. This includes but is not limited to tuberculosis (TB), pneumonia, gonorrhoeae, skin/soft tissue infections. Some metrics refer to public health priorities as specific pathogen-drug combinations that are in most need of therapeutic alternatives (e.g., CDC Biggest Threats, WHO Priority Pathogens).

**Product scope:** Any technology that has the potential to positively impact bacterial infections and/or resistance including but not limited to antibiotics, vaccines, novel approaches to address AMR and diagnostics. Throughout, we refer to AMR-relevant products.

**Geographic scope:** Metrics are relevant globally, to the whole world where patients in need may reside independently of country GDP/wealth.

**Survey scope:** A broad product definition has been adopted relative to research and development to allow for as yet 'unknown' solutions to AMR-challenges. Certain metrics pertain only to post-launch activities and hence may not be relevant to many signatories who may not yet have experience in this space.

### 12.3.2 METRICS & ASSUMPTIONS

Alliance member companies self-report their performance against the metrics in a survey, for which in 2017 SustainAbility was contracted to develop and manage. SustainAbility accepts the data submitted by all responding companies and assumes for the survey and reporting purposes that it is true to the best of their knowledge at the time of reporting. SustainAbility conducts a basic review to check that data is submitted appropriately, aggregates the data and calculates the metrics.

## METRICS FRAMEWORK

The Alliance's metrics on combating AMR have been developed across four areas: Access, Appropriate use, Research and Science, and Environment. These areas correspond to the commitments in the Davos Declaration (and Roadmap), and are further divided in to the sub-areas detailed on the following page. Here we list the metrics and any associated sub-metrics.

## RESEARCH & SCIENCE

- EARLY R&D
- CLINICAL DEVELOPMENT
- COLLABORATION
- INCENTIVES



## ACCESS

- STRATEGY
- STAKEHOLDER ENGAGEMENT
- SUPPLY
- QUALITY



## APPROPRIATE USE

- POLICY DEVELOPMENT
- SURVEILLANCE
- EDUCATION
- PROMOTION
- ANIMAL HEALTH
- ADDITIONAL ACTIVITIES



## MANUFACTURING & ENVIRONMENT

- COMMITMENT
- MANUFACTURING
- SUPPLY CHAIN
- STAKEHOLDER ENGAGEMENT



### RESEARCH & SCIENCE

**1.1 Financial R&D investment dedicated to AMR-relevant products:** The percentage and absolute number of companies that have made financial R&D investment dedicated to AMR-relevant products either in-house or in collaboration and their aggregated sector investments.

**1.1.1** If and when those companies that have not made any financial investment in R&D dedicated to AMR-relevant products intend to make such an investment.

**1.1.2** The amount of financial investment in R&D dedicated to AMR-relevant products in 2016.

**1.2 Early-stage research and development to address AMR:** The percentage and absolute number of companies that have been active in early-stage research and development to address AMR.

**1.2.1** Those companies whose early-stage research likely/has the potential to addresses a CDC Biggest Threat, WHO Priority Pathogen or represents a breakthrough mechanism of action.

**1.2.2** If and when those companies that are not active in early-stage research to address AMR intend to become active in this area.

**1.3 Innovative or adaptive AMR-relevant products in development:** The percentage and absolute number of companies that have had innovative or adaptive AMR-relevant products in late-stage research and development.

**1.3.1** The number and name of products that are:

- Antibiotic/s (patented)
- Antibiotic/s (generic), AMR-relevant vaccines
- AMR-relevant novel approaches
- AMR-relevant diagnostics
- Other

**1.3.2** The number of products progressing between:

- early-stage to late-stage R&D
- late-stage R&D to filing
- filing to marketing authorisation
- product sold or out-licensed for commercialisation
- adaptive incremental innovation or repurposing.

**1.3.3** Whether the phase progress in (1.3.2) has taken place in the last two years and for which of those products.

**1.3.4** Whether the phase progression in (1.3.2) has taken place in the last two years.

**1.3.5** Which of the above products in (1.3.2) address a CDC Biggest Threat, WHO Priority Pathogen or represent a breakthrough mechanism.

**1.3.6** If and when those companies that have responded 'no' to this metric will have an innovative or adaptive AMR-relevant product in development in the future.

**1.3.7** If those companies responding 'no' to this metric have begun thinking about the post-market environment for products launching into the AMR-space.

**1.3.8** If those companies responding 'no' to this metric have previously had an AMR relevant product, and the reason that development did not progress to late-stage R&D.

**1.4 Data exchange on off-protection antibiotics:** The percentage and absolute number of companies that have facilitated data exchange on off-protection antibiotics.

**1.4.1** How companies have facilitated data exchange: through publication, with other companies, and/or industry initiatives, with Product Development Partnerships (PDPs), with academia, other.

**1.4.2** If and when those companies that have not yet facilitated data exchange on off-protection antibiotics intend to do so and with what likely time horizon.

