Exploring new business models

Rising to the challenge of antibiotic development

Researching and delivering any new drug to patients is difficult. But the challenges confronting developers of antibiotics are especially daunting because they involve both science and economics. The business models that are required to make and keep new antibiotics on the market are different from those for any other pharmaceutical product. Given the price constraints, it is easy to see why many companies avoid the field. Yet there is an urgent public health need for more enterprises to be involved in antibiotic development and to bring new products to the market.

In this article, we review the current state of antibiotic development with a particular emphasis on evolving business models for these products.

The current state of play

The status of global antibiotic development is monitored by the World Health Organization, the US Centers for Disease Control and Prevention and the Pew Charitable Trusts. Pew publishes a biannual update and interactive database of which the most recent edition was in March 2019[1]. This showed that 42 antibiotics were in development at the time, counting candidate products in Phase 1 through to submission of a new drug application (NDA) with the US Food and Drug Administration.

To put this into context, the Pew database only includes systemically acting antibiotics under development. Topical, ophthalmic and inhaled products as well as drugs targeting mycobacterial infections and non-traditional vaccines, probiotic and antibody candidates are not included. Also excluded are products that are expected to be used as an adjunct to standard of care treatments, rather than as standalone interventions in their own right. A further 30 vaccine, probiotic and antibody candidates are included in a separate Pew trust database covering non-traditional products under development[2].

Since the publication of this database, Phase 3 programmes for Polyphor AG's murepavidin and Dong Wha Pharmaceuticals Co's zabofloxacin have been discontinued. On the other hand, Nabriva Therapeutics Plc's lefamulin has been granted approval by the FDA. This brings the number of systemic antibiotic candidates under development to 39 globally. The number of antibacterial products under development in all formulations and positioning is not collated in a central repository, but this number would be expected to be significantly higher.

In the domain of mycobacterial research, the FDA's approval of Janssen Pharmaceutical's Sirturo (bedaquiline) in August 2019 has added a new combination treatment for multidrug resistant tuberculosis for use with adolescent patients where all other treatments have failed[3].

Diagnostics and devices continue to be recognised as challenging areas to work in, particularly for WHO critical list pathogens[4, 5]. This is despite calls for rapid and accurate diagnostic strategies and technologies.

The explosion of technology in contemporary society continues to generate a groundswell of scientific knowledge and process innovation. This has the potential to improve diagnosis and treatment – in the face of resistance by bacteria to current treatments.

A drive is now evident in the biotechnology and biopharmaceutical industries towards discovering new antibacterial compounds and understanding the mechanisms of action of these compounds. Increasingly, there is recognition that this drive needs to move in the direction of novel rather than me-too compounds[6].

Data-rich scientific strategies and technologies are receiving increasing attention. In this regard, use of molecular strategies such as next-generation sequencing to repurpose old drugs and to predict likely drug responses and resistance potential look set to play an increasingly central role in diagnostics and therapeutics[7]. Use of quorum sensing has been identified as an approach to understand and reduce pathogens' ability to produce virulence[8]. This could play a role in enhancing the impact of existing antibiotics as could other non-traditional approaches such as phage therapy, microbiome manipulation and immunomodulation. Vaccines and rapid point-of-care companion diagnostics for confirmation of bacterial infections, identification of the type of bacteria and description of the bacterial resistance profile are also increasingly receiving attention as ways of minimising the development of antibacterial resistance[9].

Other non-traditional interventions aimed at breaking the cycle of resistance include the use of antibacterial peptides, targeted human antibody therapies and proteome engineering. These technology platforms present promising opportunities to provide tailored, narrow-spectrum bacterial interventions.

Other more established avenues for antibacterial resistance management continue to be adopted and expanded. These include the generation and storage of surveillance data, implementation of antibacterial stewardship practices and better hygiene to prevent the development and transmission of infection.

This multipronged approach to managing antibacterial resistance is good news but only addresses part of the problem. The best and most interesting science will not be able to generate impact or sustainable economic benefit in the absence of a fit-for-purpose business model to make sure that all individuals who are in need of treatment have access to the new products.

Exploring new business models

The unfolding global health crisis in which bacteria are becoming resistant to more and more drugs adds urgency to the need to develop new products, methods and approaches to antibacterial drugs. It is well documented that a mismatch exists between the scientific and regulatory requirements of antibacterial development and the economics of developing and selling these drugs. Maintaining and growing a pipeline of new and effective products while ensuring the commercial health of developers is the subject of much debate – and so far

unresolved.

The current business model for antibiotic development is much like that for other categories of drugs, which is to deliver a financial benefit to a company's shareholders through high prices. But antibiotics are not like other medicines. They cannot command high prices and doctors have been advised to prescribe antibiotics sparingly, in order to avoid the build-up of resistance. This means that stewardship is a priority.

At the same time, public authorities are making efforts to increase supply by developing novel compounds. In recent years, more and more initiatives have been launched to fund research and development. These are called 'push' incentives and include CARB-X (Combating Antibiotic Resistant Bacteria Biopharmaceutical Accelerator), the Innovative Medicines Initiative's ND4BB (New Drugs for Bad Bugs) and DRIVE-AB programmes, the Longitude Prize, the privately-held Novo Holdings A/S's REPAIR fund and US government projects through agencies such as the National Institutes of Health and the Biomedical Advanced Research and Development Authority. The 'push' initiatives have included finance, scientific advice to achieve regulatory milestones, business acceleration facilities and changes in regulatory procedures. Taken together, they have been successful in stimulating discovery of new antibiotic candidates.

