DRIVE-AB Stakeholder Meeting

European small and medium enterprises focused on antibacterial drug research and development

Introduction

This stakeholder meeting was the first to be organized under the DRIVE-AB project. DRIVE-AB (Driving reinvestment in research and development and responsible antibiotic use) is a project composed of 16 public and seven private partners from 12 European countries funded by the Innovative Medicines Initiative (IMI). IMI is a joint undertaking between the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA). DRIVE-AB has been launched to find ways policymakers can stimulate innovation, responsible use and global access to antibiotics to meet public health needs. A central objective of DRIVE-AB is to engage with all interested stakeholders during the three year project to develop and test new economic models for antibiotic development and use.

Project partners recognized that as the investment of large pharmaceutical companies in antibiotic research and development (R&D) has declined rapidly in the last two decades, the experiences of small and medium enterprises (SMEs) in this area will be a critical factor in identifying new business models that will stimulate investment in R&D for new antibiotics.

The purpose of the meeting was to understand the environment in which SMEs operate, their motivations and the challenges they face in undertaking antibacterial R&D and to discuss possible incentive mechanisms. In addition the founding of a new European association of SMEs involved in antibacterial research was discussed.

The meeting was attended by representatives of 26 European companies, DRIVE-AB partners and observed by members of the independent Review on Antimicrobial Resistance (Jim O'Neill review) established by the UK government. A list of companies and other attendees is at Annex 1. The meeting was conducted under the Chatham House rule.

After introductory presentations about the IMI programme and DRIVE-AB, participants were divided into four roundtables each of whom addressed a series of the same questions devised by DRIVE-AB in one morning and one afternoon session.

The DRIVE-AB stakeholder meeting took place on Monday, 9 February 2014, 10.00-17.00 at the Royal Automobile Club, London.

This report was jointly authored by Enrico Baraldi, Charles Clift, Cornelia Körber and Ursula Theuretzbacher based on notes of the discussions taken by other members of DRIVE-AB listed in Annex1.

Brief company introduction

The responses indicated the very wide diversity in SME origins, approaches, funding and R&D portfolios. The scope of R&D activities varied widely, but there was more focus on narrow spectrum products to tackle specific problems (such as hospital-acquired infections due to multi-drug resistant pathogens or specific resistance mechanisms of known antibiotics) rather than broad spectrum antibiotics capable of responding to a wide range of bacteria. Some approaches were pathogen-specific, while others focused on preventive or adjunctive approaches such as vaccines, monoclonal antibodies, phages, addressing dormant bacteria or protecting the intestinal flora. Firms used a variety of novel R&D approaches (such as utilising new screening methods or natural products from unexplored sources) as well as known approaches. Some were investigating antibiotics from new chemical classes or new modes of action, while others were exploring the rejuvenation potential of older antibiotics. Some were focusing on antibacterial programmes only; others also conducted R&D in other areas. Programmes generally fell between the discovery phase and Phase 2 clinical trials.

Companies varied greatly in size, from virtual companies with no employees (hiring competence from partners on a contract basis) to more integrated operations with dozens of employees. There were also important differences in their entrepreneurial and business experience, with some companies involving mostly people with academic backgrounds and others involving former employees in the large pharmaceutical sector.

While most companies operated out of a single location, some had offices in more than one country, notably in the USA, as a means to access local public funding opportunities. There was considerable diversity in their business models in terms of which R&D stage they aimed to reach, in the choice between single product or multi-product approaches, and in the degree of vertical integration (with a predominance of companies outsourcing to external parties most of their operations).

Reasons to enter the antibacterial field and strategies

The majority of the companies had their background in an academic setting. Typically this might be based on the discovery of a promising technology with a potential antibacterial application which led to the establishment of a spin-out company to explore further the science and applicability of the technology. Alternatively highly experienced industry experts in the antibacterial field (perhaps from the large pharmaceutical sector) had formed a new company and acquired a new technology from a university. A third category included companies spun out from the large pharmaceutical sector, perhaps created for strategic purposes as part of a strategy to exit the antibacterial field.