**1.5 Collaborative initiatives in research and development:** The percentage and absolute number of companies that have pursued collaborative ways of working in research and development initiatives.

**1.5.1** The type of collaboration engaged in: early-stage R&D, Late-stage R&D, Clinical trial networks

**1.5.2** The kinds of partners collaborated with: B2B – with larger companies, B2B – with Small and Medium Enterprises, Academia, Government, Public private partnerships (PPPs), Other.

**1.5.3** How active companies consider themselves in research and development (Very active to not engaged)

**1.5.4** For those companies answering 'no' to any of those areas above (I – III), if and when they may/foresee themselves become engaged in those areas.

**1.6 Dialogue to address market challenges:** The percentage and absolute number of companies involved in efforts for national or global dialogues seeking to address new valuation mechanisms, commercial models or market or regulatory barriers that specifically address the unique challenges of this market.

I. The level (national, regional or global) of such projects, initiatives or dialogues.

II. The perception of companies' own engagement in these efforts.

III. If and when those companies not currently engaged in such efforts intend to do so.

**1.7 Progress that addresses market challenges:** Companies' own perception, at the time of reporting, of the progress being made to address new valuation mechanisms, commercial models and market or regulatory barriers to development given the unique challenges of this market.

**1.8 Research & Science – Investment incentives:** The percentage and absolute number of companies that cite these new valuation mechanisms, commercial models or market/regulatory barriers:

- a) Push incentives;
- b) Pull incentives;
- c) Market or regulatory mechanisms;
- d) None;
- e) Other policy frameworks or incentives than those listed in (a) to (c);

**1.8.1** New valuation mechanisms, commercial models or market/regulatory barriers that have had the most influence over their investment decisions.

**1.9 New valuation mechanisms and commercial models:** The percentage and absolute number of companies that will respond to the following scenarios:

- a) Valuation mechanisms and commercial models remain as they currently are;
- b) Valuation mechanisms and commercial models improve from where they are;
- c) Valuation mechanisms and commercial models worsen from where they are.

**1.10 Conditions required to increase investment in AMR related research:** Qualitative assessments from participating companies on their view of what would be required in order for them to increase their investments in AMR related research.

## ACCESS

**2.1 Strategies to improve access:** The percentage and absolute number of companies that have a current strategy, policy or plan in place that includes principles or efforts to improve access to AMR-relevant.

**2.1.1** The number of launch plans for AMR-relevant products that have been tailored to companies' access strategies, policies or plans by product type.

**2.1.2** The clinical development stage that launch plans were tailored for access.

**2.1.3** Whether those companies with strategies, policies or plans to improve access to their products address the following access aspects:

- Broad global registration(s), including low and middle-income countries
- Affordability, including taking country income levels into account
- Production continuity
- Supply chain challenges
- Collaborative global access mechanisms
- Other aspects

**2.1.4** For those companies that do not have a strategy, policy or plan that includes efforts to improve access in place, if and when they will develop such a strategy, policy or plan.

**2.1.5** Whether those companies have made their strategies, policies or plans to improve access to their products publicly available.

**2.1.6** For those companies that have not made publicly available their strategies, policies or plans, if and when they will do so.

**2.2 Engagement with stakeholders regarding access to AMR-relevant products:** The percentage and absolute number of companies that have engaged with external stakeholders regarding access to AMR-relevant products.

**2.2.1** Where companies have engaged with stakeholders, the objective(s) of said engagement(s).

**2.2.2** The types of stakeholders engaged.

**2.2.3** The areas or issues addressed or acknowledged in the engagement.

**2.2.4** Whether any of those engagements have led to initiatives that have been implemented, and if so, in which areas.

**2.2.5** If and when companies that have not engaged with external stakeholders regarding access to AMR-relevant products intend to do so.

**2.2.6** If those companies who have not yet had engagements that have led to initiatives that have been implemented, have any initiatives that are in development and according to what approximate timeframe.

**2.3 AMR-relevant product delays or interruptions:** The percentage and absolute number of companies that have been aware of delays or product supply interruptions for AMR-relevant products.

**2.3.1** The steps that companies have taken to identify and overcome barriers to production continuity of AMR-relevant products through their global manufacturing capabilities.

**2.3.2** How companies sought to address supply disruptions that were caused by supply chain challenges.

**2.4 Measures to reduce the prevalence of substandard and falsified products:** The percentage and absolute number of companies that have in place a specific strategy, policy or plan to help reduce the prevalence of substandard and falsified medical products.

**2.4.1** Whether policies or measures that help reduce the prevalence of substandard/falsified products apply specifically to AMR-relevant products.

**2.4.2** Whether companies have in place detection and reporting systems to capture incidents of substandard/falsified AMR-relevant products.

