BEAM Alliance Position Paper 2017

Key Guidelines to implement effective measures toward SMEs to revive the antibacterial R&D field

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2017 marks the beginning of the most collective fight ever against the superbug threat. All over the world – be it on the local, the national and the international level – important initiatives have been started to address the challenge of antimicrobial resistance (AMR) and to spend substantial amounts of funding to bring forward research and development (R&D) in the field. The long-term success of these measures will depend on whether stakeholders are able to integrate the perspectives of small and medium-sized enterprises (SMEs). With the largest pipeline of innovative products, SMEs are the major innovation engine in the AMR field to provide patients with effective drugs in the fight against AMR. However, to ultimately revive antibacterial R&D, further specific support of SME-driven innovation is key.

The BEAM Alliance, representing over 40 small and medium-sized Biopharmaceutical companies from Europe innovating in AntiMicrobial resistance research, wishes to acknowledge the contributions made this year by many stakeholders worldwide, following the eye-opening report of Lord Jim O'Neill in May 2016:

- The **United Nations** for starting the Interagency Consultative Group (IACG) on antimicrobial resistance in March 2017 and their efforts to link AMR issues to the Sustainable Development Goals (SDGs)
- The **AMR CallToAction organisers** – WHO, IACG, Wellcome Trust, Government of United Kingdom, of Ghana and of Thailand – for having brought together all stakeholders in science, business, finance and policy on a global level in October 2017 in Berlin to coordinate a global action plan
- The funding bodies **CARB-X, GARDP and their respective founding members** – Wellcome Trust, BARDA, NIAID, the governments of UK and Germany – for their pioneering action of implementing global PUSH instruments that both support R&D innovators and actively contribute to developing the ecosystem for innovative R&D projects to flourish worldwide
- The **German Presidency of G20** for having driven an ambitious political agenda on AMR with the Berlin Declaration of the G20 Health ministries in May 2017 and for the installment of the Global AMR R&D Hub to coordinate funding measures in the international AMR R&D field
- The European initiative **DRIVE-AB** for providing the most compelling analysis of potential solutions to address the issues pointed out by the O'Neill report
- The European regulatory bodies **MHRA and EMA** for having open ears to jointly discuss existing challenges of clinical study designs in the AMR field
- **National European governments** of Germany, United Kingdom, the Netherlands, Spain, Sweden, Denmark or France for increasingly supporting antibiotics research to strengthen national scientific capacities and accelerate drug development

- **T**he **US government and its regulatory body FDA,** pioneer in the introduction of incentives and fast track routes for antibiotic drug developers such as the Qualified Infectious Disease Product (QIDP) designation under the GAIN Act.

Strong need for further action to revive antibacterial R&D

The existing initiatives demonstrate that longtime warning of microbiologists and health care professionals is now heard. From now the world is acting on many fronts. However, bacteria are evolving resistances faster than policy makers are implementing actions. Even in European and in Northern American hospitals, the rise of AMR leaves patients with no treatment option; back to the Pre-Penicillin era.

This is because of the versatile properties of bacteria to exchange genetic materials, to adapt their metabolism almost instantaneously in case of threat and to find compensatory survival mechanisms, thus easily outpacing human efforts to control them. From this background, it is of enormous importance to ultimately revive R&D in AMR by developing compelling surveillance data, encouraging out-of-the-box thinking, rewarding R&D evidence, strengthening existing scientific expertise, further developing scientific capacities and enlarging infrastructure on the national and international level. Only these strategies will provide innovative, effective and sustainable treatments for AMR patients worldwide.

New measures to support SMEs for being the crucial innovation engine in the AMR arena

Today, the antibacterial therapeutic area is recognised to be the most underserved segment of the pharmaceutical industry. Only very few large pharmaceutical corporations are actively involved in innovative R&D efforts. However, there are about 250 biotech companies worldwide who are mainly focusing 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.**

In numbers, members of the BEAM Alliance together contribute over 120 potential new antibiotic compounds or curative and preventive technologies to this pipeline. Of these, a majority target critical pathogens as mentioned by the WHO priority list and approximately 80% investigate new mechanisms of actions or new targets, thus representing a high diversity of innovative approaches to fight AMR. The SMEs in the BEAM alliance also represented half of the signatories of the “Declaration by the Pharmaceutical, Biotechnology and Diagnostics Industries on Combating Antimicrobial Resistance” which was launched at the World Economic Forum in Davos, Switzerland, in 2016.

From a European perspective, BEAM is convinced, that a call to action from policymakers is not enough to counter act the current situation. While this certainly gives hope to all parties invested in the cause to stop superbugs, it did not reach yet the inflection point that would give the confidence to private investors to revive investment in the R&D field.