Most of the attending companies took an opportunistic approach to the exploitation of a promising new technology rather than having any preconceived intention or formal plan to enter the antibacterial field based on a prior assessment of promising market opportunities. Generally, because of the early stage of technology development, the financial and economic potential of the enterprise was difficult to assess with any certainty – entry was based on a judgement that such potential existed based on an understanding of medical need and niche sectors where specific opportunities for new treatments were present, and the absence of

strong competition in the chosen area was a criterion. In general participants agreed the increasing resistance problem is the main driver for antibacterial R&D. An important motivation was the opportunity to pursue science in a creative and innovative manner with the prospect of contributing to human health. The prospect of financial gain was in many ways less important.

Challenges for SMEs in the antibacterial field

This section focussed on non-financial challenges to SMEs. One of the key challenges described was the lack of people with the necessary knowledge and expertise in the field. As large companies had mainly exited the field, the supply of trained people had diminished and knowledge from a decade or more ago was outdated. SMEs experienced in particular a shortage of chemists with expertise in compound development as universities rarely offered targeted programmes in medicinal chemistry. This impacted directly on the companies themselves in terms of recruiting necessary expertise, but the absence of the necessary expertise in other organizations with which companies had to deal (e.g. medicines regulators or reimbursement organizations) was also a constraint.

As regards collaborating with other organizations the following points were made:

- Finding suitable clinical research organizations (CROs) was difficult and there was heavy competition for their services. Consulting services were usually not helpful with creating an overall vision and R&D strategy.
- Relations with universities were often problematic – technology transfer offices often had too high expectations concerning the potential value of university technologies and their priorities (for example as between publication and patenting) were often at odds with commercial reality.
- European Union (EU) funding was difficult to access because of the restrictive conditions relating to forming collaborations and overly bureaucratic processes, which were not in line with SME needs and involved time-consuming and arduous application procedures which SMEs lacked the time and resources to comply with.

Other challenges highlighted by the European SMEs include:

- Lack of diagnostics.
- The need to take short cuts in R&D because of limitations in funding and time as well as the dependence on serendipity.
- The rapid rate of change in the way R&D was being done and the nature of collaborations required.
- The difficulty of affordable access and poor quality and availability of data such as data on specific potential markets and resistance surveillance for specific fields.
- Negotiations over intellectual property rights particularly in the context of exit and buy-outs – and sometimes in respect of the creation of collaborative platforms with peer organizations.
- High risks due to generally narrow product portfolios which could threaten the existence of the SME if the programme fails.

- The different standards set by regulators (e.g. between the EU and USA) and limited experience in novel approaches in the antibacterial field, although recent improvements in regulatory practice were apparent.
- Lack of regulatory guidance including on the design of clinical trials in areas outside the mainstream.
- Absence of adequate animal or in vitro models and a lack of other development tools when it comes to novel approaches. Regulatory pathways were not developed for novel approaches and put a burden on small companies.
- Potential collaborators might not understand new approaches.

Financial barriers to investment

Some SMEs had long-term investors and this alleviated financial concerns, but most depended on venture capital firms (VCs), 'angel' investors and public funds for the start-up phase. Very little public money was available for later phases of R&D. Access to private funding can be problematic for several reasons:

- Many VCs have little expertise in the field and therefore could not identify the true potential of an antibacterial venture.
- VCs tended to follow fashion, exhibiting herd behaviour concerning the preferred field of investment. Investors prefer well-known paths and may treat innovative R&D approaches sceptically.
- The absence of a well-planned business model for most SMEs, inherent in the nature of their R&D, further deterred VCs.
- As it was impossible to gauge at an early stage of R&D the likelihood of ultimate regulatory approval, investors believed the risk of failure was not compensated by the likely returns in the case of success.
- Return on investment calculations were often required by investors but were regarded as a meaningless number by most SMEs, given the inherent uncertainties of product development, especially for new approaches.
- Investors are deterred by the lower product prices prevalent in the antibacterial field compared with the much higher prices obtainable in some other fields.
- Investors look either for extreme niche products, which could justify high product prices or else favour broad spectrum products with a potentially much larger market.

Other financial issues raised included:

- Potential sales were often considered small relative to other infectious diseases such as HIV or hepatitis C.
- US-based investors seemed to believe that European reimbursement and HTA systems were too complex and demanding.
- IMI and other European funding opportunities (FP7 and Horizon 2020) were not suited to SMEs as the rules were inflexible and it was too time-consuming and labour intensive to build consortia in relation to the likelihood of success.
- IMI projects such as ENABLE did not address adequately the concerns of SMEs regarding intellectual property (IP) issues especially when IP is not settled yet in early discovery programmes and broad access to unprotected information was given to a big consortium including large pharmaceutical companies.

