Back to Health

Antibiotics development has faced tough times over the last few decades – from neglect by Big Pharma, to the growth of resistant infections leading to a mounting public health crisis. But smaller biotechs and regulatory moves are now fuelling an R&D renaissance in this area

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Developing new antibiotics is daunting. A variety of highly virulent and adaptable pathogens, multiple sites of infection and dynamic pharmacokinetic (PK) issues make it a scientific and logistical challenge to deliver agents in sufficient concentrations to kill bacteria and prevent resistance without causing toxicity.

Layered on these complexities is strict regulatory oversight that seeks to ensure public health through the approval of safe and effective therapies to treat these infections.

HAP/VAP Indication

The challenges facing antibiotic development are well-illustrated by examining the clinical indications for hospital-acquired pneumonia (HAP) and ventilator associated pneumonia (VAP). While considerable effort has been made to reduce the incidence of these diseases, VAP still affects 10-20 per cent of intensive care unit (ICU) patients in the US, while nearly 90 per cent of HAP cases in the ICU occur in ventilated patients (1-3).

As such, endotracheal intubation remains a key risk factor for pneumonia, by colonising respiratory tract with bacterial pathogens. Additional risk factors for VAP include comorbid conditions such as diabetes and malignancy, severity of underlying illness, organ failure, increasing age and prior surgery.

Even with appropriate empiric antibiotic treatment, VAP is associated with mortality rates upwards of 50 per cent, longer ICU and hospital stays, and hospitalisation costs that are increased by between $10,000 and $40,000 per patient (4-6).

Traditional Approach

Given the severity and high mortality rate of patients with HAP/VAP, placebo-controlled superiority trials face insurmountable ethical concerns. Thus, the traditional approach to clinical development of antibiotics for HAP/VAP has been randomised, double-blind, comparator-controlled equivalence studies, with the primary endpoint being clinical response after completion of therapy.

In the past, such studies were very complex, and further complicated by a wide range of dynamic and sometimes competing variables. These included multiple Gram-positive and Gram-negative pathogens with numerous resistance mechanisms; the need for combination antibiotic therapy; and differences in standards of care within participating ICUs. Trials were slow to recruit and costly, but sponsors still pursued this indication for its defining power of a potential blockbuster antibiotic.

Non-Inferiority Analyses

Over time, regulatory authorities required sponsors to use non-inferiority (NI) analyses instead of equivalence. Since there was no standardisation of the NI margin, sponsors often defaulted to using a margin of -20 per cent in the lower bound of the 95 per cent confidence interval of the difference without formal justification.

The US Food and Drug Administration (FDA), worrying about "NI creep", began demanding narrower margins and more rigorous justification of the selected margin, as well as the primary endpoint used to determine NI. It also demanded more PK and pharmacodynamic (PD) analyses, target attainment analysis, specific tissue-level PK and restricted prior antibiotic use before enrolment in pivotal trials – an issue that is still hotly debated. A period of several years of discussion and regulatory uncertainty subsequently ensued.

R&D Drought

During this period, there were drugs that failed to gain approval, despite large and expensive global clinical studies. Theravance failed to get HAP/VAP approval for telavancin after completing two large global Phase 3 studies using a pre-specified NI margin on clinical response at TOC.

Toward the end of the studies, the FDA started shifting to all-cause mortality as the primary endpoint. Unfortunately, Theravance failed to achieve a -10 per cent margin on all-cause mortality in one of the studies, even though the combined analysis did achieve the margin. There were other casualties as well, such as oritavacin and iclaprim for acute bacterial skin and skin structure infections (ABSSSI), ceftobiprole for community-acquired bacterial pneumonia (CABP), and feropenem for multiple indications.

Given the complexity of antibiotic development, moderate returns and regulatory uncertainties, many large pharmaceutical companies abandoned their antibiotic discovery and R&D programmes to focus on other more lucrative markets. This exodus from antibiotic development was compounded by the many mergers and acquisitions that have occurred over the past three decades (see Table 1). Most of the legacy companies had antibiotic programmes that were essentially eliminated after consolidation.

