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Regulatory opportunities to encourage technology solutions to antibacterial drug resistance

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Regulatory agencies play a critical role in the licensing of new antimicrobial agents. To address the pivotal role played by regulatory agencies, particularly in the context of a paucity of new drugs active against bacteria resistant to currently available drugs, the BSAC formed the 'Urgent Need' Working Party to address the regeneration of antibacterial drug discovery and development. The Working Party identified a number of issues, including: increased application of pharmacokinetic/pharmacodynamic principles to expedite drug development; the need to prioritize licensing of drugs (including 'orphan' drugs) active in life-threatening infections; and expansion of the use of surrogate markers and rapid point of care diagnostics to facilitate drug development.

Keywords: antibiotics, antibiotic resistance, diagnostics, drug licensing, clinical trials

Introduction

Licensing is a pre-requisite to the granting of market authorization for all medicines. Hence the central role of regulatory and licensing agencies in determining whether or not new and previously approved agents can be used in the treatment or prevention of human disease. They are the interface between industry (the providers of medicinal products) and healthcare organizations (the purchasers of medicinal products). The multitude of regulatory agencies worldwide has inevitably made the process of international licensing bureaucratic, costly and uneven in the demands placed on industry. Agencies such as the European Medicines Agency (EMA) and US FDA assume greater importance as a result of the size of the markets they guard. Hence it is unsurprising that drug development is firmly steered in the direction dictated by these agencies, in particular the FDA.

Barriers to innovation

Drug development and therapeutics are, by their nature, experimental. New science, new compounds and new applications require a framework for licensing that is adaptive and supportive, while minimizing the risk of harm to the public by ensuring that medicines are not only effective and of an acceptable quality but also safe. This fine balance between supporting the public health agenda through the licensing of innovative medicines and safeguarding the public from harm is inevitably a constant tension. In the case of antibacterial drugs, this tension is now viewed as an obstacle to innovation. Criticisms of regulatory agencies, largely by industry, include: ever-increasing stringency in the licensing requirements; a licensing process that is bureaucratic, costly and slow and is also inconsistent in its requirements consequent upon the lack of international harmonization (notably between the FDA and EMA).[1,2] All these factors contribute to uncertainty and the risk of failure in a lengthy and expensive development process.

Clinical need for new antibiotics

From a clinical perspective, the slow trickle of newly licensed agents over the past decade, at a time when major increases in drug-resistant pathogens are being reported worldwide, is of particular concern.[3,4] Licensed indications for recently marketed agents have largely addressed only a limited number of indications, notably community-acquired pneumonia (CAP) and complicated skin and skin structure infections (cSSSIs), for which there is already a surfeit of agents to choose from. In contrast, few agents targeting drug-resistant Gram-negative bacillary pathogens have been developed.[4] This has resulted in a serious mismatch between what is needed and what is being licensed and in part reflects the way in which current approaches to drug development and the licensing process have skewed the direction of drug development. Indications such as CAP and cSSSIs have been particularly common choices in recently licensed drugs, and reflect a clearly defined pathway for drug development and approval.

Cost issues in drug development

The bulk of the costs of drug development are incurred during the Phase III clinical trial programme. It is here that major changes in regulatory requirements have had their most significant impact, notably in the design of the randomized controlled trial (RCT). Until recently, the accepted design was one that demonstrated non-inferiority between test and control agents. Now placebo-controlled or superiority studies are promoted for indications such as upper respiratory tract infection and acute bacterial exacerbations of chronic bronchitis, largely driven by concerns that many infections are either self-limiting or viral in nature.[5] The power of such studies and the numbers of patients required to reduce the delta to much lower rates has compounded the issue. However scientifically desirable this may be, it is currently decreasingly achievable economically because of the prohibitive costs of such studies, even though it can be argued that it is to industry's advantage to demonstrate superiority, rather than the current situation where new agents are often simply shown to be non-inferior to cheaper generic agents.

The Urgent Need initiative

The pivotal role of drug licensing and regulation led the BSAC Working Party on 'The Urgent Need: Regenerating Antibacterial Drug Discovery and Development'[6] to take evidence from leaders in industry, academia and regulatory agencies to identify current obstacles and potential new approaches that might facilitate new drug development, without compromising patient safety. The key points identified included: expanding the application of pharmacokinetic and pharmacodynamic (PK/PD) science to facilitate and expedite drug development; the need to give priority licensing to drugs active in life-threatening infections, especially those caused by multidrug-resistant pathogens; expansion of the concept of 'orphan drug' approval for the treatment of life-threatening infections such as ventilator-associated pneumonia resulting from pathogens such as *Pseudomonas aeruginosa*; promoting a process that might grant 'conditional approval'; and expansion of the use of surrogate markers and rapid point-of-care diagnostics to facilitate drug development and use.