To advocate re-investing in the field, we need to implement new measures that ultimately translate into achievements for existing players in the field and inspire new ones. **BEAM members propose herein a series of guidelines to help ensure that the current collective effort made by policymakers, foundations, international organisations and others is effectively targeting the needs of SMEs in the biotech sector**.

SME-driven innovation in the AMR R&D field is key for future success. For this reason, we describe herein 10 recommendations to support our needs:

1. Adequately-shaped incentive mechanisms that ultimately rewards R&D evidence
2. Health Technology Assessment recognising the true value of SME innovation
3. Dedicated regulatory pathways to support the specific needs of AMR projects and act as pre-qualification criteria to some PUSH/PULL incentive mechanisms
4. PUSH incentives and funding mechanisms that are directed to SMEs, calibrated and accessible for SMEs in practice
5. Calibrated Market Entry Rewards (MER) to ensure continuous and sustainable innovation from academics to biotech companies and to large pharma players
6. R&D prizes and phase entry rewards as effective PULL mechanisms for SMEs to incentivise the most underserved indications in AMR
7. Targeted tax incentives specifically addressing SMEs to incentivise private investments into AMR-focused companies and/or avoid de-prioritization
8. Going beyond to exploit all possibilities for AMR from SMEs
9. Support education to strengthen attractiveness of the field for R&D professionals/scientists
10. Long term thinking and wisely usage of AMR innovations combined with appropriate diagnostics development

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Abbreviations

AMR: Anti-Microbial Resistance
BARDA: Biomedical Advanced Research and Development Authority (US)
BEAM: Biotech companies from Europe innovating in AntiMicrobial research
CTA/IND: Clinical Trial Approvals (Europe)/ Investigational New Drug application (US)
EUnetHTA: European network for Health Technology Assessment
FDA: Food and Drugs Administration
GAIN (act): Generating Antibiotic Incentives Now (US)
GARDP: Global Antibiotic Research & Development Partnership
GLP: Good Laboratory Practice
ICU: Intensive Care Unit
IMI: Innovative Medicines Initiative
HTA: Health Technology Assessment
MER: Market Entry Reward
MIC: Minimum Inhibitory Concentration, the lowest concentration of a chemical which prevents visible growth of a bacterium
NIAID: National Institute of Allergy and Infectious Diseases (US)
PK/PD: PharmacoKinetics / PharmacoDynamics
PRIME: Priority Medicines designation (Europe)
QIDP: Qualified Infectious Disease Product (US)
R&D: Research & Development
ROI: Return on Investment
SME: Small and Medium size Enterprises
TPP: Target Product Profile
WHO: World Health Organization

1. SMEs, R&D arm of the fight against AMR, require adequately-shaped incentive mechanisms that ultimately rewards R&D evidence

Within the innovation ecosystem that brings drugs to patients, **SMEs comprise the major R&D arm which feeds new drugs into the development pipeline**. The core activities of SMEs spans from early stage research to clinical proof-of-concept.

In biotech companies, innovation is the state of mind. By essence biotech companies turn ideas into R&D projects and products, to fill the innovation gap identified by practitioners. We work on expressed unmet medical needs, as well as needs foreseen by visionary microbiologists and experts in research institutes which we collaborate with.

For each idea SMEs build a business case to attract investors, which encompasses development costs & duration, an addressable patient population, a value proposition and IP protection to secure the innovation. If the case looks solid enough SMEs can attract and retain investors. This is a dynamic process, challenged at every fundraising round. For an investment opportunity to be considered "solid" for a private investor means to have gathered all the followings:

- Identified medical need from which a **market potential can be derived**
- A clear development path where **clinical trial design, clinical endpoints & evaluation criteria are able to prove the concept AND differentiate the added-value of the compound**
- The potential to "exit" the project, meaning most of the time **appetite from mid-size or large pharma players to license or acquire the drug and bring it to the patient**. This potential is usually assessed by investors through "market comparables" (liquidity of listed companies, partnering and financial terms) to weight the likelihood to partner and value the potential financial terms

When an acceptable business case is evident, the expected ROI (Return on Investment) is assessed and benchmarked against other investment cases to decide where to allocate the funds. This is true for investment in an AMR-focused biotech company, as well as prioritization between projects within a biotech company working in different therapeutic area.

The AMR area is currently the most underserved area in pharma as it is not possible to build a compelling business case that is predictive enough, compared to any other areas of diseases. This is already true for incremental innovation and even more for breakthrough innovation in the Antimicrobial Resistance area.