Table 1: Mergers and acquisitions that contributed to an exodus in antibiotic development

Contemporary companies	Legacy companies
Pfizer	Warner-Lambert, Parke-Davis, Pharmacia, UpJohn, Searle, Wyeth, Lederle, Praxis, Parkedale Pharmaceuticals, King Pharmaceuticals
GlaxoSmithKline	Smith-Kline, Beechem, Glaxo, Beckman, Burroughs, Wellcome
AstraZeneca	Astra AB, Zeneca Group, Novexel, MedImmune, KuDos, Amylin, Spirogen
Sanofi	Rhone Poulenc, Hoeschst AG, Marion Merrell Dow, Roussel, Sythelabo, Pasteur, Aventis, Dermik Laboratories
Merck	Sharp & Dohme Inc, Frosst Ltd, Schering AG, Plough Inc
Novartis	Ciba, Geigy, Sandoz
Johnson & Johnson	Ortho, McNeil Laboratories, Janssen Pharmaceuticals, Peninsula Pharmaceuticals, Cilag, DePuy, Ethicon, Tibotec

Antibiotic Resistance Crisis

Meanwhile, the bacteria causing life-threatening infections have continued to become resistant to antibiotics and, in some cases, multi-drug resistant (MDR) and extremely drug resistant.

Of particular importance are a group of pathogens known as the ESKAPE pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumanii*, *Pseudomonas aeruginosa* and *Enterobacter* species) that cause most of the infections in hospitals and have evolved to 'escape' the actions of available antibiotics.

ESKAPE pathogens are the most important contributors to the antibiotic resistance crisis in the US, European Union and other countries. The latest actors on this stage are members of the Enterobacteriaceae family, with some now resistant to nearly all antibiotics. These are the new 'super bugs' prompting the declaration of a public health crisis by the media, academic circles and government agencies.

Unfortunately, these are not one-off occurrences. In fact, there are now reports from the US that carbapenem-resistant enterobacteriaceae cause more than 17 per cent of central line-associated bloodstream infections and catheter-associated urinary tract infections in long-term care hospitals and larger hospitals. The new generation of resistant infections has become almost impossible to treat.

Government Relief

This public health crisis has not gone unnoticed by US government officials. Congress was spurred into action with the passing of one key piece of legislation – the Generating Antibiotic Incentives Now (GAIN) Act – and two pending pieces of legislation: the Strategies to Address Antimicrobial Resistance (STAAR) Act and the Preservation of Antibiotics for Medical Treatment (PAMT) Act.

The GAIN Act calls for a five-year extension on the exclusivity period for qualified infectious disease products, priority review and fast-track designation. The STAAR Act contains measures to re-authorise the inter-agency Antimicrobial Resistance Task Force, building upon existing research efforts by the National Institutes of Health (NIH) and the Centers for Disease Control and Prevention, and developing and testing quality measures on antimicrobial use. The PAMT Act requires the FDA to re-review seven classes of antibiotic approvals for animal feed uses that are also important to human medicine. Approvals would be cancelled for any found to be unsafe due to resistance.

Regulator Moves

The FDA has released several new guidance documents for HAP/VAP, ABSSSI, CABP, complicated intra-abdominal infections, and complicated urinary tract infections. For HAP/VAP, in search of an efficacy anchor, exhaustive literature searches have been undertaken to find either placebo-controlled studies or natural endpoints from the pre-antibiotic era.

Based on historical evidence, an all-cause mortality clinical endpoint for HAP/VAP was justified with an NI margin of -10 per cent. Although still challenging, this helped to remove some of the regulatory uncertainty by providing clearer and better defined objectives.

