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Meeting the societal need for new antibiotics: the challenges for the pharmaceutical industry

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The rise of antibiotic resistance is leading to clinicians being increasingly faced with clinical failure due to the lack of effective and safe treatment options. New antibiotics are needed now for current multi-drug resistant infections but also in preparation for emerging and anticipated threats. There are significant challenges for the pharmaceutical industry to discover and develop new antibiotics including a business model that balances reasonable reimbursement with appropriate use. This summary reviews the key challenges and collaborative interventions that may contribute to addressing a societal problem.

Introduction

Antibiotic resistance is a global problem that is multifactorial in its causes and consequences and thus interventions will need to be wide ranging and address the problem at all levels [1]. A priority focus for immediate intervention is the public health crisis of physicians faced with clinical failure due to the lack of treatment options available for patients with infections due to bacteria that are multidrug resistant (MDR) [2, 3].

The pharmaceutical and biotech industries are one of the key stakeholders expected to address the societal problem described as a perfect storm of increasing multidrug resistance and the lack of suitable new antibacterial agents. The clinical failure of untreatable infections is a consequence of a chain of events including poor infection control, inappropriate use and inadequate market incentives for innovation leading to inadequate treatment options. The pharmaceutical industry needs to collaborate with other partners in society to address the challenges of increasingly untreatable bacterial infections.

The challenges for industry to bring new antibacterial agents forward can be categorized as a combination of discovery, development and economic.

Discovery challenge

The promise that came from the development of high-throughput screening (HTS) against defined targets and rational drug design has led to disappointment due to issues associated with identifying synthetic compounds that could effectively penetrate cells [4]. The presence of an effective penetration barrier in bacteria and in particular the cell membrane and outer envelope of Gram-negative species and the lack of compounds able to penetrate are two of the key reasons for the lack of progress in identifying novel candidate drugs.

Compound libraries may need to be produced that focus on properties of penetration. Previously libraries have been developed or screened based on Lipinski *et al.*'s rules for physiochemical properties that are desirable for oral bioavailability and thus potentially removing

compounds that have a capability to penetrate bacterial membranes [5]. However those properties for penetration that would enable successful screening of compound libraries need to be developed.

Development challenge

Selection of clinical candidate drugs

Before the evaluation of an antibiotic in the intended patient population the therapeutic index and pharmacodynamic (PD) target must be determined and demonstrated. Many compounds fail in pre-clinical toxicity and in first time in man evaluations due to the concentration selected to maximize penetration and achieve PD target attainment being at the edge of the therapeutic range [6, 7]. The need to deliver high concentrations of a compound substantially increases the risk of toxicity, thus reducing the probability of generating clinical candidate drugs.

Registration of new antibiotics

Society does not simply need a large number of new antibiotics but what it does need is antibiotics that are expected to treat serious conditions and provide significant improvements in safety and efficacy over existing therapies and provide a treatment option where there is currently clinical failure. A major hurdle for the development of new antibiotics has been an inflexible regulatory pathway with a resulting complexity in the design and conduct of late phase clinical trials.

Clinical failure is increasingly the reality when treating hospital acquired infections caused by carbapenem resistant Enterobacteriaceae (CRE) or opportunistic pathogens such as *Pseudomonas aeruginosa* and/or *Acinetobacter baumanii*. These causative organisms are multidrug resistant due to a combination of acquired and innate resistance mechanisms and although associated infections are still comparatively rare they are endemic in some regions and institutions and emerging in others [2, 3, 8].

Classical regulatory pathways have been indication or disease driven requiring two large phase III studies, for initial registration, per indication such as complicated intra-abdominal infections (cIAI) or complicated urinary tract infections (cUTI) [9]. These non-inferiority designed trials are large and complex often with significant design and operational challenges. Infections due to CRE or *Pseudomonas* spp are sporadic and heterogenous [8] and conducting trials under the classical indication driven framework are not practical and would result in very long, expensive and impractical clinical development programmes. We cannot wait until a problem such as CRE infections is a global endemic to provide the numbers for indication specific registration trials.

We need a flexible framework that balances the amount of clinical data required for registration with the extent of unmet medical need. A cross-industry group demonstrated the opportunity to utilize existing regulatory frameworks by proposing a tiered approach with a totality of evidence concept for registration of an antibiotic [9]. This would result in scenarios for new agents for CRE, *Pseudomonas* and *Acinetobacter* infections where single randomized comparative studies or open label studies *vs.* best available therapy (BAT) supported by extensive pharmacokinetic and pharmacodynamic dosing evaluation across a range of resistant phenotypes may be suitable for registration. Futhermore these data may be supported by observational studies to define BAT and assess clinical outcomes and estimate a placebo like response rate for selected infections and outcome measures.