- There was a variation in the stage when the so-called 'valley of death' is reached where additional significant funding is required to leap over it. This could be in the phase of lead optimisation for some or between one of the clinical trial phases for others.

Role of SMEs in relation to other organizations in the antibacterial field

SMEs often depended on universities for their initial technologies and on large pharmaceutical companies as the market for their outputs, including the outright sale of the SME. On the one hand, as noted previously, universities often had unrealistic expectations regarding the value of a technology. On the other hand, SMEs faced great uncertainty in the market for their outputs which was to a degree dependent on the decisions of large pharmaceutical companies. An SME might want to sell or out-license a particular asset, or sell the whole company as an exit strategy. But large companies were risk-averse and what they wanted was unpredictable. And as the latter's antibacterial portfolios had diminished there were fewer companies to collaborate with, and the market for SME outputs had become thin.

The SMEs' viewed their major weaknesses as follows:

- Lack of business experience and resources in general, which was often not possible to overcome via collaborations with universities or other partners, as such relationships were also demanding on SME's limited resources.
- A higher risk of failure, as SMEs, unlike large companies, were extremely vulnerable because of their reliance on one or very few products.
- Many SMEs did not see a realistic way to commercialise products by themselves. Their speciality was innovation, making them dependent on large companies to complete product development and obtain marketing approval. However, recent examples of successfully completed phase 3 studies, product registration and market access spurred discussion about keeping value in the company as long as possible.

On the other hand, the SMEs identified also a series of strengths compared to larger companies:

- They were innovative, more risk-taking and gave researchers more freedom
- Their criteria for success were less stringent than in larger companies, which motivated them to pursue opportunities with lower or more uncertain return expectations.
- They were more cost-effective than large companies, as they did not have such high overhead costs and were slimmer organizations.
- Their economic model was different: their R&D entailed lower cost and they did not seek blockbuster products.

As regards the future role of SMEs, attendees discussed the risks inherent in planning their exit strategy and considered the possibility of alternative approaches including continuing their development activities for longer before exit. This discussion suggested the need to reconsider the role of SMEs as limited only to linking academic research with later-stage development. Views varied on the role of SMEs along the discovery-development continuum and in relation to larger companies. Some favoured earlier and stronger input from large companies and greater willingness for them to share risk. There was a tension between the options of aiming

at exit prior to commercialisation, and attempting to build a sustainable company by raising equity funding supported by a stream of income from licensing deals, but the latter option presupposed an unusual degree of success in discovery.

Response to medical needs and resistance patterns

Several SMEs did not find these issues very relevant and discussion was brief. But all companies agreed that early warnings about resistance emergence and high-quality surveillance data were important to avoid pursuing inappropriate R&D paths. SMEs naturally focused on solving resistance problems because that was the principal market opportunity. However, co-resistance was also seen as a potential risk. Many SMEs focussed on niche markets and hospital care because these areas were capable of realising higher prices. By contrast, broad spectrum antibiotics used in primary care were not attractive.

Meaningful incentives in addressing the challenges faced by SMEs

This discussion generated a wide range of ideas about incentives and mechanisms that would stimulate SME investment. As regards funding, SMEs generally were not particular about which specific mechanisms should be implemented. They were more concerned that the recent political and media attention to antibiotic innovation should result in tangible and sustainable increases in investment. However, they expressed reluctance to dilute significantly their equity as well as any mechanism that deviated largely from today's reimbursement norms. High prices were often mentioned as the solution both as an investment incentive and as a disincentive for overuse. (Access implications to high-priced novel antibiotics seem not to have been considered.) Other key ideas included:

- Public-private partnerships to fund and coordinate antibacterial R&D, although only if designed for and targeted at the circumstances of SMEs.
- Involvement of foundations such as the Bill and Melinda Gates Foundation.
- Antibiotic R&D should be a priority topic for funding, deserving earmarked calls for applications rather than competing directly with other fields.
- Simpler ways to apply for funding.
- Targeted in-kind support such as incubators with adequate discovery services, centralised high quality CROs for developing new models and R&D tools for new antibacterial approaches.
- Payments tied to achievement of milestones.