In contrast, 'pull' funding initiatives aimed at creating market-based incentives for potential antibiotic developers are less well developed and have achieved significantly less traction. It is here, according to current sentiment, where innovation now needs to take place if inroads are to be made to ensure a sustainable antibacterial pipeline.

To date, a range of potential carrot and stick measures have been proposed. One carrot would be for public authorities to give companies that get regulatory approval for their new antibiotics a market entry reward in the form of an attractive reimbursement[10]. The Public Health Agency of Sweden has proposed, for example, that substantial financial prizes be made available to companies for the achievement of preclinical and Phase 1 milestones[11].

Another initiative has been described as transferable exclusivity extension vouchers[12]. Awarded for successful approval of newly approved antibacterials, this voucher could be sold to a third party to generate immediate revenue or retained as a way of generating deferred revenue through extended protection against generic drugs.

Combinations of these measures have also been suggested. The PAVE Award suggested by the Margolis Center for Health Policy at Duke University, US is a case in point where initial post approval support of a company in the form of a market entry reward would be transitioned into a subscription model with value-based payments over the longer term[13].

A so-called 'play or pay' approach where the cost of antibacterial development is distributed across all companies by charging those that do not actively invest in ways to prevent antibacterial resistance, represents a stick approach. Details as to how this would be applied, who would be targeted, the size of the incentive or disincentive and how the funds generated would be used remain to be seen.

One way ahead is to combine the strengths of different industry partners in broader R&D collaborations to facilitate the development of novel antibiotic classes. An example is Nosopharm SAS's new collaboration with Evotec SE under which the two companies will develop a candidate antibiotic in a class of drugs called Odilhorhabdins. These inhibit the bacterial ribosome and are intended to treat nosocomial infections caused by *Enterobacteriaceae*[14].

This parallels suggestions made by Evotec's chief executive, Werner Lanthaler, of a role for mid-sized biotechnology companies to bridge the gap between small enterprises and large pharma. This could also work as a transition to late-stage development and commercialisation partnerships with large pharma organisations[15].

Together with a realistic and accurate estimation of market potential, organisational mergers have also been proposed as a way of reducing the considerable commercial cost of generating a market for approved products[16].

Another version of the subscription model was recently proposed by the UK government. This would involve paying pharmaceutical companies upfront for access to drugs based on their usefulness to the National Health Service[17]. Concerns have however been voiced as to how this model will increase revenue rather than merely reduce costs[18]. Details of how such a model would work in practice are yet to be released.

Another cost efficient suggestion is to create designated antibiotic R&D non-profit organisations to ensure the sustainability of funding as new drug candidates progress into more costly stages of development[19]. These organisations would use a combination of non-dilutive funding to cover the costs of research and early development and market-related rewards and partnerships for later stage deals. The circular reinvestment of revenues generated in this way would go into ongoing research at these organisations.

Innovative Medicines Initiative

The EU Innovative Medicines Initiative's DRIVE-AB project has also proposed long-term grant funding as a basis for early research. But it has recommended that commitments to and mechanisms for, coordinated research and long-term antibiotic supply be adopted as well[20].

Brad Spellberg of the University of Southern California, US, further suggests that the role of infectious disease societies could be expanded to include the production and distribution of guidelines and educational materials around new medications as a way of reducing marketing costs and encouraging increased clinician and payer uptake of newly developed medications[21].

From technical and regulatory perspectives, changes that might be made include the use of adaptive designs for clinical trials which enrol small patient populations. Developers would then use real-world evidence to generate data to demonstrate the value of the treatment for reimbursement purposes.

In the US, two Senators have introduced a bill to the Senate aimed at incentivising antibiotic R&D. Called Developing an Innovative Strategy for Antimicrobial Resistant Microorganisms (DISARM), the act would increase the reimbursement that Medicare pays for antibiotics used by the elderly. The Act would also promote the appropriate use of antibiotics[22]. The Infectious Diseases Society of America provided guidance that informed the proposed legislation.

The concept of value and how this is interpreted and quantified is becoming increasingly central to the process of novel antibiotic and antibacterial development. This is feeding into discussions both in North America and Europe

about value-based healthcare, which is essentially matching payments for drugs with the outcomes that they achieve for patients. While value-based healthcare is discussed more frequently, its application is still patchy[23]. Successful adoption by some Swedish regional authorities of payment on the basis of achieving specified outcomes within a value-based healthcare context has been reported[24], as it has in some US situations[25]. The feasibility of using this framework with antibiotics has yet to be demonstrated in the absence of a universally accepted definition of antibacterial value.

Throughout these discussions, there is an awareness that intellectual property (IP) is an issue. How IP is handled is crucial in view of its role as a primary revenue generator for biotechnology companies. Towards this end, the potential for non IP-based legal innovations is a fertile area for investigation.

Looking to the future

Antimicrobial resistance, taking into account infections from bacteria and other microbes, is a complex and emotive topic.

There is much innovative science being carried out which targets the unmet medical need. This science will not be translated into tangible products that have an impact on patients' lives without proportionate and appropriate regulation, and a robust and sustainable business model. Challenges in accomplishing these aims require strategies to address complex problems.

Fundraising models for early stages of R&D are currently more plentiful and straightforward than those for later stages where a mix of solutions may be required. This is no small challenge and may well require a system-wide overhaul of disease targets and strategies if we are to avoid a swing back into the abyss. The upside is that we still have an opportunity to make a difference should we choose to do so, for the benefit of current and future generations.

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This article was written by Heather Graz, commercial development manager, at Neem Biotech Ltd in the UK.