Advances in PK/PD science when applied to new drugs have had a major impact on therapeutics and drug development.[7] Although PK/PD studies were initially adopted to define dosage regimens for specific indications and drug exposure profiles to target pathogens, they are now increasingly used for predicting therapeutic outcomes and for strategies to minimize the emergence of drug resistance during treatment. The opportunity to further expand the application of PK/PD to defining the duration of treatment raises important questions as to whether such modelling could reduce the number of clinical studies required to demonstrate efficacy.[3] Closer collaboration between academia and regulatory authorities is recommended to explore this opportunity.

Linking such PK/PD studies to a more limited Phase III programme might permit 'conditional approval' of new drugs for specific indications subject to a robust pharmacovigilance programme post-approval. This in turn could provide reassurance of efficacy while also addressing the need to develop a full safety profile. Provided no significant adverse experiences were identified, conditional approval could, in turn, lead to full market authorization. A further expansion of the application of PK/PD might also lead to the acceptance of a single study for a specific indication, a concept to which regulators appear sympathetic.[8]

Other proposals included a rolling programme of approval by indications which might initially be targeted at non-life-threatening infections and subsequently extended to include more serious illnesses. The possibility of extrapolating approval to indications that share a common population of pathogens and drug distribution characteristics was also felt worthy of consideration; for example, intra-abdominal sepsis and gynaecological sepsis or acute otitis media and acute bacterial sinusitis.[3,8] Other proposals related to rare or uncommon pathogens which, by their nature, are difficult to study. Pooling data for such infections and comparing outcome with that of major indication RCTs might be possible, especially if there is consistency of response between these study populations.

There has been much interest in the role of surrogate markers and rapid point of care diagnostics in relation to defining disease, its severity and its response to therapeutic intervention.[9] Candidate markers, such as C-reactive protein and procalcitonin, have their advocates.[10,11] The era of rapid diagnostics in bacterial diseases is slowly emerging as an everyday reality. Nonetheless, the benefits of rapid diagnostics in clinical medicine have been well rehearsed.[9] Could these benefits also be applied to antibacterial drug development? The potential advantages would include: precision in case definition; a reduction in the number of unevaluable patients or infections; the enrichment of studies that target drug-resistant infections; and finally a means that may more accurately define the microbiological endpoint and clinical value and positioning of the new agent. All in all, these approaches could reduce the target number of patients required for clinical trials, thereby containing the costs of drug development.

However, there are likely to be some obstacles to this approach. Novel diagnostics would need to be developed and evaluated and their performance approved, often by the same regulatory agencies involved in drug licensing, thus adding another potentially bureaucratic hurdle to drug approval. A more immediate concern is the current largely separate commercial activities of the pharmaceutical and diagnostics industries, which would need to be synchronized more efficiently to meet the time lines of drug development.

In conclusion, many ideas, some fresh, some well-rehearsed by others, were proposed by the Working Party. All are worthy of consideration and some of active exploration, adoption and evaluation as part of a new model for antibacterial drug development. In an age when drug innovation is at a nadir and bacterial drug resistance is reaching new heights, inaction is not an option.

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Members of the Working Party

The BSAC Working Party comprised Professor Richard Wise (Chair), Dr Richard Bax (Transcrip Partners LLP, UK), Dr Frances Burke (Eli Lilly, UK), Professor Ian Chopra (University of Leeds), Dr Lloyd Czaplewski (Biota Europe Ltd, UK), Professor Roger Finch (Molecular Medical Sciences, University of Nottingham and Nottingham University Hospitals NHS Trust, Nottingham, UK), Dr David Livermore (Director, Antibiotic Resistance Monitoring and Reference Laboratory, Health Protection Agency Centre for Infections, London UK), Professor Laura J. V. Piddock (President, BSAC; University of Birmingham, UK) and Tony White (BSAC Council member).

Transparency declarations

R. F. has provided consultative advice Destiny Pharma, GlaxoSmithKline, Menarini Recherche and Novartis. R. B. is currently a senior partner at Transcrip partners LLP and works with several large and small pharmaceutical companies in the area of antibiotic development. He is also a non-executive director of Helperby therapeutics Ltd. F. B. is an employee of Eli Lilly and Company Ltd. I. C. is a member of the Scientific Advisory Board of Destiny Pharma Ltd, and has recently received research funding from Cubist, Destiny, Galapagos, Leo, Pfizer, Novartis and Novacta. D. L. has received conference, speaking and research support from numerous pharmaceutical companies. He holds shares in AstraZeneca, Merck, Pfizer, Dechra, and GlaxoSmithKline, and, as executor, manages further holdings in GlaxoSmithKline and Eco Animal Health. He is an employee of the UK HPA and is a UK taxpayer. T. W. is an independent consultant, a retired employee and shareholder of GlaxoSmithKline, and in the past 5 years has received financial remuneration for consultancy or presentations from GSK, and Chiron/Novartis. The remaining Members of the Working Party have none to declare.

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