BEAM Alliance Position Paper

Key Actions to Reinvigorate Investment and R&D in the antibacterial field Now

The emergence and spread of multi-drug resistant bacteria has led to a major and global public health crisis that urgently demands a fresh boost of innovation. Novel antibiotics, preventive approaches and alternative strategies to antibiotics, need to be made rapidly available to patients and the medical community to combat antimicrobial resistance and its consequences[1]. Unfortunately, there is today a well-acknowledged gap between this dramatic medical need and the shrinking pipelines of antibiotics focused companies. As they face major scientific, clinical, regulatory and economic challenges[2], it has become increasingly difficult to develop and market innovative products. Furthermore, investments of large pharmaceutical companies in antibacterial research and development have been declining across the globe, due to the lack of economic attractiveness of this therapeutic area. As a result, innovation in this sector is now predominately driven by small and medium biopharmaceutical companies which have become key players in developing novel solutions to combat antibiotic resistance.

The BEAM Alliance (*Biotechs of Europe innovating in Anti-Microbial Resistance*) is a group of 40 small and medium biopharmaceutical companies from 11 European countries committed to fending off antibiotic-resistant pathogens by developing innovative products. The BEAM members are collectively at the forefront of the combat against antimicrobial resistance: **they are developing almost 100 new compounds focused upon the cure and prevention of bacterial infections** (small molecule antibiotics, antibiotic combinations, phages, antibodies, prophylactic and therapeutic vaccines, peptides, prebiotics, other bioproducts, adjunctive therapies and medical devices). 20 of these compounds are currently in clinical development with the potential to improve patient care in Europe and beyond (see product pipeline in Appendix).

The BEAM Alliance has been founded to be the voice of small and medium European biopharmas involved in antimicrobial innovation. Even though the EU, and some of its member states, have already initiated efforts towards overcoming this public health threat, they still need to engage more extensively. The USA have adopted inspiring policies to incentivize the development and commercialization of new antibiotics by implementing the "Generating Antibiotics Incentives Now Act" (GAIN Act) in 2012 and releasing an ambitious "National Action Plan for Combating Antibiotic Resistant Bacteria" in 2015. European-wide and national actions are needed to create equally ambitious and appropriate incentives to stimulate innovation in Europe in this crucial field.

[1] Louis Valiquette and Kevin B Laupland, 'Antimicrobial Shortages: Another Hurdle for Clinicians', *The Canadian Journal of Infectious Diseases & Medical Microbiology* 26, no. 2 (2015): 67–68; Jim O'Neill, 'Antimicrobial Resistance : Tackling a Crisis for the Health and Wealth of Nations', *The Review on Antimicrobial Resistance*, December 2014, http://amr-review.org/sites/default/files/RARJ2810_Review_Launch_Paper_09.12.14_WEB_OUTLINED.pdf.

[2] Kevin Outterson et al., 'Repairing The Broken Market For Antibiotic Innovation', *Health Affairs* 34, no. 2 (2 January 2015): 277–85, doi:10.1377/hlthaff.2014.1003.

EXECUTIVE SUMMARY

In this Position Paper, the BEAM Alliance identifies the challenges faced by small and medium biopharmas and proposes policies to enhance the attractiveness of antibacterial therapeutic research, and to accelerate the development and patient access to new products.

We support **three short term actions** to be implemented immediately, and a **long-term strategy**, to tackle antimicrobial resistance now and in the future.

Proposal n°1: We propose the creation of **a specific fund** dedicated to small and medium biopharmas developing innovative antibacterial products. It would finance projects from discovery to clinical proof of concept, with a specific focus on "death valley" i.e. early clinical development. European-wide, this fund would provide a direct support to small and medium biopharmas with non-dilutive grants and therefore attract additional funding by private investors.

Proposal n°2: We propose **stronger market incentives** to increase the Return on Investment for products tackling antimicrobial resistance through the **creation of a special status for curative and preventive antibacterial products**. Tax breaks, along with the extension of market exclusivity and the revision of pricing models, would reinvigorate the attractiveness of antibacterial R&D and replenish the pipeline of antibacterial products. More specifically, granting a fairer and higher price to new antibacterial products, taking into account their true value for both patients and society, should be a top priority. European laws and directives are needed to define a common framework for the implementation of these three key policies by Member States.