There is now a consensus formed across industry, medical societies and regulatory agencies on the need to introduce flexible limited population and pathogen directed development pathways for MDR infections as an example of clear unmet need.The encouraging news is that both the FDA draft guidance [10] and EMA addendum [11] (*Addendum to the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections*) released during 2013 contain clear guidance on streamlined and limited development programmes for priority antibiotics that contain many of the concepts discussed and published over the last couple of years.

Improving clinical trial efficiency – the role of rapid bacterial identification

A rapid bacterial identification test that is strongly predictive of a positive bacterial culture would obviously inform antibiotic use in practice and enhance antibiotic stewardship. Also the availability of such a test (e.g. to detect *P. aeruginosa* or *A. baumanii*) could improve clinical trial efficiency by enriching the study population for patients with these infections. A rapid test does not need to have 100% certainty of predicting positive culture to make an impact. A test that can rapidly predict the likelihood of the presence of an organism of interest from 30% to 50% could reduce study size dramatically with a concomitant reduction in cost and time.

Improving clinical trial efficiency – building clinical trial capability

A key challenge to the development of antibacterial agents is the lack of operational and clinical experience of antibacterial clinical trial conduct especially in areas of the globe where multidrug resistance is a problem. Limited population programmes will need to be conducted in areas where the pathogen is endemic and thus there is a need to build capability through the creation of investigator and laboratory networks to ensure consistency and efficiency in the conduct of innovative clinical trials. Futhermore such networks may facilitate collaboration

and improve co-ordination with a positive impact on feasibility assessments and study start-up times and also could provide a rapid response to evaluate compounds in newly identified outbreaks of resistant pathogens.

The Transaccelerate Biopharma initiative programmes and Clinical Trials Transformation Initiative (CTTI) are addressing innovation and inefficiencies in clinical development *per se* and this work can be complemented by specialist antibacterial clinical research networks modelled on the Aids Clinical Trials Group (ACTG) or successful Oncology organizations (e.g. European Organization for Research and Treatment of Cancer). Specific anti-bacterial clinical trial networks are now being set up with the US NIAID funded antibacterial research leadership group (ARLG) led from Duke University and the European IMI COMBACTE Consortium discussed later in this editorial.

The economic challenge – do we have a viable business model?

Many of the key solutions to the development of antibiotics are related to reducing the time and cost of clinical trials. The current cost of development accompanied by a restricted use policy to preserve new antibiotics means that a reimbursement model linked to price and sales volume does not present a viable return on investment for pharmaceutical companies [12]. Is a sales volume model fit for purpose? How do we both preserve new antibiotics and promote appropriate use within a model based on price and sales volume.

Due to increasing antibiotic resistance maximizing sales volumes of antibiotics may not be in the interests of global public health. Is it now time to consider seriously removing the connection between the funding of antibiotic R&D and sales volume? Push and pull incentives can make a significant difference, such as development cost-sharing partnerships (e.g. US Biomedical Advanced Research and Development Authority (BARDA)) and the additional 5 years of exclusivity provided through legal measures such as the US Gain (Generating antibiotics incentives now) Act [13]. There may also need to be market incentives to protect antibiotics as a valuable resource from overuse and to ensure global access.

Adaptable business models should be in place with a priority on a model that focuses on preventing a scenario of untreatable infections with high quality antibiotics that treat serious bacterial infections with improved efficacy and safety.

Interventions – a societal response to a societal problem

The perfect storm of increasing antibiotic resistance and a lack of new antibacterial agents cannot be abated by individual stakeholders. Partnerships, including but not limited to academia, governments and industry, to share expertise, resources, risk, costs and where possible returns can be a solution to addressing the antibiotic crisis.

There are many different types of partnership approaches across all aspects of drug development, including antibiotics, from discovery to market, that can make an impact but are not panaceas for all ills:

- Open access and source sharing approaches – e.g., TB drug discovery initiative
- Government and philantrophic collaboration and funding – Wellcome Trust Seeding Drug discovery, Critical Path to TB Drug Regimens, US Biochemical Advanced Research and Development Authority (BARDA)
- Product development partnerships – e.g. drugs for neglected diseases initiative (DNDI)
- Public–Private research collaborations – e.g. EU Innovative Medicines Initiative (IMI) New Drugs 4 Bad Bugs (ND4BB) Programme

The European commission and the pharmaceutical industry joined forces to respond to the challenge of antibiotic drug development with the launch of the ND4BB project under the IMI, a public–private partnership in which the European Union and the European Federation of Pharmaceutical Industries and Associations (EFPIA) provide matched funding to confront Europe's major health challenges. The research supported is aimed at tackling the bottleneck and challenges to bring new antibacterial agents forward as treatment options.

