

MARCH 2019



Supporting financial investments on R&D to de-risk antimicrobial development

About the BEAM Alliance

The BEAM Alliance (Biotech companies from Europe innovating in Anti-Microbial resistance research) represents over 50 European SMEs that develop solutions to fight antimicrobial resistance on a European and national level. The BEAM members are collectively developing over 120 new, diversified R&D projects focused upon both the cure as well as prevention of bacterial infections and covering the whole range of pharmaceutical drug development. The goal of the BEAM Alliance is to maintain and promote awareness of SME-driven innovation in the field and to support policymakers in understanding economic business models around AMR. The BEAM Alliance closely cooperates with all stakeholders dedicated to the fight against AMR. Although being a member of and closely collaborating with the AMR Industry Alliance to curb antimicrobial resistance, the BEAM Alliance is advocating for the specific SME needs with regards to investment in R&D to meet public health needs with new innovative diagnostics and treatments.

Key messages

- Antimicrobial resistance (AMR) is a global, multi-sectoral issue that affects all countries and, if unaddressed, will become one of the most formidable health crises of the century
- Market failures and limited guidelines heavily impact the risk level associated with AMR R&D
- Currently, SMEs are by far the largest contributors to the AMR drug pipeline. SMEs are not cash flow positive and compete with other indication fields to capture equity and non-dilutive funding
- Funding instruments dedicated to the AMR community should be designed, in particular to move forward preclinical and clinical products, as a European complement to the CARB-X and BARDA initiatives
- The upcoming Horizon Europe framework programme offers various opportunities to set-up such targeted instruments

Antimicrobial resistance: a global public health threat

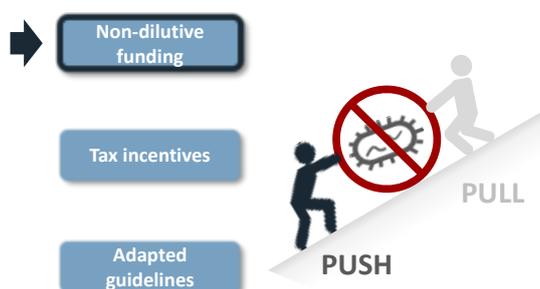
Antimicrobial resistance (AMR) is the resistance of a microorganism to antimicrobial drugs that were originally effective at treating the related infections. In particular, the emergence of bacteria that are resistant to multiple drugs, or classes of drugs, result in prolonged illness, higher healthcare expenditures, and a greater risk of death and, lastly, pose a significant risk of spreading the resistant strains in the community. AMR is increased by the excessive use (and often misuse) of antibiotics in humans and animals and stewardship for novel antibiotics is paramount. Societal and economic impacts of AMR are already significant (*ca.* 50,000 yearly deaths across EU and US, causing healthcare costs of nearly €18 billion). Previous reports state that AMR is one of the most urgent public health threats and by 2050 will be killing more people than cancer, with a cost to world economy of *ca.* \$125 trillion in reduced global GDP.

Unfortunately the development of new antibiotics has not kept pace with the rise of bacterial resistance. Thus, although more than 20 new classes of antibiotics reached the market over the 1940-62 period, only a few molecules – belonging only to two new classes – have been approved since then; clearly not enough to fend off the rising threat. Even if the complex science behind bacterial resistance partially explains this lack of achievements, the economic unattractiveness of the AMR field plays the most critical role.

An emergency to save the on-going AMR pipeline

Although the AMR problem is now fully recognized by governments and authorities (UN, WHO, CDC, ECDC, etc.), the area remains the most underserved segment of the pharmaceutical industry. Only very few large pharmaceutical corporations are actively involved in innovative R&D efforts. On the other hand, about 250 biotech companies worldwide are focusing mainly on antimicrobial drug development to bring novel therapies from bench to bedside. As a matter of fact, biotech companies constitute the crucial innovation engine in the AMR arena with the most significant pipeline of new antibiotics or novel antimicrobials as alternative treatments. But they are facing dramatic and urgent funding hurdles, as the AMR business model is clearly broken and private investment is difficult to attract¹. How to compete when the net present value (NPV) of a new antibiotic is only about \$100 million, compared to approximately \$1.1 billion for a drug used to treat a neuromuscular disease?²

There is a high risk of massive deprioritization of AMR programs as SMEs face ever-growing challenges to fund their R&D efforts. This would lead to drugs of compelling value to patients never making their way to the global pipeline. It is thus of tremendous importance to develop new incentives able to fix current market failures, to leverage private investments again, and implement them urgently to safeguard our future armamentarium.