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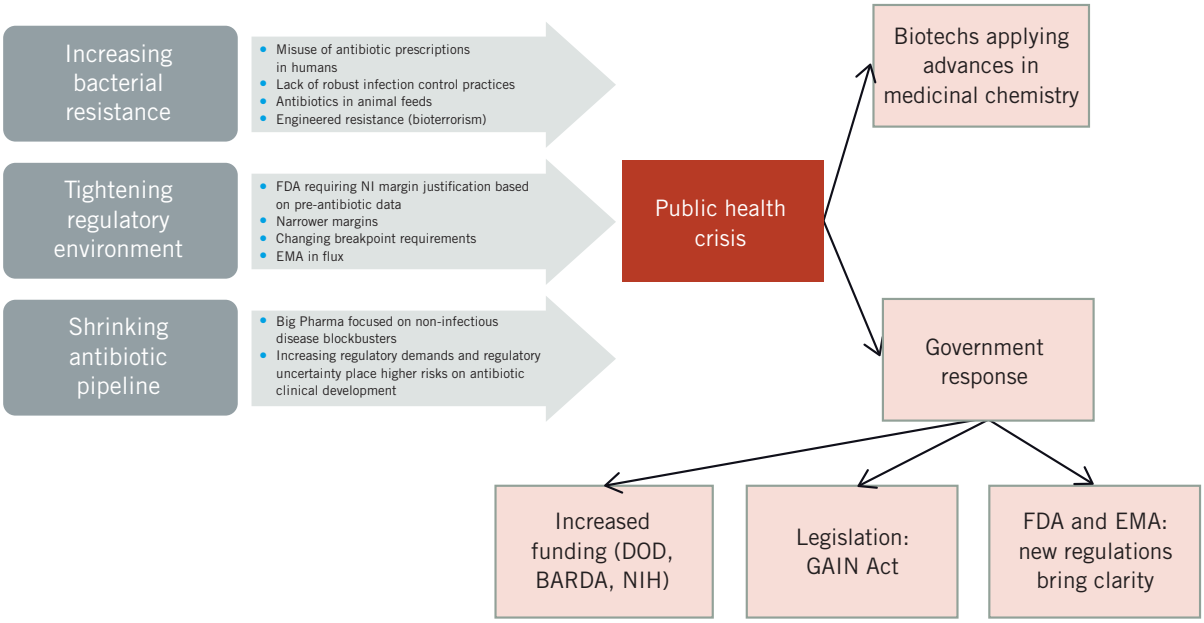
Figure 1: From crisis to opportunity



In addition, the FDA has issued new guidance on antibiotic therapies for patients with an unmet medical need for treatment of serious bacterial diseases, including resistant pathogens. Displaying a more open attitude towards discussion of novel trial designs with sponsors, the FDA has developed more realistic policies about prior treatment with antibiotics and NI margins.

There has also been a willingness to consider externally or historically controlled studies and to enhance the role of PK/PD as tools to shorten timelines when bringing new antibiotics to market. Finally, the FDA has suggested that safety databases as small as 300 patients might be acceptable in the context of unmet needs.

Concurrently, the European Medicines Agency (EMA) has issued guidance on bacterial infections that provides the most clarity for development in challenging indications. The EMA expects approvals for drugs to treat MDR organisms, based on trials in indications like HAP/VAP that "are not expected to enrol sufficient numbers of patients infected with multi-resistant organisms to allow for an assessment of efficacy". Clinical efficacy could be "based only on well-documented cases collected from a prospective non-randomised study that enrols patients regardless of the site of the infection".

Biotechs and Financing

While many large pharma companies have pulled out of the space, smaller biotech firms are filling the void. Contemporary medicinal chemistry programmes are now revitalising older and existing antibiotic classes, as well as advancing completely novel targets. This is being fuelled by non-dilutive sources of financing, particularly in late-stage development.

The Biomedical Advanced Research and Development Authority (BARDA), under the US Department of Health and Human Services, is one of the primary sources of non-dilutive financing. With $1.7 billion allocated from Congress, BARDA has now funded several biotech companies – including Cempra, Basilea, Achaogen and Tetraphase – allowing them to advance into late-stage development, with grants ranging from $17 million to over $100 million.

Significant Surge

As well as these smaller biotechs, BARDA has granted GlaxoSmithKline up to $200 million to help develop a portfolio of antibiotics. Other government sources of non-dilutive funding that are helping to fuel this renaissance of antibiotic drug development include Department of Defense (DOD) agencies such as the Chemical and Biological Defense Program; the Defense Threat Reduction Agency; the Defense Advanced Research Programs Agency; and the National Institutes of Allergy and Infectious Diseases. Under these programmes, several biotech companies have received tens of millions of dollars for preclinical and early-phase clinical development of antibiotics.

In addition, some private foundations, such as the Wellcome Trust in the UK, have funded antibiotic development programmes focused on unmet medical needs through grants or convertible loans. Despite timeline adjustments and oversight requirements, these sources of funds are attractive and highly sought after by investors and senior management of biotech companies.

With increased sources of funding, easing in government regulation, and an unprecedented unmet medical need

and public health crisis, there has been a significant surge in the number of antibiotics in development. There are now some two dozen antibiotic compounds in various stages of development, several of which will be seeking approval in the next couple of years and will target some of the worst MDR Gram-negative pathogens.

While much more is needed to address the rise in resistant bacterial pathogens, there is a sense of renewed hope and opportunity in antibiotic clinical development.

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