Proposal n°3: We propose to strengthen the already existing actions of the European Medicines Agency (EMA) to **accelerate and simplify regulatory pathways** for products tackling antimicrobial resistance: automatic fast track status, simplification and clarification of the regulatory framework and worldwide harmonization of the development expectations from regulatory authorities.

On the longer-term, we believe that complementary actions are needed to foster antibacterial innovation. First, the R&D environment must be strengthened at all levels: a strong expertise at every stage of the antibacterial drug development should be preserved in Europe, especially since the industry has faced decreasing investments in the antibacterial field. Second, European stakeholders need to think ahead and better value the societal benefits of antibacterial innovative products. Last, we ask to reinforce the support to European biopharmas towards the direct commercialization of their products tackling antimicrobial resistance.

KEY PROPOSALS

Proposal n°1: Increase investments targeted to small and medium biopharma companies

The BEAM Alliance greatly acknowledges the recent political and media interest in antibiotic resistance and strongly encourages the translation of this awareness into a substantial increase in investments in antibacterial R&D.

The primary hindrance encountered by small and medium biopharma companies is the lack of appropriate funding to support the particularly lengthy developments in the pharmaceutical business. In the past decade, both public and private investments in the antibacterial sector have been scarce, limiting the ability of innovative companies to raise sufficient funding for their antibacterial R&D activities.

This public health crisis requires the mobilization of an adequate and durable long-term funding. Antibacterial R&D should clearly be designated as a priority topic for financing, with funds and grants specifically dedicated to stoke antibiotic pipelines. It could take the form of earmarked money in already available (and praised) instruments such as H2020 or Eurostars. Additional public funding would also attract private money in the area thus satisfying the financing needs of innovative companies.

The BEAM members therefore call for a specific fund dedicated to small and medium biopharmas developing innovative antibacterial products. This fund will finance projects from discovery to clinical proof of concept, with a specific focus on “valley of death” i.e. preclinical and early clinical studies up to phase II studies. We suggest 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 company with no obligation to build public-private consortia.

Proposal n°2: Ensure an adequate Return on Investment (RoI)

Companies highlight the crucial need for market incentives that would provide sufficient and predictable rewards for novel drugs, biological antimicrobials, vaccines and any new technology or approach tackling resistance. The Return on Investment (RoI) of antibacterial products is notably low compared to products in other therapeutic areas, which explains the decreasing interest of some large pharma companies formerly involved in this field. To increase the RoI and reinvigorate the declining R&D for new antibacterial products, we propose to create a special status for curative and preventive antibacterial products, and deploy three actions for the therapies which would be granted this status:

- **implementing tax breaks** on the revenues coming from innovative antibacterial drugs;
- **extending the market exclusivity** for innovative approaches. The GAIN Act, enacted in the USA in 2012, provides an inspiring example: therapies targeting priority pathogens obtain a Qualified Infectious Disease Product (QIDP) status that grants them 5 extra years of market exclusivity . The QIDP status further grants an

additional 6 months for products marketed along with a companion diagnostic test, hence ensuring proper use of antibiotic therapies. This strategy has been proven to efficiently stimulate antibiotics investments since then. The EU and US legislations for Orphan Drugs represents another successful example of increased market exclusivity to incentivize the pharmaceutical R&D in one given field. As shown by these examples, the creation of a similar status in Europe for **curative and preventive antibacterial products** would substantially increase the RoI and trigger an immediate interest from investors. However, as the GAIN Act is too narrowly focused on small-molecule antibiotics only, we advocate extending this measure in Europe to all innovative strategies fighting antibiotic resistance; including vaccines, preventive approaches, medical devices, alternative treatments and novel biologics such as phages;

- **reconsidering the pricing model for antibacterial products to grant them with a fair and stable price**. The current model fails to take into account the inestimable value of antibiotics for our society: newly marketed antibiotics would obtain a low price that does not reflect the collective benefit coming from the availability of alternative drugs to thwart the spread of antibiotic resistance. Furthermore, antibiotics are rightly considered as a scarce resource that must be preserved with limited use[3], which further decreases the expected revenues for sponsor companies. As a result, we support much higher and fairer prices for antibiotics, reflecting their true value for both patients and society. Even further, we call for a guaranteed stability of price for these products. Because the determination of drug prices is a national process, the EU needs to propose a commonly shared paradigm for the pricing of new antibacterial therapeutic strategies.