In this document, we assess the non-dilutive funding landscape for AMR R&D and make specific recommendations on possible ways to further de-risk antimicrobial development in support of AMR biotech companies, in particular European SMEs.

¹ <https://beam-alliance.eu/wp-content/uploads/2019/03/2017-11-16-beam-alliance-position-paper.pdf>

² Sharma, Priya and Towse, Adrian, New Drugs to Tackle Antimicrobial Resistance: Analysis of EU Policy Options (October 1, 2010).

Grants are non-dilutive, non-refundable funding and are very effective for triggering a leverage effect on private investments. A significant breakthrough was recently achieved by the CARB-X instrument. CARB-X was founded by US government agencies (BARDA and NIAID) and the Wellcome Trust³. It is a spot-on action to reinvigorate the AMR R&D field because it is aligned with the usual way companies develop their products. Among other features, it allows significant funding (up to 70% of project cost) and avoids the requirement for large cumbersome, cross border partnerships thus reducing administrative burden for small companies.

Within just 2 years, CARB-X already has 33 projects in the pipeline for a total investment amount of \$91.1M plus \$96.5M if milestones are reached. This has helped 15 companies raise \$762M in private funds. In 2018 alone, more than 400 proposals were evaluated, demonstrating the significant innovation potential carried by the sole AMR field. The BEAM Alliance applauds the initiative, and the impact it also had on European SMEs so far. BEAM recognizes the strong efforts of CARB-X to increase its footprint in the EU by establishing 4 new accelerators in 2018 and looks forward to see an even stronger impact on European SME in the near future.

As recently summarized⁴, several initiatives were implemented in the recent years to follow-up on the roadmap set in the European Action plan (2012), in particular to favour partnerships and collaborations at the European level. A number of networks and task forces are also being built to increase capacity and expedite progress towards curbing the rising trend of AMR. However, on the product-driven development side, the Horizon 2020 programmes failed to support European SMEs and have many unnecessary hurdles that discourage the participation of SMEs in such a multi-sectoral approach. A few examples are:

🌐 **The H2020 Societal Challenges/LEIT instruments** only rarely offer opportunities to apply and frequently require the building of large consortia to embrace a wide spectrum of activities (see SC1-BHC-14-2019) that can be far from the core activity of a product-developing SME. As a result, companies involved in such intensive R&D tend to avoid this kind of funding instruments. In turn, within the 3 first years of H2020, only 7.5%⁵ of SMEs have taken up the challenge to coordinate a consortium and attempt to ensure alignment of project objectives with the SMEs' strategic needs. In many cases, SME beneficiaries are just service providers.

🌐 **The EIC SME Instrument** looked well-suited to fulfil SMEs' needs; however, the AMR community is again severely underserved. More than €375M have been granted so far under the overall health theme⁶; but fewer than 30 projects addressed the bacterial threat for a little more than €19M funding, of which more than €16M were allocated to the development of diagnostic products. The SME Instrument is indeed more suited to projects that are mature enough (TRL 6 and above), with minimal capital intensity and short return on investment, favouring medical device projects over therapeutic approaches. Moreover, with sound economic viability being a key criteria, AMR SMEs are prevented from competing on an equal footing, as the AMR business model is broken.

🌐 **The IMI2 ND4BB programme** has received more than €315M funding from the EU. Among various precompetitive activities, some projects (ENABLE, COMBACTE, etc.) were intended to develop a product

³ Funding partners now include the Bill & Melinda Gates Foundation (USA) and the UK government

⁴ Arjon J. van Hengel, Laura Marin "Research, Innovation, and Policy: An Alliance Combating Antimicrobial Resistance", Trends in Microbiology, In Press, Corrected Proof, Available online 9 January 2019

⁵ "Analysis report on SME success factors and best practices", Access4smes accessible online at: <http://www.access4smes.eu/publications/>

⁶ Data analysis from <https://sme.easme-web.eu/#> (accessed 2019.01.21)

pipeline from early preclinical to late-stage clinical trial, initially mainly from the EFPIA companies' portfolio; unfortunately with little success. Few SMEs were also given a chance to have their product included. Both direct and indirect funding to product developer SMEs only reached *ca.* €20M. In addition, the general feeling from participating BEAM members was that the overall efficiency could have been a lot better, for example, if the consortium had included seasoned contract research organizations and been more aligned with the specific strategic goal to move a compound through the development milestones to facilitate the submission of a marketing authorization. Indeed, complex/critical development stages are sometimes better handled by experienced professionals as it could, in the end, save time and money and reduce risk of program failure.