**2.4.3** The stakeholders with whom information on detected substandard/falsified products is shared.

## APPROPRIATE USE

**3.1 Development of appropriate use strategies, policies or plans:** The percentage and absolute number of companies that have an appropriate use strategy, policy or plan for an AMR-relevant product in place.

**3.1.1** The number and names of relevant products for which appropriate use strategies have been implemented across the following categories:

- Antibiotics(patented)
- Antibiotics (generic)
- AMR-relevant vaccines
- AMR-relevant biologics
- AMR-relevant diagnostics
- Other

**3.1.2** The clinical development stage that launch plans were tailored to appropriate use strategies.

**3.1.3** The number and percentage of companies whose current strategies, policies or plans address the following areas/aspects of appropriate use:

- Infection prevention and control (IPC)/hygiene
- The development of preventative (vaccines) or diagnostic products that facilitate appropriate use or IPC
- Surveillance
- Education
- Promotion
- Minimising animal use
- Reducing uncontrolled use (i.e. over-the-counter and non-prescription internet sales)
- Other (e.g., working to improve our brochure/packaging to facilitate appropriate use)

**3.1.4** If and when those companies without a current appropriate use strategy, policy or plan in place for an AMR-relevant product will develop an appropriate use strategy, policy or plan.

**3.1.5** The areas from (IV) in which companies are active despite not having a formal strategy, policy or plan in place or which they are developing to include in their strategy, policy or plans.

**3.2 Collection of surveillance data:** The percentage and absolute number of companies that are planning to or currently collecting or supporting the collection of surveillance data:

**3.2.1** The type of surveillance data companies are (planning to or currently) collecting or supporting the collection of.

**3.2.2** The methods for collecting surveillance data.

**3.2.3** Whether companies are sharing surveillance data externally, and if so:

- With whom surveillance data is shared
- Through what means surveillance data is shared
- Whether companies have plans to collect or share data differently in this future i.e.
  - Collect more data
  - Share data with more stakeholders
  - Provide findings back to institutions providing data
  - Share data more systematically and collaboratively
  - Other

**3.2.4** If and when those companies not currently sharing surveillance data plan to do so.

**3.3 AMR-related education programs:** The percentage and absolute number of companies (planning to or currently) that have been engaged in activities around stewardship.

**3.3.1** Those companies that directly or indirectly help educate:

- Health professionals on the importance of effective stewardship
- Non-medical healthcare workers/payers etc. on effective stewardship
- Patients on the importance of appropriate use
- Internal company staff on appropriate use
- General public on appropriate use
- Other

**3.3.2** If and when those companies that are not currently involved in AMR-related education programs plan to be involved in such programs in the future.

**3.4 Appropriate promotional practice:** The percentage and absolute number of companies that have examined, or are intending to examine, their promotional activities to ensure they are consistent with the goal of advancing stewardship.

**3.4.1** For those companies that have not examined their promotional activities as the metric, if and when they intend to do so.

**3.4.2** Those companies that have modified any company-specific or company-developed promotional activities as a result of examining their promotional activities as per the metric.

**3.5 Progress against Health for Animals commitments:** The percentage and absolute number of companies that are signatories to and reporting progress against the Health for Animals commitments and actions on antibiotic use.

**3.5.1** If and when those companies not reporting progress against the Health for Animals commitments intend to do so.

**3.6 Maximizing impact to facilitate appropriate use:** Qualitative description of additional ways in which companies are currently maximizing, or planning to maximize, their impact in facilitating appropriate use and decreasing the burden of AMR globally.



**3.7 Ensuring antibiotics are used only in patients that need them:** Qualitative description of ways companies work to ensure that their antibiotics are used only in patients that need them.

## MANUFACTURING & ENVIRONMENT

**4.1 Commitment to the Industry Roadmap for Progress on Combating Antimicrobial Resistance:** The percentage and absolute number of companies that are signatories of and reporting progress against, the Industry Roadmap for Progress on Combating Antimicrobial Resistance.

**4.1.1** When signatories to the Industry Roadmap anticipate applying the common framework for managing antibiotic discharge across their manufacturing and supply chain.

**4.1.2** When signatories to the Industry Roadmap anticipate committing to the targets for discharge concentrations for antibiotics.

**4.1.3** When signatories to the Industry Roadmap anticipate beginning to implement good practice methods to reduce environmental impact of manufacturing discharge.

**4.1.4** When signatories to the Industry Roadmap anticipate transparently demonstrating that their supply chains meet the standards in the framework.

**4.1.5** When those signatories to the Industry Declaration that have not yet signed the Industry Roadmap anticipate they will sign the Industry Roadmap.

**4.1.6** Reasons why companies have not signed the Industry Roadmap.

**4.1.7** Additional information pertaining to company action on the above aspects.

**4.2 Reduce the negative impact of antibiotic manufacturing processes to AMR:** The percentage and absolute number of companies that have in place a current strategy, policy or plan that addresses the issue of the release of antibiotics in internal manufacturing effluents that may contribute to AMR.