Proposal n°3: Accelerate and simplify product development up to drug approval

BEAM members acknowledge the positive actions undertaken these past years by the European Medicines Agency (EMA) to accelerate and simplify the regulatory procedures for innovative antimicrobial products. However, we urge the EMA to focus its future actions on several crucial points:

- automatically grant fast track status to all innovative products developed to tackle antimicrobial resistance;
- clarify the regulatory framework for novel approaches (for example for bioproducts such as phages or other alternative strategies);
- extend the existing centralized procedures to a centralization of indications in Europe, while taking into account specificities of territories;

[3] Ramanan Laxminarayan, 'Antibiotic Effectiveness: Balancing Conservation against Innovation', *Science* 345, no. 6202 (9 December 2014): 1299–1301, doi:10.1126/science.1254163; Gelband Hellen et al., 'The State of the World's Antibiotics, 2015' (CDDEP, September 2015), http://cddep.org/sites/default/files/swa_2015_final.pdf.

- further encourage adaptive pathways, shortened developments and quicker patient access for products targeting the highest medical needs and notably for patients facing a therapeutic stalemate[4];
- engage with other drug regulatory authorities (e.g. FDA, PMDA, KFDA…) to harmonize the development criteria and create mutual-recognition mechanisms to allow small and big pharmas to register their antimicrobials in multiple regions at the same time, thus limiting the regulatory burden for antibacterial innovators. Moreover, worldwide availability of antibacterial products is fundamental as it is necessary to combat the increasingly globalized antibiotic resistance and react to outbreaks of resistant pathogens.

Towards a special status for innovative products combating antimicrobial resistance?
Creating a special status for innovative products combating antimicrobial resistance, recognized all over Europe, could ease the implementation of the above proposed policies: extra earmarked funding, market exclusivity extensions and increased market incentives. Granted by the EMA, this status would allow to identify all products that could benefit from those measures, as it is done with the Qualified Infectious Disease Product (QIDP) status in the USA and Orphan Drugs in the USA and EU.

FOOD FOR THOUGHT ON LONGER-TERM PERSPECTIVES

Strengthening R&D at all levels

One of the key challenges described by the small and medium biopharma companies members of BEAM **is the lack of people with the necessary knowledge and expertise** in the field. A product is never developed without numerous interactions within a global R&D environment.

National, European and international efforts should be pursued and funded to **strengthen antibacterial expert clinical networks and create efficient structures to monitor the epidemiology of resistance**. Public R&D centers and coordination efforts on antimicrobial resistance enable the concentration of expertise at the preclinical and clinical stages, which strengthen the whole value chain.

Furthermore, the decline of pharmaceutical investments in antibiotic R&D has lead to massive layoffs of experienced antibiotics researchers. To preserve know-how in the field, specific translational medicine and drug discovery programmes led by universities and academic institutions could incentivize the recruitment of those experts and participate to the education of young researchers.

[4] R. Bax and S. Green, 'Antibiotics: The Changing Regulatory and Pharmaceutical Industry Paradigm', *Journal of Antimicrobial Chemotherapy* 70, no. 5 (1 May 2015): 1281–84, doi:10.1093/jac/dku572; John H Rex et al., 'A Comprehensive Regulatory Framework to Address the Unmet Need for New Antibacterial Treatments', *The Lancet Infectious Diseases* 13, no. 3 (March 2013): 269–75, doi:10.1016/S1473-3099(12)70293-1.