Risk-sharing/loan-type cofunding initiatives are non-dilutive funding with a return-based mechanism. Such instruments may offer the financial capacity to cover late stage clinical development. Financing phase 2 and 3 stages is rather problematic in the AMR field, as opposed to other disease area where large pharma corporations usually take the lead from there up to market. SMEs with products against antimicrobial resistance in the portfolio are thus forced to pursue clinical development, even sometimes up to commercialization. The US BARDA Broad Spectrum Antimicrobials programme has been one of the few organizations to provide significant non-dilutive funding to offset the high costs of clinical development phase without which several new antibiotics would still be in phase 3 development.

- **The EIB InnovFin Infectious Disease Finance Facility (IDFF)** provides financial products ranging from standard debt to equity-type financing (from 7.5 to €75M) and dedicated to EU organisations developing vaccines, drugs and medical and diagnostic devices. However, experience gained so far from BEAM members has highlighted a clear requirement for investing in companies with products reaching market in less than 4 years (equivalent of Phase 2/3 stage) and high value return, while drug discovery and development is by essence very long term (10-15 years), in addition to the additional risks that can be associated with AMR products. The evaluation mechanism should be adapted to AMR innovative products with some capacity to accept higher levels of risk specifically in the field, considering the high medical need and limited investment resources.

Grants and loans should be designed to help attract and retain private funding in the AMR arena but their operating conditions need to be adapted to the constraints SMEs in the field are facing.

How could Horizon Europe improve the situation? BEAM Alliance's recommendations

The IMI-funded DRIVE-AB project recently advocated⁷ for a 50% increase of the push funding level to an overall amount of *ca.* €680M. The upcoming Horizon Europe framework programme could contribute to this objective, offering a new opportunity for boosting European innovation in the field of AMR. We are urging stakeholders to design suitable instruments to support the vibrant AMR community, building on the H2020 successes and taking advantage from the areas of progress identified above. Also, owing to the tremendous societal and economic burden AMR may represent in a near future, it is critically important to make sure that an adequately amount of funding is being made available.

⁷ <http://drive-ab.eu/wp-content/uploads/2018/01/CHHJ5467-Drive-AB-Main-Report-180319-WEB.pdf>

1. Missions

Missions, as defined under the article 7 of Horizon Europe regulation proposal, are a key novelty of the upcoming framework programme. They should address societal challenges, be needs-driven, and include indicators to monitor societal impact. The required technological development should attract research and innovation activities that otherwise would likely not be undertaken by private actors, providing the justification and legitimacy for public intervention.

A major R&I mission to fight **antimicrobial resistance is fully in line with the proposed definition**. It has a clear EU-added value, a wide societal, environmental and economic relevance and offers cross-disciplinary and cross sectorial opportunities. Further thinking is needed to identify a relevant and achievable objective, but it clearly looks feasible. This would imply substantial funding of at least €1 billion, in order to support true innovation and deliver the expected results.

Such mission-oriented approaches reflect the typical state-of-mind of an SME. To ensure the target objective can be achieved, constraints must be set to a minimum. Therefore a dedicated Carb-X/SME Instrument-like approach should be favoured, offering true opportunities to concentrate on core tasks.

2. Joint Programming Initiative on Antimicrobial Resistance (JPI-AMR)

The Joint Programming Initiative on Antimicrobial Resistance (JPI-AMR) that started a few years ago, has financed important basic and preclinical research in the field of antimicrobial resistance. Already more than € 55 million have been invested by participating countries in research projects to date, thereby addressing a significant part of the AMR R&D challenge. While significant, this level of investment is dwarfed by the economic damage that AMR will cause if we do not curb the problem adequately (€125 trillion by 2050).