**4.2.1** Whether companies have in place a strategy, policy or plan that addresses the issue of environmental impact of their business, where environmental impact is any negative effect to human, plant or animal life that may arise as a result now or in the future from business operations.

**4.2.2** Whether companies have in place a strategy, policy or plan that addresses the release of antibiotics in manufacturing effluents that may contribute to AMR and acknowledges or addresses the following:

- Identification of environmental risks
- Determination of emissions control (discharge limits) procedures
- Implementation of procedures and measures to determine discharge concentrations
- Externally disclosed reporting of strategy, policy or plan, including breaches
- Internal compliance and / or external oversight procedure
- Other

**4.2.3** Whether companies have reviewed their manufacturing operations with respect to said factors in (4.2.2).

**4.2.4** Whether companies have made any changes or modified any operations as a result of review of own manufacturing operations in (III).

**4.2.5** The timeline for those companies to incorporate any of the above commitment or steps if they have not done so at the time of reporting.

**4.3 Supply chain impacts of business operations on AMR:** The percentage and absolute number of companies with antibiotic manufacturing operations that currently have a strategy, policy or plan addressing the environmental impact of their business operations on AMR that also covers their supply chain.

**4.3.1** The percentage of companies that have implemented plans with respect to:

- Reviewing operations of suppliers.
- Inserting standards/new terms (e.g., checks/balances) into supplier contracts
- Increasing the public transparency of findings regarding suppliers.
- Any other measures that address the environmental impact on AMR of their suppliers' operations.

**4.3.2** The timeline for companies to incorporate in to their strategies, policies or plans, measures that address the environmental impact on AMR of their suppliers' operations.

**4.4 Engagement in stakeholder discussions on impact of business operations on AMR:** The percentage and absolute number of companies with antibiotic manufacturing operations that have engaged in industry or other external stakeholder discussions concerning the environmental impact of their business operations on AMR.

**4.4.1** The objectives of the engagement(s).

**4.4.2** The types of stakeholders engaged.

**4.4.3** If those companies not currently engaged in discussions with industry or other external stakeholders intend to engage in these discussions in the future and, if so, when it is anticipated these engagements will commence.

## 12.4 APPROPRIATE USE IN HUMANS

Appropriate Use in humans, as defined for antimicrobials, by the AMR Industry Alliance:

*The availability of effective antimicrobials is fundamental to modern medicine – not just to prevent and treat infectious diseases, but also to enable other medical advances, such as surgery and chemotherapy. The prompt initiation of antibiotics to treat infections has been proven to reduce morbidity and save lives.<sup>43</sup> However, use of antibiotics has contributed to the development of growing threat of antimicrobial resistance. The pharmaceutical industry is committed to promote patient-centred antimicrobial stewardship to slow the emergence of resistance, prolong the activity of antimicrobials and improve patient outcomes and population health.*

*We define “Appropriate Use” of antimicrobials as the right patient receiving the right drug at the right dose in the right formulation at the right time for the right duration for the right pathogen and site of infection. This is consistent with WHO’s definition of appropriate use: “the cost-effective use of antimicrobials which maximises clinical therapeutic effect while minimising both drug related toxicity and the development of antimicrobial resistance”.<sup>45</sup>*

*Appropriate prescribing is embedded within appropriate use and the treatment must be taken as prescribed by a qualified medical professional. Pathogen identification through diagnostic tests and susceptibility testing of the causative pathogen(s) should determine which treatment agent is needed whenever possible. In all cases, treatment selection should be guided by recent local susceptibility data and resistance prevalence data for the likely causative pathogen(s). Local surveillance data and subsequent evidence-based guidelines should be regularly re-assessed to ensure these remain accurate. Therapy must be of the appropriate efficacy and optimal dosage to ensure maximal reduction in pathogen load, with the ultimate aim of pathogen eradication. Choices of the agent, dosage and course should be based on pharmacokinetic and pharmacodynamic principles that predict efficacy and the ability to eradicate pathogens at drug concentrations attainable during therapy and within the shortest course that has proven efficacy. Antibiotic therapy must be limited to appropriate use only to treat bacterial infection. Patients should be educated in how to manage symptoms of non-bacterial infections, adherence encouraged and self-prescription discouraged.*

*Therefore, promotional activities that align with the goal of advancing stewardship will have the primary goal of supporting appropriate use, as set out here, leading to a reduction in inappropriate use. Consistent with the IFPMA Code of Practice, promotional activities are broadly defined as any interaction (face to face, materials, digital, written, via a sponsored event etc.) with a healthcare provider by commercial representatives of a company that has the potential to impact prescribing decisions in their management of infectious diseases.*