Apart from funding, other changes could provide greater incentives. All well-known incentives were discussed and it was mentioned that some only partly benefitted SMEs, while others were directed at VCs. Suggestions included:

- General measures to increase awareness of the AMR problem, in order to attract more support from all parts of business and society.
- Public investment to address the expertise deficit and infrastructure issue.
- Forms of guaranteed purchase arrangements including for products not used immediately for conservation reasons.
- More collaborative arrangements with CROs, universities, governments, and large companies, although IP challenges were again mentioned.
- Earlier collaboration and more risk sharing with large companies.

- Better and rapid diagnostics.
- Creating homogenous data frameworks and data sharing.
- Lower costs for SMEs in the regulatory process.
- Regulatory changes to allow earlier patient treatment.
- Public patent pool.
- Extending tax breaks for antibacterial R&D.
- Saleable market exclusivity vouchers.
- Higher prices (e.g. $20000 a treatment) were discussed as both an incentive for producers and a disincentive for overuse.

In general, the need for more pull incentives was emphasised. Issues concerning patient access were not a significant consideration for SMEs.

Conclusion

The European SMEs attending the London meeting exhibited a wide variety in terms of scientific approaches, typologies of products under development as well as background and business models. This variety can be viewed as a positive feature in the search for novel approaches to antibiotic development - “Let a hundred flowers bloom, let a hundred schools of thought contend”. These companies occupy the important market space between academic/basic research and late stage development, where a multiplicity of novel technical and business approaches offers more possibilities for identifying new antibacterial solutions, by comparison with just a few dominant actors pursuing similar strategies. It was particularly encouraging to see that there are a few companies capable of bringing products to Phase 3 and even market launch.

On the other hand, taken individually these SMEs suffer from several weaknesses (limited business competence and resources, and higher risk of failure). They also face considerable financial barriers, such as VCs sceptical of an antibacterial market viewed as too risky and small, and inadequate quantity and accessibility of public funding. Additionally, SMEs face a whole range of other challenges, ranging from problems in collaborations (e.g., with academia or CROs) to high risk of failure, from inadequate market data in niche areas to lack of diagnostic tools, from IP disputes to unclear regulatory standards for niche approaches. Not surprisingly, many of the incentives preferred by SMEs address these and the other challenges they identified: for instance, on the *cost* side incentives that reduce R&D costs such as continued improvement in regulatory procedures and in the supply of suitably trained personnel; on the *public funding* side simplified and targeted grant applications; on the *revenue* side sellable exclusivity vouchers and higher prices; on the *other resources* side better public infrastructure for R&D and collaborations or access to key data. While improving the operations and economic performance of SMEs, these interventions would indirectly also make VCs more willing to invest in antibacterial ventures.

Annex 1

SMEs	
ABAC Therapeutics	ES
Absynth Biologics	UK
Adenium Biotech	DK
AiCuris	DE
Allecra	DE
Antabio	FR
Arsanis Biosciences	AT
Bioversys	CH
Biovertis	DE
Da Volterra	FR
Debiopharm Group	CH
Destiny Pharma	UK
e-Therapeutics	UK
Evotec	UK
FAB Pharma	FR
Fundacion MEDINA	ES
Helperby	UK
Lamellar Biomedical	UK
Madam Therapeutics	NL
Northern Antibiotics	FI
Nosopharm	FR
Novacta	UK
Pherecydes Pharma	FR
Polyphor	CH
Redx Pharma	UK
Summit PLC	UK

DRIVE AB	
Christine Årdal	Norwegian Institute of Public Health, NO
Enrico Baraldi	Uppsala University, SE
Francesco Ciabuschi	Uppsala University, SE
Charles Clift	Chatham House, UK
David Findlay	GlaxoSmithKline, UK
Judith Hackett	AstraZeneca, USA
Cornelia Körber	Uppsala University, SE
Cecilia Kållberg	Norwegian Institute of Public Health, NO
Carl Kronlid	Uppsala University, SE
Steve McKeever	Uppsala University, SE
Brigitte Nolet	Roche, CH
Ursula Theuretzbacher	Center for Anti-Infective Agents, AT

AMR Review	
Hala Audi	AMR Review, UK
Anthony McDonnell	AMR Review, UK