Despite all recent efforts, SMEs still find it hard to put together convincing business cases since they are still lacking certain hard data points:

- **Identification of patient population:** surveillance data is in its infancy, better assessment is needed regarding the practices, use of diagnostic and the actual drivers for selected treatment algorithm, in hospitals and in the community
- **Value for innovation reaching the market:** a pricing that integrates the medical need addressed, the reduction in treatment time, ICU/hospitalization time, the protection against further spread of a superbug threat and especially the social impact of drugs that cure patients in a short treatment time

- **Clear Development path**: a European designation equivalent to QIDP and/or breakthrough / PRIME designation for rare deadly infections, the path for early discussions on trial design for novel approaches
- **Differentiation criteria:** new suitable evaluation criteria to differentiate innovation and allow the assessment of products that cannot be assessed by the MIC – PK/PD method
- **Appetite to partner or attract interest from mid-size and large pharma players:** results from the lack of the above-mentioned aspects

Fundamentally, for SMEs who generally operate early on in the value chain, there needs to be a reasonable chance for efforts in R&D to be rewarded. This is key to enable biotech companies to survive and operate in this therapeutic area.

To ensure that the few SMEs engaged in this area stay and inspire others to develop projects, policymakers should promote incentive mechanisms that ultimately reward -directly or indirectly- biotech investors for having financed R&D up to reaching evidence, preferably at each major stage for the biotech lifecycle *(early preclinical proof of concept – toxicological data – proof of concept in human)* **as this could make R&D more dynamic.**

Support for SMEs is critical in order for investors to engage in or continue funding innovative antimicrobial product development. If measures are adequately designed for SMEs; beneficial effects will unlock in 2 successive steps:

1) The implementation of new measures gives companies or investors the motivation to look at the AMR area and/or to maintain existing investment
2) A rejuvenated industry with clear evidence of the commercial success of biotech companies active in this area (e.g. successful biotech company IPOs or mergers or acquisitions) will give the necessary confidence to allow new investors to step in and maintain their presence in this area

It is important that SMEs already working in this field should not be complacent. The time for action is now! We urge National States and the European Commission to build relationships with their innovative SMEs to make sure they are not falling short financially before the incentive mechanisms are implemented. In particular:

- SMEs engaged at early stage with disruptive approaches that are not yet covered by the scope of CARB-X or GARDP
- SMEs currently engaged in clinical stages

2. Need for Health Technology Assessment that recognizes the true value of SMEs innovation

A first signal for innovation makers to confirm that countries combating AMR actually recognize the existing burden and the threat posed by AMR would be to develop adapted Health Technology Assessment (HTA) approaches. The latter shall take into account the numerous unmet medical needs addressed by biotech companies' innovations which range from:

- preventing infection of at risk patients
- preventing the infection of people around the patient
- preventing the development of virulence
- preventing the development of resistance
- curing the patient
- reducing hospital stays by preventing infection or by curing the patient faster
- limiting the amount of side effects
- allowing the normal course of other life-saving interventions (eg, transplant, chemotherapy)

Current HTA procedures do not fully recognize the economic value of new antimicrobial approaches toward patients, population at risk and society. In the European AMR Action Plan launched in June 2017, the European Commission committed to "develop new or improved methodological HTA approaches and foster methodological consensus-building."

BEAM members encourage EUnetHTA as well as each country's HTA agency to engage with us in order to better seize the innovative nature of the projects under development, the unmet medical needs addressed and how much they contribute to a change in paradigm in the fight against super bugs.

We urge European countries to translate their strategy to combat AMR in HTA that fully-reflects the added-value of the innovation in AMR.

3. Dedicated regulatory pathways to support the specific needs of AMR projects and act as pre-qualification criteria to some PUSH/PULL incentive mechanisms

BEAM members acknowledge the positive actions undertaken in recent years by the MHRA, the EMA, the FDA, and other regulatory authorities to accelerate and simplify the regulatory procedures for innovative antimicrobial products - GAIN act, QIDP designation, PRIME, workshops and the continued evolution of regulatory approaches to enable new antimicrobial approaches, in particular narrow spectrum antibiotics and bacteriophages. Together these demonstrate both the need and the will of the regulators to support R&D in the AMR space.

However, the existing regulatory ecosystem is not complete enough to stimulate sufficient R&D in the field. It requires further adaptation to fit the specific needs of AMR R&D - especially novel approaches – and release constraints inherited from work in silos which impact R&D duration and time to access patients around the globe.