## 12.5 COMMON ANTIBIOTIC MANUFACTURING FRAMEWORK

The Antimicrobial Resistance (AMR) Roadmap Companies recognize and understand concerns raised by stakeholders regarding the presence of pharmaceuticals in the environment (PIE). The major source of pharmaceuticals entering into the environment is via patient excretion following use of medicine that is taken to prevent, cure or alleviate a medical condition. A comparatively smaller contribution to PIE stems from emissions from industry during manufacture of the pharmaceuticals.<sup>46</sup>

While the overall contribution of pharmaceutical manufacturing to PIE is relatively low, there is the potential for localized impacts to be created in cases where manufacturing emissions are inadequately managed. Ensuring the use of appropriate environmental risk management measures to adequately control manufacturing effluent emissions remains an important area of focus for the pharmaceutical industry and is an approach already in place in a number of companies.<sup>47</sup> We are aligned in our intent and are ready to build and share common practices.

Reports of active pharmaceutical ingredients (APIs) in water from pharmaceutical manufacturing indicate concentrations have reached potentially harmful levels when wastewater discharges are not sufficiently controlled at some facilities,<sup>48</sup> highlighting the importance of effective control of API emissions from manufacturing, both in production of the API itself and its formulation into drug products for patient use.

Environmental regulations pertaining to wastewater discharges from manufacturing, already generally apply to pharmaceutical production. However, many socially and environmentally responsible companies go beyond compliance with the basic regulatory requirements for chemical manufacturers (e.g., control of pH, biological oxygen demand, chemical oxygen demand)<sup>49</sup> and establish environmental protection goals to evaluate and reduce potential environmental risk from production of their products.

Currently, most programs focus on potential toxicity to aquatic species, upsets to wastewater treatment plants or potential toxicity in human drinking water. Emission limits, specifically for preventing antimicrobial resistance, are currently under development. The AMR Roadmap signatories are committed to achieving this goal and are reliant on the evolving science as a means to arriving at a consistent methodology for these limits by 2020.

The attached Antibiotic Manufacturing Framework provides a methodology and set of minimum requirements needed to conduct a site risk evaluation of both macro and micro controls in our supply chains. Company expectations, including this Framework, will be communicated within the AMR Roadmap signatory companies and their supply chains.

## ANTIBIOTIC MANUFACTURING FRAMEWORK

### MINIMUM EXPECTATIONS:

- Compliance with:
  - Local laws and regulations
  - Environmental permits
  - Company standards, Codes of conduct
  - Pharmaceutical Supply Chain Initiative's (PSCI) Pharmaceutical Industry Principles
  - No untreated discharge of manufacturing waste containing antibiotic
- Robust EHS programs, evaluated periodically for efficacy
- Appropriate training is completed in line with industry best practice
- Exercise appropriate duty of care for all discharges and waste streams containing antibiotics
- Allow / facilitate audits as requested, develop and execute plans to address audit findings
- Follow-up conducted for assessments and audits conducted

**Note:** Audit reports will remain confidential between the company and the supplier or manufacturing site subject to the audit. Audit reports can be shared on the PSCI data base with those member companies that have been granted permission from the supplier. (PSCI shares audit reports among member companies with the supplier's agreement). Companies may opt to publicly report aggregate audit information as part of their overall EHS program reporting.

### MINIMUM REQUIREMENTS FOR ENVIRONMENTAL PROGRAMS:

The Framework elements below focus on environmental compliance and appropriate antibiotic discharge management, in addition to expected air emissions control, safety, and health programs.

#### WATER MANAGEMENT PROGRAM

**Principle:** Compliance with all applicable regulations. All required environmental permits, licenses, information registrations and restrictions are in place, available for review, and their operational and reporting requirements are followed. Systems are in place for the management of water discharges. Any wastewater or wastewater sludge from on-site wastewater treatment operations with the potential to adversely impact human or environmental health is managed, controlled, and treated prior to release to the environment. Systems are in place to prevent and mitigate accidental spills and releases to the environment.

1. Site possesses a valid authorization/license/permit for water intake (i.e. from groundwater, river or public system) and discharge. Compliance with each condition in the authorization/ license/ permit is demonstrated.
2. Levels of antibiotic in process wastewater are quantified e.g., mass balance.
3. Wastewater sources from operations are characterized and evaluated for treatability and control.
4. Effective wastewater treatment is provided (e.g., neutralization, clarification, settling, inactivation, biological or chemical treatment).
5. Water/wastewater monitoring devices and treatment systems are in good operating condition and appropriately maintained (e.g., in accordance with manufacturer's recommendations).
6. Biomass from fermentation is managed in compliance with all local regulations.
7. Sludge from process wastewater treatment is managed in compliance with all local regulations.
8. Assessments are conducted to determine potential risk from sludge application to land.
9. Samples are collected, stored, and analyzed with results reported in accordance with local regulatory requirements.
10. Drinking water is treated to be safe for human consumption and meet local regulatory standards or WHO drinking water guidelines in absence of local standards. Water systems that could be impacted by contamination are tested for compounds of concern.
11. Process areas (e.g., tanks, container storage areas, and process sewer systems) are designed, constructed and operated to prevent spills or releases to the environment.
12. Systems are in place to prevent soil, surface water, or groundwater contamination.