ND4BB was launched in June 2012 and to date three consortia, consisting of European pharmaceutical companies, academic centres, hospitals, microbiology laboratories and small medium enterprises, have been formed with four further research topics launched and undergoing application and evaluation.

1. TRANSLOCATION aims to increase the overall understanding of how antibiotics can penetrate into multi-resistant Gram-negative bacteria such as *Escherichia coli* and *Klebsiella pneumoniae* and to avoid efflux. In sharing the knowledge and data discovered, TRANSLOCATION aims to develop guidelines for designing and developing new drugs to tackle antibiotic resistance and create an information centre for pre-existing and on-going antibacterial research data which will be used to establish best practices for future antibacterial drug discovery efforts.
2. ENABLE is building a drug discovery platform to optimize hits from public partners and pharmaceutical companies into candidates and progression into the clinic.
3. COMBACTE is the first clinical development consortium formed under the ND4BB programme with a goal of building capability in Europe to improve efiiciency in

clinical trial design and to deliver antibiotic clinical trials. COMBACTE has established three networks:

a) CLIN-net – a European wide clinical investigator network intended to be prepared and experienced in performing high quality clinical studies including expanding into southern and eastern European areas of endemic multi-antibiotic resistance.
b) LAB-net is a complimentary laboratory network within COMBACTE composed of diagnostic and specialized microbiology research laboratories and a highly qualified central laboratory. LAB-net will provide 'state-of-the-art' laboratory investigations needed to underpin the development of optimal diagnostics and therapeutics in clinical trials.
c) STAT-net is intended to be a biostatistical centre of excellence investigating approaches to innovative and effective phase 2 and 3a clinical trials to support the clinical development of new antibacterial agents. This will be achieved by establishing a preclinical and clinical data repository on which advanced biostatistical analyses and pharmacokinetic/pharmacodynamic modelling will be performed. Novel clinical trial designs and supporting data will be generated and discussed with regulatory authorities as a means to build alignment around what is considered robust evidence of efficacy and safety in future antibacterial drug development.

COMBACTE will also deliver clinical trial programmes for two key assets, GSK1322322, representing a new class of antibiotics with a novel mode of action, peptide deformylase (PDF) inibition, with activity against methicillin-resistant *Staphylococcus aureus* (MRSA) and MEDI4893, a new human immunoglobulin monoclocal antibody targeting *S. aureus* alpha toxin, for the prevention of ventilator-associated pneumonia and surgical site infection.

4. Further research topics under evaluation and planned to start in 2014 and 2015 include the following:
   a) A unique research consortium to develop options for a new sustainable commercial model that will ensure future R&D investment in antibacterial agents leading to new products to combat emerging resistance while supporting the appropriate use of all antibacterial agents, both old and new.
   b) Clinical development of antibiotics for the treatment of serious MDR Gram-negative resistant infections, in particular in areas or Europe with an emerging and endemic carbapenemase resistance problem.
   c) Epidemiology research and development of novel systemic antibacterial molecules against healthcare-associated infections due to Gram-negative pathogens.
   d) Development of novel-inhaled antibiotic regimens in patients with cystic fibrosis and non-cystic fibrosis bronchiectasis.

IMI ND4BB is an expanding programme of collaborative research that can make an important contribution to solving the problems of antibiotic resistance and the lack of treatment options. However this public–private partnership and other European and global undertakings such as the joint programming initiative on antimicrobial resistance (JPIAMR) and the US National Institute of Allergy and Infectious Diseases antibacterial clinical research network, for example, will benefit from increased cross-border co-ordination, harmonization and global integration to deliver sustainable impact against the challenge of antibiotic resistance.

The theme of partnership and collaboration is very relevant also to the need for society to think beyond antibiotics and focus on infection prevention and management and alternative treatment strategies. The sharing of effective hospital level prevention measures with institutions in areas with endemic resistance can help especially if built on a background of improved sanitation, access to clear water and a general improvement in living standards at a community level. Alternative therapies based on vaccination or via immunological modifiers or antibody based products can be an important approach in disease prevention and also as an adjunct to antibiotic therapy for infections due to multidrug resistant serious bacterial infections.

Competing Interests

The author has completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declares no support from any organization for the submitted work, no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years and no other relationships or activities that could appear to have influenced the submitted work.

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