Generate regulatory pathways adapted to AMR

To support the entire scope of innovation in the AMR space, it is crucial to broaden access to specific designations & regulatory pathways to:

- All types of compounds/strategy (e.g. biologics, prophylactic, diagnostic, immune-targeting, microbiome-based, phage-based therapies, anti-biofilm agents...)
- All administration routes (e.g. injectable, topical, tablet, transplant…)

These require European and national health authorities to define better-suited guidelines and accelerated pathways to allow the clinical development and approval of innovative products tackling AMR. While European regulatory guidelines specific to AMR are currently being discussed, BEAM stresses the need to focus specific attention on 3 specific areas:

- novel approaches/novel targets that have no precedent in the area and require novel trial designs and evaluation criteria
- rare infections that are challenging for clinical trial timelines and drug supply
- infections that pose a major threat to the infected patient and their environment

Support "out-of-the-box" innovation by early integration of new concepts

To combat AMR, hospitals and physicians require a complete toolbox of tailor-made strategies, using antibacterial and/or non-antibacterial compounds. This means a One Health mindset applied to Healthcare systems.

To develop such an arsenal and allow new adapted healthcare practice toward the AMR challenge, we need regulatory bodies to facilitate the integration of new concepts early on.

In practice, SMEs need early on signals and guidance from regulatory bodies on pre-clinical packages (models and criteria to be used), especially for novel approaches for which existing evaluation methods cannot assess preclinical nor further clinical efficacy (eg, compounds with no MIC).

We believe that the integration of additional evaluation criteria using complementary scientific approaches is key to allow:

- clinical development, approval and market access of novel approaches, novel strategies to combat AMR
- adapted clinical trials tailor-made to unveil the AMR characteristics of each compound
- better differentiation of existing and new compounds to optimize the use of each and therefore update guidelines
- ultimately to move from Stewardship to greater Education of medical practice and improved management algorithms for the patient

Harmonize regulatory bodies internationally to release unnecessary R&D constraints

Historically, regulatory bodies operate nationally, which results in:

- heterogeneous requirements in terms of pre-clinical package, clinical trial designs and endpoints.
- geographical constraints to enroll patients which translate into longer trial duration and duplication of studies
- longer time and higher uncertainty for compounds to access patients over the globe

BEAM members urge regulatory bodies to release geographical constraint on patient enrolment wherever patient populations and indications are similar and to optimize development timeline, cost and speed up patient access for products targeting the highest medical needs and notably for patients facing a therapeutic stalemate

Furthermore, regulatory bodies should continue efforts to engage with each other (e.g. FDA, PMDA, KFDA…) to harmonize clinical endpoints, evaluation criteria and create mutual-recognition mechanisms to allow small and large pharma companies to register their antibacterial and non-antibacterial compounds in multiple regions at the same time, thus limiting the regulatory burden for antibacterial innovators and ensuring rapid global access. This is key to speed up worldwide availability of antibacterial products is fundamental to react to outbreaks of resistant pathogens.

We urge the regulatory authorities to focus its future actions on several crucial points:

- **generate adapted regulatory frameworks for antibacterial and non-antibacterial compounds, especially novel approaches** (for example for bioproducts such as phages, anti-virulence or for other alternative strategies) and allow product differentiation
- **automatically grant fast track status** to all innovative products developed to tackle antimicrobial resistance
- **Support workshops and study groups working on novel approaches** with no MIC, actively brainstorm and provide early guidance to give a sense of what is expected to fulfill CTA/IND requirement.
- **Collaborate at a global level to ease clinical studies** by removing geographical constraints and harmonizing clinical requirements.

4. Make sure PUSH incentives and funding mechanisms are directed to SMEs, calibrated and accessible for SMEs in practice

The availability of substantial non-dilutive financing tailor-made to suit the needs of small and medium-sized biotech companies is required. It is especially a matter of accessibility in the current absence of a solid market perspective (see investment case criteria from investors p.5). While a large proportion of the existing funding mechanisms initially intended to address the needs of SMEs, it occurs that many of them are not relevant, barely accessible or rarely granted to SMEs.

Below is a summary of the main reasons, identified by themselves, why these incentives fail to address the SME target and key guidance to make sure in the future they are made accessible.

Contrary to large pharma players, SMEs have low or no annual cash flow coming from market sales to allocate to support functions. Non-dilutive funding providers cannot easily consult with the SMEs because they are small, widespread throughout countries and have no Public Affairs departments to facilitate communication. Not being academic or large industry players, they fall under the radar. It results that PUSH incentives targeting SMEs are often developed based on academic or large industry players' needs. None of those are adapted to SME capabilities or needs.