Think ahead to better value antibacterial innovative products

As mentioned in our proposal n°2, the current paradigm to determine the price of antimicrobial products – because it does not take into account their global value for both patients and society – failsto address the public health issue of resistant bacteria. **A model of "delinkage" could be a solution to encourage responsible sale and use of such narrow-spectrum antimicrobials while supporting the development of new drugs**[5]. A practical solution proposed by the Review on Antimicrobial Resistance[6] consists of a "global buyer" that would guarantee a sufficient and predictable Return on Investment by a full buyout of the product - the "global buyer" would then be in charge of distributing the product around the world, also ensuring its responsible use. The BEAM Alliance believes this solution to be of great interest, but highlights that it would only suit the case of last-resort antibiotics.

BEAM members' innovations exhibit a wide variety in terms of scientific approaches and products under development**.** In order to cope with the problem in its entirety**, the strategies that are developed to tackle the threat of resistance to anti-bacterials have to be considered in the value chain**. Developing new antibacterial drugs with novel mechanisms of action that minimize the emergence of resistance, combining several antibiotics to decrease the selection of resistance, using phages or peptides to increase the targeted action on the infectious site, encouraging vaccination approaches to minimize the use of last-resort antibiotics, limiting the impact of antibiotics on the microbiota, decreasing the virulence of a multi-resistant strain to minimize its dissemination, using fecal transplants or cocktails of bacteria to minimize resistance carriage etc… are all novel curative and preventive solutions to be considered. These solutions carry great societal and ecological value for combating bacterial resistance. Such ecological and societal benefits represent a novel paradigm in addressing healthcare products. **They should therefore be evaluated and valued by regulators and payers, not only for their capacity to treat infectious diseases, but in the light of their potential contribution to better control infection risks and resistant bacteria dissemination**.

Supporting small and medium biopharmas up to commercialization

Currently, most of small and medium biopharmas out-license their innovative assets during their development phases because they cannot access sufficient funding to build their own sales forces. We encourage the reinforcement of initiatives such as *InnovFin Infectious Diseases* from the EIB, with adapted financial products (non dilutive and dilutive) to finance the developments from clinical Phase II up to initiation of marketing and sales. This would **offer small and medium biopharmas the possibility to take their products up to market themselves**,. It would contribute to the creation of new European biopharma champions and would equally preserve expertise and jobs in Europe.

[5] Kevin Outterson and Royal Institute of International Affairs, *New Business Models for Sustainable Antibiotics* (London: Royal Institute of International Affairs, 2014), http://www.chathamhouse.org/sites/default/files/public/Research/Global%20Health/0214SustainableAntibiotics.pdf.
[6] O'Neill, 'Antimicrobial Resistance : Tackling a Crisis for the Health and Wealth of Nations.'

BEAM members

ABAC THERAPEUTICS Spain	**ABGENTIS** UK	**ABSYNTH BIOLOGICS** UK	**ADENIUM BIOTECH** Denmark	**AICURIS** Germany	**ALAXIA** France
ALLECRA Germany	**ANTABIO** France	**ANTIBIOTX** Denmark	**ARSANIS BIOSCIENCES** Austria	**AUSPHERIX** UK	**BIOVERSYS** Switzerland
BIOVERTIS Austria	**CANTAB ANTI-INFECTIVES** UK	**DA VOLTERRA** France	**DEINOBIOTICS** France	**DESTINY PHARMA** UK	**DISCUVA** UK
ELIGO BIOSCIENCE France	**EVOTEC** Germany	**FAB PHARMA** France	**HELPERBY** UK	**IMMT** Slovenia	**IMMUNSYSTEM** Sweden
LAMELLAR BIOMEDICAL UK	**MAAT PHARMA** France	**MGB BIOPHARMA** UK	**MUTABILIS** France	**NAICONS** Italy	**NORTHERN ANTIBIOTICS** Finland
NOSOPHARM France	**NOVABIOTICS** UK	**OLMIX** FR	**PHERECYDES** France	**POLYPHOR** Switzerland	**PROCARTA** UK
REDX PHARMA UK	**SETLANCE** Italy	**SETUBIO** France	**TECHNOPHAGE** Portugal		