## SOLID WASTE MANAGEMENT PROGRAM

**Principles:** Compliance with all applicable regulations. All required environmental permits, licenses, information registrations and restrictions are obtained and available for review, and their operational and reporting requirements are followed. Systems are in place for the safe handling, movement, storage, recycling, reuse, and disposal of waste. Waste with the potential to adversely impact human health or the environment is managed, controlled and treated prior to release to the environment. Systems are in place to prevent and mitigate accidental spills and releases to the environment. Any unpermitted release is reported to the proper authorities and remedial measures are instituted to prevent reoccurrence and address impacts associated with said release. Solid waste management is important to demonstrate control and to prevent an unintended subsequent release.

1. Waste classification, labeling, storage and disposal methods are in accordance with the hazard characteristics of the waste, and in accordance with regulatory requirements, including:
  - a) Waste containers are labeled with contents, hazard characteristics (e.g., flammable, biological), and closed once waste is placed in the container.
  - b) Disposal methods are based on waste characteristics. Records (e.g., waste classification determinations including analytical results, letters from waste contractors, and certificates of destruction) are maintained.
  - c) Waste disposal contractors possess authorizations/certifications from regulatory authorities to manage specific waste streams in accordance with local regulations.
2. Waste is stored in a manner to prevent discharges and unsafe conditions, such as:
  - a) Material is stored in quantities not exceeding the capacity of spill containment and is sheltered from weather/elements.
  - b) Spill containment integrity is inspected, documented and maintained in satisfactory condition to prevent the discharge of waste materials into the environment.
  - c) Incompatible wastes and their spill containment are properly segregated (e.g., acids and bases)
  - d) Solid wastes are stored in a manner to prevent discharge as the result of rain/storm water run-off.
  - e) Biomass from fermentation is managed in compliance with all local regulations to prevent environmental pollution.
  - f) Waste containers are in good condition and compatible with the materials being stored (e.g., free from corrosion, dents, bulges or other impairment that would impact adequate containment) and are maintained closed except during filling and emptying operations.
  - g) Materials are stored in a manner to prevent events resulting from undesired reactions, incompatibilities, decomposition and/or self-ignition.
3. Fire risks are assessed in the waste storage area. Suitable fire management and suppression measures are applied (e.g., smoke detectors, fire extinguishers, separation walls, fire water retention). Waste storage areas are segregated and with access limited to authorized personnel.
4. Any landfills or permanent disposal areas for wastes are specifically authorized by regulatory authorities. Containment and monitoring programs are in place.
  - a) Programs are in place to manage soil or groundwater contamination from spills.

## AUDITS OF ANTIBIOTIC MANUFACTURERS

To ensure that internal and external antibiotics manufacturing facilities (including active pharmaceutical ingredient and formulation) within the supply chain minimize their environmental impact, on-site EHS audits will be performed. The below description concentrates on environmental compliance and antibiotic discharge minimization, but in addition specifies that appropriate air, safety and health assessments will be part of the audits as well. Assessments and audits should be performed by qualified and competent auditors.

### FACILITY AUDITS

1. Audit antibiotic suppliers at least once every 5 years
  - a) Audits may be performed more frequently based on result of previous audits or discovery of heightened risk at the facility
2. Audit scope:
  - a) Facility tour
  - b) Regulatory compliance assessment (local laws and regulations)
  - c) Operating permit compliance verification
  - d) Auditing against a defined protocol or management system (e.g., company's supplier standards, PSCI Auditing guidance).
  - e) Focus is on areas for Environmental Management, including:
    - i) Water management