SME resources are limited and 100% is dedicated to pre-defined R&D projects that should meet tight deadlines. The vast majority of SMEs cannot dedicate a full-time equivalent to manage the procurement and operational requirements of the various incentive mechanisms existing. **As a result, many incentive mechanisms are out of reach for SMEs.**

For example, it is frequently not feasible for SMEs to put together complex grant applications requiring large consortia, combined with often specific call requirements regarding the project. Successful applications for funding should aim at quick turnaround times to be awarded in less than 6 months from the application date. SMEs mostly operate on short runways and cannot afford to wait before implementing activities for up to a year. The risk that in the meantime resources are already re-allocated somewhere else is too high.

Being constrained in time and resources, SMEs focus on the PUSH mechanisms that offer the most straight forward framework, conditions and amounts that can have the most positive impact on a business case in particular:

- SMEs prefer to avoid large consortia, as they require a lot of dedicated financial and human resources setting up legal frameworks, coordination and monitoring efforts to meet the tight timelines that SME have to adhere to
- SMEs favor mechanisms that allow flexibility on the selection of partners, allowing work with private companies experienced in operating in a highly regulated environment (GLP, clinical trial, statistical analysis…)
- SMEs favor a situation when IP ownership stays untouched for technologies at an early R&D phase to continue attracting follow-up finance for commercialization
- Many SMEs favor technical application criteria that relate primarily to the scientific approach, the addressed medical need and the ability to manufacture for pre-clinical and clinical stage trials, and not criteria which distract from the main objectives to develop new antibacterial products.

- Grants can often be too low for the effort involved to apply and manage the award if successful. Most SMEs favor single amounts above EUR 1m (per project) to support early stage development and above EUR15m once at mid-clinical stage.
- Grants dedicated to SME, such as the Horizon 2020 SME vehicle must take into account the specificities of drug development, adjusting the "technology readiness levels" to account for the long development times for new drugs.

Such issues noted above are typically encountered with national grant calls, IMI calls and Horizon2020 mechanisms. Regarding initiatives such as CARB-X, we would suggest postponing the definite market access commitment until a point when the technology is at an advanced stage such as preparing for Phase 3 development.

In summary, **SMEs incentive mechanisms need to be simple, easily accessible both time AND resource-wise and only require inputs related to SME core competencies which are the scientific approach, regulatory path & medical need.**

Two years ago, the BEAM members called for a specific fund dedicated to small and medium biotech companies developing innovative antibacterial products in Europe. This fund would finance projects from discovery to clinical proof of concept, with a specific focus on the "valley of death" (early stage to proof-of-concept) via non-dilutive funding tickets ranging from 5 to 10 million euros per project. As opposed to many existing instruments, it would mainly offer individual grants to companies with no obligation to build public-private consortia.

Thanks to the Wellcome Trust, BARDA and NIAID, CARB-X was created, the first initiative of this kind. The BEAM Alliance members would like to warmly thank CARB-X and its donors as their initiative is designed to meet SMEs' requirement and is designed to be accessible for companies at the early stage of product development. They are at the forefront of innovative funding in AMR and have proven it is possible to take action within a few months to make the difference.

We encourage more CARB-X - like initiatives to be established, which like them and GARDP, to be complementary and not competitive. Diversity is a source of dynamism whereas mono/oligopoly situations can often result in reduced scope of innovation. Bacteria evolve resistance faster than science and clinical practice can respond with new technologies. A diversity of funding bodies is needed to allow rapid responses, different prioritizations, different focus, support at different stages of product development and different approaches to external validation for R&D projects.

This having been said there are still some mechanisms specifically targeted at SMEs that are difficult to access despite the willingness of the funding agencies to serve the AMR cause. This generally occurs when the inherent risk profile of AMR biotech companies does not fit with the governing body of the funding body. This is typically the challenge SMEs face with the European Investment Bank and the Innov'Fin mechanism. Their mechanisms are built for mainstream of innovation, meaning areas where the development time is often around 5 years (not 10-15 years like in pharma). While incentive and funding mechanisms from the European Commission and the European Investment Bank are in the course to be renewed and relaunched, SMEs have not as yet been consulted. We express our concern regarding mechanisms that may eventually miss their target simply through lack of appropriate coordination.

BEAM urges that for **each PUSH incentive implemented, the governing body shall make sure the intended beneficiary is clearly defined and, if intended is readily available and accessible to SMEs in a way which allows SMEs to derive value from the investment as programs progress.**

5. Market Entry Reward shall be calibrated to ensure continuous innovation

A Market Entry Reward (MER), implemented in a sustainable manner, appears to be a way to stimulate innovation for new antibiotics or products addressing small or unpredictable target patient population. Concomitantly policymakers want to improve prophylaxis, prevention, and diagnostics, which would result in using antimicrobial compounds in a more sustainable manner and based on a case-specific approach.