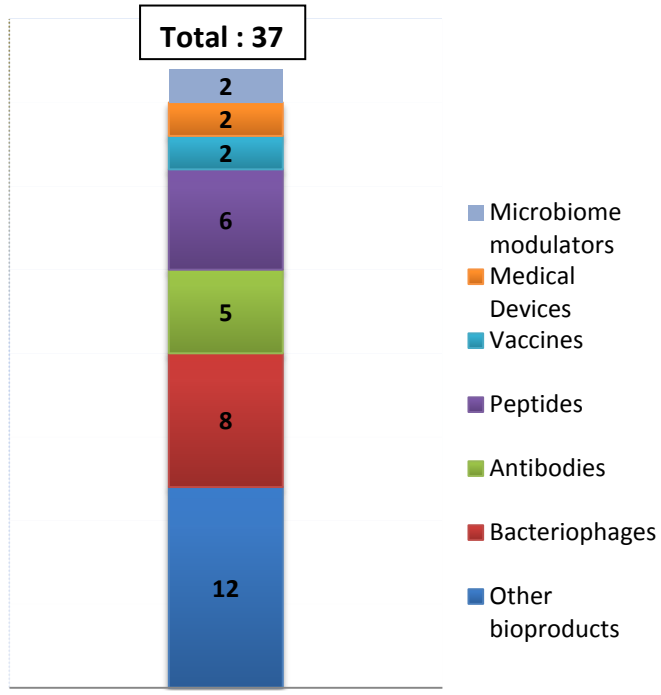
BEAM Alliance Members Product Pipeline

40 companies in the BEAM Alliance, in 11 different countries in Europe

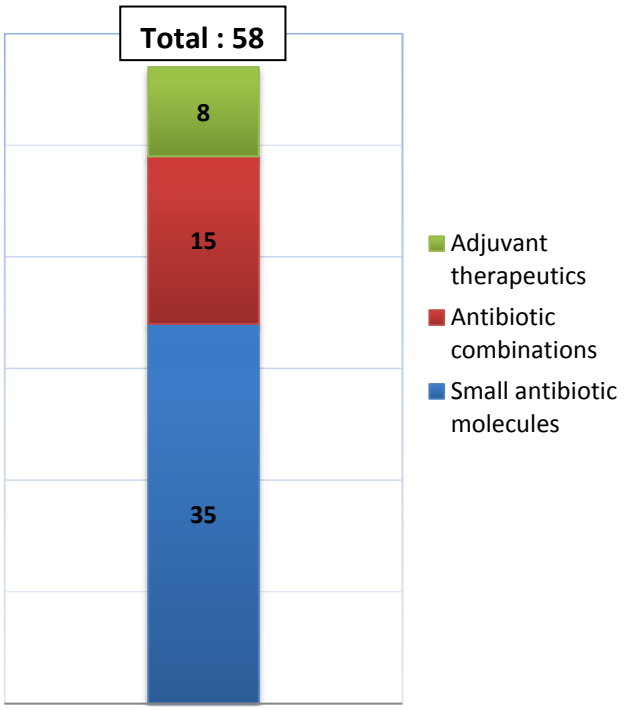
95 Antibacterial Products in development:

- **82%** are novel **Curative Treatments**
- **18%** are new **Preventive Approaches**
- Over 50 have a **novel mechanism of action**
- Almost 40 correspond to innovative approaches, **alternative to antibiotics**