Moreover, SMEs, being also R&D intensive stakeholders, should be able to take part in JPI-AMR projects without restrictions, as opposed to the current situation where national funding constraints are limiting their participation to a few countries. With matching funds from Horizon Europe, the JPI-AMR funding mechanism could be made much more effective, provided that SMEs can also benefit from these funds, so that true public-private partnerships can be created to fight AMR.

Also, the upcoming JPI-AMR Virtual Research Institute is intended to create a global network of researchers, facilities and infrastructures, and would probably benefit from SMEs participation⁸.

3. EU funded pre-clinical and clinical trial networks

Over the years, the EU has funded various networks that could be efficiently used for development programmes. Examples include the pre-clinical trial capacity provided via the IMI ENABLE programme. Also, the building of the European Clinical Research Alliance on Infectious Diseases (ECRAID), originating from both FP7 PREPARE (primary care sites) and IMI COMBACTE (>950 clinical care sites), will allow the faster and easier conduct of clinical research.

For SMEs it is of crucial importance that CRO services can be included as part of the resources within the programme to ensure compliance to GMP, GLP and GCP standards. Further support to harmonize and further integrate these networks would be helpful in ensuring that clinical trials become more efficient.

4. IMI/Industry partnership on health innovation

IMI is currently Europe's largest public-private partnership. IMI's research agenda today has a strong focus on chronic diseases such as cancer, asthma, respiratory diseases and diabetes. While these are threats to

⁸ The BEAM Alliance is coordinating a network of SMEs participating to the building of the JPI-AMR VRI

European public health, and thus of economic interest to the European pharmaceutical industry, we believe that IMI could be much more inclusive with regards to the health needs of LMICs.

With the newly proposed Industry partnership on *health innovation, for the rapid development, deployment and safe use of medical treatments, devices and technologies enhanced by digital technologies*, we call upon the Commission to ensure that ownership of the agenda is not exclusively that of corporate pharmaceutical industry. SMEs, Product Development Partnerships (PDPs) and universities, where true product innovation to fight AMR is taking place, should also be treated as partners. It is well understood that EFPIA partners match via IMI the EU contribution with private capital. While SMEs could be considered to do the same as, generally, all SMEs in drug development have also raised significant private funds in equity investment, the administrative burden to lead an IMI topic is too much for companies often having less than 50 employees. For this reason it would be of great benefit to society to develop an IMI type funding scheme specifically designed for SMEs, or open up the IMI program further to SMEs as in the recent IMI2 AMR accelerator, respecting IP ownership requirements for SMEs, as their entire existence is based on such IP ownership.

5. Invest-EU

The Invest-EU Programme will bring together under one roof the multitude of EU financial instruments currently available to support investment in the EU, making EU funding for investment projects in Europe simpler, more efficient and more flexible. We understand that existing funding instruments, such as InnovFin/Infectious Disease Finance Facility, will be integrated in this new mechanism.

We call upon the Commission to ease the requirements for these instruments. Also, the current EU instruments are not well aligned with instruments of other large funders. As a consequence, many products are not developed beyond early phases as there are no suitable funding mechanisms to support such studies, which generally become more costly and hence more risky at later stages of development.

We also call upon the Commission to support new investments in phase 2 and phase 3 studies, which can take the form of soft-loans or equity investments, which are aligned with other global funding instruments (as well as instruments from other DGs such as DG-SANTE and DG-DEVCO). A relevant new initiative is a proposal for an AMR impact fund to fill the gap in the funding of phase 2 and 3 clinical trials, which has been recently proposed by WHO at the World Investment Forum in Geneva⁹. With a target size of 1 billion EURs, projected returns of 2-3%, and targeted investments from both private and public stakeholders, such a fund could have a very significant impact on AMR R&I. Such a new fund supported by EIB should be designed to stimulate product development in those areas that suffer from market failure issues (such as AMR, TB, NTD).

Conclusion

As beneficiaries of Horizon 2020, the members of the BEAM Alliance know from first-hand experience how essential the EU framework programmes are to effectively conduct the research urgently needed to tackle today's big societal challenge of antimicrobial resistance. The intention of this Memo is to provide different suggestions to help ensure that the instruments from Horizon Europe can be efficiently channelled towards effective research and innovation R&I impact in this area, which saves lives and has a substantial economic return on investment for Europe, while creating quality jobs and driving scientific excellence.

⁹ <https://worldinvestmentforum.unctad.org/session/fostering-investment-in-the-development-of-new-antibacterial-prevention/>