BEAM members support this courageous plan, as we believe this is for the greater good of every patient and best medical practice. However, at the same time, this renders any assessment almost impossible of both the future patient population per pathogen/indication and the future threats.

We agree that the MER is a potent tool to replace traditional market approaches which are currently unattractive and would be even less in the near to mid-term as patient numbers affected by severe multi-drug resistant infections will go down if the measures proposed today are effective. Once such a tool is in place and provided it is implemented in a sustainable manner, it gives a new predictive scheme to promote innovation in AMR.

The most important pieces of work to date on the MER are the reports from DRIVE AB (*DRIVE AB Final Report, 2017*) and Duke Margolis (*Value-based strategies for encouraging new development of antimicrobial drugs, 2017*). Our intention below is to provide comments to support the more technical aspects of development of MER mechanisms from the SME perspective.

Target

We recommend a flexible approach that allows discussions on a case-by-case basis with Health Authorities based on a target product profile (TPP). While we believe high level TPPs offer guidelines to the R&D field and support incentive mechanisms, it is of upmost importance that they **enable out-of-the-box thinking**, which is the key role played by SMEs in the R&D arena, especially during early stage/pre-clinical R&D.

To ensure this, BEAM members suggest that TPPs refers to **any intention to diagnose, prevent or treat in terms of either "medical plausibility"** (as in orphan status) **or "added-value"** (as in PRIME designation). Both terminologies shall be available. Such an approach is critical as it can stimulate a broad range of R&D approaches – antibacterial and non-antibacterial, and allow for a specific designation to be granted as early as pre-clinical stage.

This way, consideration of the patient remains central to the decision to assign a MER status whereas with static criteria on drug type, pathogens or indications do not fit the reality of early stage R&D and also forces to frequently revise the formal MER scheme as it does not anticipate the threats to come.

Eligibility

Pre-qualification

To stimulate innovation from SMEs it is crucial to give early on a sense of whether the scientific approach would allow for a MER. However, depending on the technology, it is not realistic to edit a validated TPP before the end of preclinical stage.

For private investors/the market, the biotech area is an event-driven market. The value of a biotech company develops upon reaching critical R&D milestones.

BEAM members propose to have an early signal (advice or designation) from Health Authorities that acts as pre-qualification criteria to a MER. At that point of time, SMEs can be still several years and several fundraising rounds ahead of reaching IND/CTA. This signal is not yet a confirmation that a

MER will be granted but acts as a first selection, meaning a first external validation of the science. Knowing both the currently limited state of knowledge regarding data requirements associated with establishing "medical plausibility" or "added-value" in the field of AMR and the diversity of alternative approaches requiring different evaluation criteria, we encourage Health Authorities to be open-minded and allow learning from the experiences to come.

As for the Breakthrough/PRIME Designation, a granted designation can be rescinded anytime due to the evolving treatment landscape or failure to support "medical plausibility" or "added-value".

Application to a MER

As for the Orphan/Rare Disease or the Breakthrough/PRIME Designation, SMEs could apply as soon as they have collected sufficient evidence to support their TPP. Depending on the technology and stage of readiness, this can happen from the pre-clinical GLP stage up to the end of Phase II.

As suggested by the DRIVE AB consortium and in line with the Breakthrough/PRIME Designation**, the MER should be a voluntary program**. In this process, as in the PRIME Designation, we would appreciate that SMEs benefit from a specific path that takes into account their smaller size and resources as compared to large pharma players.

Delinkage

A partially delinked MER is to our view the most relevant MER mechanism to implement. Firstly, because it still offers flexibility over the years to reward the added-value of the compound. Secondly because from a private investor/market view, this is easier to assess and still partially uses the mechanics from the rest of the industry, which potential business partners are familiar with. In order to attract more investors in the AMR field, it is important to keep some features that do not require significant specific knowledge to understand whether to invest in the area or not.

Offering the flexibility to have value-based payments to reward R&D which is the most innovative and potentially impactful to the benefit of the patient is welcomed by SMEs.

Ensuring a series of MER milestones to further develop the potential of a compound toward targeted patient subgroups and indications is always crucial to exploit the full potential of each scientific approach over time.

Number of MERs granted

Innovations come by cluster; as a result, the first innovation is not necessarily the one that gathers the most attractive features. In the case of AMR, we believe it is of utmost importance to allow for several MERs in the same area of pathogen/indication/scientific approach. Not doing so would potentially result in an early termination of all R&D projects in such an area where 1 or 2 MERs have already been granted stifling the industry.

We should consider the impact of certain old classes of antibiotics in our ability to treat infectious disease and how the drug class evolved. The wide range of antibiotics we have available today have been derived from R&D efforts over many decades that have often made small, but crucial, changes to improve existing molecules for the patients benefit. Such innovation may have not occurred if the innovation had been stifled by the limitation of MERs to the original few molecules.