Product Type

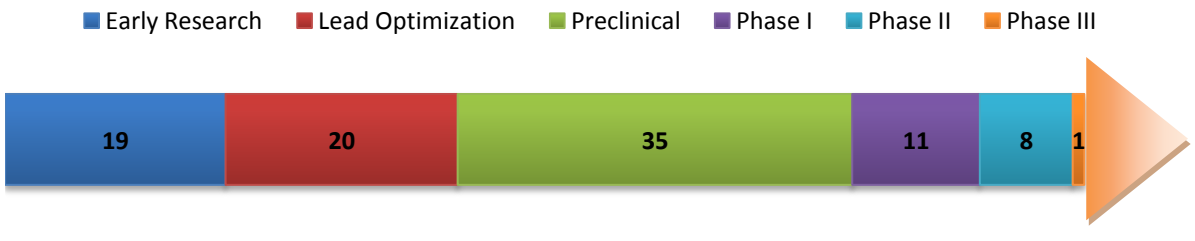


Alternative strategies and bioproducts



Small antibacterial molecules

Products Stages of Development



Products in Clinical Development

Company name	Compound name	Compound category	Product description	Current development phase
Alaxia	ALX-009	**Bioproduct**	Association of 2 endogenous substances with antimicrobial properties compensating the defective innate immune system in Cystic Fibrosis patients	**Phase I**
Ilecra Therapeutics	AAI201	**Antibiotic combination**	Treatment of suspected or confirmed gram-negative multi drug-resistant infections acquired either in the community or hospital environment	**Phase I**
Allecra Therapeutics	AAI202	**Antibiotic combination**	Treatment of hospital acquired gram-negative multi drug-resistant infections in cUTI, cIAI and respiratory indications	**Phase I**
Arsanis Biosciences	ASN100	**Antibody**	Combination of 2 human monoclonal antibodies against *S. aureus* toxins and expected to be tested both in prophylactic and therapeutic indications	**Phase I**
Fab Pharma	FAB001	**Small antibiotic molecule**	NC	**Phase I**
MGB BioPharma	MGB-BP-3	**Small antibiotic molecule (novel antibacterial)**	Novel, oral antibiotic; potential for superiority over current *Clostridium difficile* standard therapy	**Phase I**
SETUBIO	Phytogynal	**Bioproduct**	Plant bioproduct enhancing the microbiote to stimulate the immune system and fight against pathogens settlement	**Phase I**
SETUBIO	Titroléane	**Bioproduct**	Large spectrum bioproduct efficient on antibiotic resistant clinical strains	**Phase I**
Technophage	TP-102	**Bacteriophage**	NC	**Phase I**
AntibioTx	ATx2.1	**Small antibiotic molecule**	NC	**Phase I/II**
Pherecydes Pharma	PP0121	**Bacteriophage**	Mix of 13 lytic phages targeting *E. coli* for burn wound infections	**Phase I/II**
Pherecydes Pharma	PP1131	**Bacteriophage**	Mix of 12 lytic phages targeting *P. aeruginosa* for burn wound infections	**Phase I/II**
Da Volterra	DAV132	**Medical device**	Oral therapy protecting the intestinal microbiota from antibiotic-induced damage, including the prevention of *Clostridium difficile* infections	**Phase II**
Destiny Pharma	XF-73	**Small antibiotic molecule (novel antibacterial)**	Anti-Staphylococcal drug, addressing Antibiotic Resistance, nasal gel for prevention of infection in At-Risk patients	**Phase II**
Helperby Therapeutics	ARB 1-6	**Antibiotic combination**	Helperby Pipeline combinations for cUTIs (inc CREs), cystic fibrosis, nasal MRSA, gingivitis, halitosis, skin infections	**Phase II**
Morphochem / Biovertis	MCB3837 / MCB3681	**Small molecule antibacterial**	Intravenous narrow spectrum Gram-positive antibacterial for the treatment of *Clostridium difficile* infections	**Phase II**
NAICONS	CB-06-01	**Small antibiotic molecule (novel antibacterial)**	New chemical class antibiotic highly selective against *P. acnes* developed in collaboration with Cassiopea SpA	**Phase II**
NovaBiotics Ltd	Lynovex	**Adjuvant therapeutic**	Aminothiol — small molecule initially intended for use in treating respiratory infections associated with CF	**Phase II**
Polyphor	POL7080	**Macrocyclic antibiotic**	Pseudomonas selective, protein epitope mimetic targeting the LptD protein essential for outer membrane biosynthesis. Potential indication include VAP, non-CF bronchiectasis and Cystic Fibrosis	**Phase II**
Immunsystem AB	Anti-Pseudomonas IgY	**Antibody**	Prevention of lung infections caused by *P. aeruginosa* in cystic fibrosis patients	**Phase III**