- ii) Solid Waste management
    - iii) Spill prevention and response , chemical storage and handling
    - iv) Employee training
  - 3. Audits include:
    - a) Records review
      - i) Compliance with regulatory requirements and permit conditions
      - ii) Facility's environmental risk assessment of antibiotic discharges (quantified by mass balance or measurement) and assessed against applicable risk-based targets for discharge concentrations or overall load.
      - iii) Maintenance plans (for critical equipment and environmental controls)
      - iv) Incident investigation logs (corrective and preventative actions plans (CAPA)) for relevant incidents)
      - v) Supplier practices for evaluating their own supply chain
      - vi) Waste and Wastewater disposal records
    - b) Facility tour – to assess operating conditions, ensure practices are in place and are being followed as required (not a remote site or paper review)
      - i) Storm water collection and retention practices and/or systems
      - ii) On-site Waste Water Treatment Plant(s) (WWTP)
      - iii) Waste storage
      - iv) Process and domestic wastewater collection and treatment
      - v) Extraction or deep wells
      - vi) Underground and aboveground storage tanks with associated visible piping
      - vii) Fuel storage locations
      - viii) Solvent storage and recovery
      - ix) Warehouses, other physical storage sheds/locations
      - x) External tours of the entire facility (including discharge locations, pollution control devices, and receiving stream identification and observation)
      - xi) Fire water retention
  - 4. Audit report:
    - a) Identify any non-compliance with local laws and regulations
    - b) Highlight any gaps, deficiencies, or deviations from generally accepted industry practices and/or contractual commitments and communicated expectations related to antibiotics discharges
- Note:** Audit reports will remain confidential between the company and the supplier or manufacturing site subject to the audit. Audit reports can be shared on the PSCI data base with those member companies that have been granted permission from the supplier. (PSCI shares audit reports among member companies with the supplier's agreement). Companies may opt to publicly report aggregate audit information as part of their overall EHS program reporting.
- 5. Audit follow up:
    - a) Work with supplier (facility) to develop acceptable action plans for findings
    - b) Monitor supplier's performance to confirm progress of actions including subsequent remedial action closure consistent with specified timelines
  - 6. Supplier Oversight
    - a) Monitor results and determine ongoing appropriateness of suppliers

## INFORMATION SHARING – BEST PRACTICES

### PSCI WEBINARS ON MANAGING APIS IN MANUFACTURING EFFLUENT:

#### Webinar recording - managing APIs in manufacturing effluent - 27th Jan 2016

Step-by-step guidance covering the following topics:

- Why is managing active pharmaceutical ingredients (API) in manufacturing effluent important?
- What is the industry doing to improve public perceptions?
- Understanding where you stand at the moment through the maturity ladder concept.
- Establishing and calculating API discharge concentration called the Predicted-No-Effect-Concentration (PNEC).
- Simple steps to reducing API process losses to waste water and what to do when the PNEC is exceeded.
- How to advance your program to the next level.

#### Webinar recording - managing APIs in manufacturing effluent Part 2 - 15th June 2016

Step-by-step guidance covering the following topics:

- Estimating API losses from the manufacturing process (PEC)
- Establishing the acceptable discharge concentration (PNEC)
- Making low capital investment housekeeping steps to reduce the loss of APIs

## **Webinar slide deck - managing APIs in manufacturing effluent Part 3 - 25th October 2016**

This webinar looked at advanced technologies to reduce API loss with guest speakers from the Temple University WET Centre and AECOM.

### **ADDITIONAL PUBLISHED RESOURCES:**

- i. Aga DS. 2008. Advances in the Analysis of Pharmaceuticals in the Aquatic Environment. In Aga DS, ed, Fate of Pharmaceuticals in the Environment and in Water Treatment Systems. CRC Press, Taylor & Francis Group, Boca Raton, FL.
- ii. Caldwell et al, Environmental Toxicology & Chemistry Vo 35, No.4 pp813-822, 2016 <http://onlinelibrary.wiley.com/doi/10.1002/etc.3163/pdf> "A Risk Based Approach to Manage Active Pharmaceutical Ingredients in Manufacturing Effluent" (This resource may be used to identify practices for assessing potential environmental risks from APIs in manufacturing effluent and outline measures that can be used to reduce the risk, including selective application of available treatment technologies.)
- iii. Larsson et al Effluent from drug manufactures contains extremely high levels of pharmaceuticals, Journal of Hazardous Materials Volume 148, Issue 3, 30 September 2007, Pages 751-755 <http://www.sciencedirect.com/science/article/pii/S0304389407009909?via%3Dihub>
- iv. Tell et al, Limiting APIs in Manufacturing Effluent, Contract Pharma, 02.06.16 [http://www.contractpharma.com/issues/2016-06-01/view\\_features/limiting-apis-in-manufacturing-effluent](http://www.contractpharma.com/issues/2016-06-01/view_features/limiting-apis-in-manufacturing-effluent)
- v. Vestel J, Caldwell DJ, Constantine L, D'Aco, VJ, Davidson, T, Dolan, DG, Millard SP, Murray-Smith R, Parke NJ, Ryan JJ, Straub JO, Wilson, P. 2015. Use of Acute and Chronic Ecotoxicity Data in Environmental Risk Assessment of Pharmaceuticals. Environmental Toxicology & Chemistry DOI: 10.1002/etc.3260
- vi. Sargent EV, Faria E, Pfister T, Sussman RG. 2013. Guidance on the establishment of acceptable daily exposure limits (ADE) to support Risk-Based Manufacture of Pharmaceutical Products. Regulatory Toxicology and Pharmacology 65:242-250.
- vii. Cunningham V, Olson SBM. 2009. Human health risk assessment from the presence of human pharmaceuticals in the aquatic environment. Regul Toxicol Pharmacol 53:39-45.
- viii. EU EMA. 2006. Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use. In Agency EM, ed, EMEA/CHMP/SWP/4447/00. Committee for Medicinal Products for Human Use (CHMP), London, UK.
- ix. ECHA. 2008. Guidance on information requirements and chemical safety assessment. Chapter R.10: Characterisation of dose [concentration]-response for environment. REACH Regulation (EC) No 1907/2006 of the European Parliament and of the Council of 18 December 2006. European Chemicals Agency, Helsinki, Finland.
- x. Caldwell DJ, Mastrocco F, Hutchinson TH, Länge R, Heijerick D, Janssen C, Anderson PD, Sumpter JP. 2008. Derivation of an Aquatic Predicted No-Effect Concentration for the Synthetic Hormone, 17 $\alpha$ -Ethinyl Estradiol. Environmental Science & Technology 42:7046-7054.
- xi. Dolan DG, Naumann BD, Sargent EV, Maier A, Dourson ML. 2005. Application of the threshold of toxicological concern concept to pharmaceutical manufacturing operations. Regul Toxicol Pharmacol:1-9.
- xii. Schwab B, Hayes E, Fiori J, Mastrocco F, Roden N, Cragin D, Meyerhoff R, D'Aco V, Anderson P. 2005. Human pharmaceuticals in US surface waters: a human health risk assessment. Regul Toxicol Pharmacol 42:296-312.
- xiii. EPA. 2004. Estimated Per Capita Water Ingestion and Body Weight in the United States—An Update, Washington, DC.
- xiv. Anderson PD, D'Aco VJ, Shanahan P, Chapra SC, Buzby ME, Cunningham VL, DuPlessie BM, Hayes EP, Mastrocco FJ, Parke NJ, Rader JC, Samuelian JH, Schwab BW. 2004. Screening Analysis of Human Pharmaceutical Compounds in U.S. Surface Waters. Environmental Science & Technology 38:838-849.
- xv. US FDA. 1998. Environmental Assessment of Human Drugs and Biologics Application. In US Food and Drug Administration CfDEaRC, ed.
- xvi. World Health Organization 2015, Global Action Plan on Antimicrobial Resistance, ISBN 978 92 4 150976 3