We believe that MERs shall be open to incremental innovation if an unmet medical need remains, especially in terms of safety or pharmacokinetic properties. From an innovator standpoint, **a fixed quantity of MERs to be attributed to a particular drug class, could effectively kill further investment in a field and thus counteract on the goal of sustainable innovation** in AMR. This should be circumvented by some flexibility around the MERs price negotiation.

Matching private investors/market expectations

The first criteria for private money regarding MERs – like for any PULL incentive mechanism – is to be sustainable; meaning predictable, reliable, transparent and not subject to appropriations. It starts for policymakers by addressing and communicating on WHEN will this be put in place so that SMEs and their investors understand whether it will arrive on time to apply to them or not.

This said, last but not least, the MER should offer an attractive alternative to other life science investments in order for private money to allocate funds in AMR projects. This means for SMEs that this amount:

- if in the hand of a large pharma player as a resulting of partnering the project, shall allow a fair negotiation of financial terms, equaling the attractiveness of what is usually practice in the rest of the pharma area.
- if in the hand of a biotech company who decide to develop the drug themselves and become a market player, the amount permits them to step into this new core activity (large scale manufacturing and delivery) which always comes with a learning curve.

The calibration of the size of a MER has to fit the metrics of those who are in charge of the market manufacturing and access. While BEAM members are not necessarily experts in this area we very much understand that there is no one-size-fits-all MER.

Our main concern as SMEs regarding the sizing of a MER, or MERs, is that it allows for a fair redistribution of the reward to SMEs who partnered with market players. Currently partnering terms in the area of AMR are sub-optimal as compared to any other therapeutic areas, one of the reasons for the low appetite of private investors/the market to invest in AMR.

When evaluating the size of MERs it is of utmost importance for SMEs that the amount ultimately allows a fair redistribution to those who innovated and took the initial risk to bring the science through early and clinical stages.

6. R&D prize and phase entry reward can be effective PULL mechanisms for SMEs to incentivize the most underserved indications in AMR

To promote R&D in the most difficult areas we suggest the development of R&D prizes or rewards based on R&D results. Due to their position in the value chain of innovation as the R&D arm, such mechanisms act as PULL incentives for SMEs.

R&D phase entry rewards could be especially useful for neglected diseases such as Tuberculosis, *Shigella* infections or for infections affecting only a very small patient population (orphan/rare diseases). Since the entire business model of SMEs is built to generate R&D evidence and thus de-risk innovative products on their way to market, phase entry rewards could be an ideal tool benefitting SMEs. A suggested scheme could be having up to three phase entry rewards:

- after successful development candidate selection
- Phase 1 entry
- Phase 2 proof of concept

The phase entry rewards could be structured to cover the actual cost that an SME invested up to the R&D milestone, plus a reward. This would allow the private sector to invest into SMEs at an early stage, covering the risk of failure, but having the security that in case of success there is a limited time frame until a small return comes from their investment.

Furthermore, the phase entry rewards could be an appropriate tool to ensure onset of projects that aim at incremental improvements for TPP's that have already exhausted their MER capacity. As described on p.12-14, once the defined number of MERs has been granted for a certain TPP, early stage projects for this TPP may be abandoned and with them follow up class molecules which might actually have improved properties for the patient, combining efficacy on a new mode of action and better safety profile.

To assure that these molecules may reach a sufficient early clinical development allowing in depth assessment of beneficial properties, the phase entry rewards could play a very important role. Should the R&D evidence lead to the understanding that such a product would be of strong benefit for the patient, the company could negotiate with authorities the possibility of being granted a MER based on the medical plausibility for the research molecules.

R&D prizes could also act in a similar direction especially at early stage and up to Phase I results.

BEAM members believe such approaches would be beneficial to:

- **reward R&D evidence and restore the usual event-driven dynamics of pharma R&D**
- **increase financial attractiveness of AMR projects and engage more SMEs into the AMR field**
- **mitigate the risk of sudden projects drop-off inherent to a limitation of number of MERs to allocate**

We urge for such approaches to be extensively investigated and tested and we acknowledge the Wellcome Trust, Academics from the Uppsala University and the Duke Margolis Center for being forerunners in this direction. BEAM members are willing to support any such initiative in content to better seize the economic model of SMEs.

7. Targeted Tax incentives that specifically address SMEs would incentivize private money to invest in AMR-focused companies and/or avoid de-prioritization

Tax codes are different worldwide from country to country, including members of the European Union. By itself a lower corporate tax rate will not support much growth of innovation as SMEs are pre-revenue. However other aspects can be effective to attract further forces to the R&D field.

We recommend national States to:

- **remove expiry clause on accumulated loss** in the case of SMEs – at least for the portion of investment made in the AMR field
- allow SMEs – at least those involved in AMR **to keep their accumulated loss in case of ownership change** as this is an issue faced when SMEs raise capital with new investors or through strategic partnerships
- **rendering tax-deductible PUSH incentives accounted on the balance sheet at the time it is reimbursed**
- allow for **tax incentives private investors** investing money in AMR R&D

8. Going beyond to exploit all possibilities for AMR from SMEs
9. Educate and attract R&D professionals in the area

One of the key challenges described by the BEAM members is **to attract people with the necessary knowledge and expertise in to support innovative ARM R&D projects**.

Having an accelerator for early stage projects/companies in Europe would help to attract, train and retain R&D experts in our continent, and in addition help to evolve a more robust ecosystem for companies for partnering and for investors to invest.

In this regard we point out the interesting case of the BaseLaunch accelerator which is co-funded by several pharma players with no strings attached to the young start-ups, offering labs and initial funding as well as a comprehensive training and education program and direct access to experts from the industry.

The decline of pharmaceutical investments in antibiotic R&D in the last two decades has led to a massive deficit of experienced antibiotics researchers and developers globally. To preserve know-how in the field, specific translational medicine and drug discovery programs led by universities and academic institutions and public private partner programs could incentivize the recruitment of those experts and participate to the education of young researchers.

10. Think long term and use our innovations wisely

Even the most innovative compound can become obsolete if used inappropriately. Between the 1940s - 1970s virtually all of the current marketed Antibiotic classes were introduced into the market. Bacteria quickly became resistant to each class shortly after market entry, then became resistant to multiple antibiotics and now are becoming resistant to all antibiotics simultaneously.

We urge policymakers, hospitals, physicians to use our innovations wisely to ensure the greatest long-term benefit.

One should never forget the extremely dynamic nature of bacterial resistance mechanisms and the length of time scientists, practitioners, and policymakers need to understand them and act to develop countermeasures. **Tomorrow's threat may be different from today's threat, so the industry must be primed to anticipate and respond accordingly.**

The development of appropriate diagnostic/theragnostic tests is essential to guide a wise therapeutic and the correct use of antibacterial therapies. Every effort should be made to develop point-of-need tests and ensure a wide dissemination in the Healthcare ecosystem. **Diagnostic, Drug, Devices, every Antibacterial Strategy are all mutually beneficial of the surveillance data that could be generated by a widespread use of rapid and accurate diagnostic tests**

As a conclusion, we would like to remind some timeless piece of advice from Sun Tzu, The Art of War – applied to our enemy the "Bad bugs" and us "Healthcare Ecosystem":

> *"Know the enemy and know yourself; in a hundred battles you will never be in peril. When you are ignorant of the enemy, but know yourself, your chances of winning or losing are equal. If ignorant both of your enemy and yourself; you are certain in every battle to be in peril."*

This quote is true for every point-of-care, for every patient. To address it, we need to make sure the entire Healthcare ecosystem joins forces. SMEs are here to observe the Bad Bugs and their behavior, to understand medical needs and to build potential strategies to address these needs. As such, SMEs represent a crucial link in the overall innovative engine between academics and larger industry players. **Engage with your R&D pioneers.**

Signatories:

Abac Therapeutics	Spain
AiCuris Anti-infective Cures	Germany
Alaxia	France
Allecra Therapeutics	France
Antabio	France
AntibioTx	Denmark
Arsanis	United States
Auspherix	UK
Basilea Pharmaceutica International Ltd	Switzerland
BioFilm Pharma	France
BioVersys	Switzerland
Centauri Therapeutics	UK
Combioxin	Switzerland
Da Volterra	France
Debiopharm International	Switzerland
Deinobiotics/Deinove	France
Destiny Pharma	UK
Discuva Limited	UK
Eligo Bioscience	France
Helperby Therapeutics	UK
Karveel Pharmaceuticals	The Netherlands
MaaT Pharma	France
Madam Therapeutics	The Netherlands
Motif Bio	UK
Mutabilis	France
Nabriva Therapeutics	Austria
Neem Biotech	UK
Northern Antibiotics Oy	Finland
Nosopharm	France
NovaBiotics	UK
Pherecydes Pharma	France
Phico Therapeutics	UK
Polyphor	Switzerland
QureTech Bio	Sweden
Redx Anti-Infectives	UK
Septeos	France
SetLance	Italy
Ultupharma	Sweden
VaxDyn	Spain
Vibiosphen	France

For more information:
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