### **EXAMPLE COMPANY PROGRAMS PUBLISHED IN THE LITERATURE:**

#### **Managing Emissions of API from Manufacturing - An Environmental Quality Standard Approach**

Integrated Environmental Assessment and Management — Volume 8, Number 2—pp. 320–330  
2011, SETAC.

#### **Limiting APIs in Manufacturing Effluent – Contract Pharma** Tell et al, 06.02.16.

#### **IPPC Reference on Best Available Techniques for the Manufacture of Organic Fine Chemicals, Chapter 5**

This document contains the results of an exchange of information between EU Member States and industries concerning best available technique (BAT) and associated monitoring for the Manufacture of Organic Fine Chemicals.

### **REFERENCES TO PERFORM AUDITS**

- i. Pharmaceutical Industry Principles for Responsible Supply Chain Management (PSCI) - Guidance for Implementing The Principles <https://pscinitiative.org/resource?resource=2>



- ii. PSCI Audit Program Guidance
  - a) This document is designed to be used by PSCI members, audit contractors and suppliers. It provides a detailed overview of the audit process and corresponding roles and responsibilities at each stage of the process
- iii. PSCI Pre-Audit Document Request List
- iv. Full PSCI SAQ & Audit Report Template for Core Suppliers, External Manufacturers, Component and Material Suppliers
  - a) PSCI Self-Assessment Questionnaire and Audit Report Template for Core Suppliers, External Manufacturers, Component and Material Suppliers (Version 4, October 2016)
  - b) General information, Facility Background: Pages 1 – 5
  - c) Management Systems: Pages 6 – 8
  - d) Ethics: Pages 9 – 10
  - e) Labor: Pages 11 – 14
  - f) Environmental Protection: Pages 15 – 20
  - g) Health & Safety Compliance and Risk Management: Pages 21 – 32
  - h) Biological Safety: Pages 32 – 33

## 12.6 CONTRIBUTORS

SustainAbility was commissioned to support developing effective metrics for the AMR Industry Alliance and authoring this first progress report. The AMR Industry Alliance Board, Secretariat and members from Working Groups representing each area of commitment served as a review body for the report. This project was managed by Nina Grundmann, in coordination with Morgane De Pol.

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## ABOUT THE AMR INDUSTRY ALLIANCE

The AMR Industry Alliance is a coalition of over 100 biotechnology, diagnostic, generics and research-based biopharmaceutical companies and trade associations that was formed to drive and measure industry progress to curb antimicrobial resistance. The AMR Industry Alliance will ensure that signatories collectively deliver on the specific commitments made in the Industry Declaration on AMR and the Roadmap and will measure progress made in the fight against antimicrobial resistance.

[amrindustryalliance.org](http://amrindustryalliance.org)

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## ABOUT SUSTAINABILITY

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