Moving goalposts—regulatory oversight of antibacterial drugs

Randall Brenner, Evelyn J Ellis-Grosse & Roger Echols

Is uncertainty concerning the regulation of antimicrobial drug trials stifling investment in infectious disease treatments? Here, experts from a large pharma company and a biotech firm provide their perspectives.

The US Food and Drug Administration (FDA) has recently rejected new antibiotics for common infections citing the requirement that the drugs intended to treat non-serious infections prove superior to placebo rather than active controls. With the introduction of more stringent statistical criteria, inconsistencies in bacterial-susceptibility testing and renewed debate over placebo-controlled testing in antibiotic trials, how much is the regulatory regime deterring investment in the sector?

The pharma company view

Randall Brenner & Evelyn J Ellis-Grosse

Industry and other special advocacy groups have been vocal about the need for regulatory reform to provide incentives for the industry to continue to develop antimicrobial compounds. Suggestions discussed between the Pharmaceutical Manufacturers Association of America (PhRMA; Washington, DC), the Infectious Diseases Society of America (IDSA; Alexandria, VA, USA) and the US Food and Drug Administration (FDA) include more creative approaches to 'market exclusivity', clinical trials focusing on a 'low quantity, high quality' approach and clearer development guidelines. The FDA has worked to provide some reform, such as the Critical Path initiatives designed to streamline clinical research and minimize the number of patients enrolled in clinical trials. In addition, avenues to provide better industry-FDA collaboration during development have also been introduced. But the effect of these initiatives has yet to result in renewed industry commitments.

Randall Brenner is at Wyeth Pharmaceuticals, 500 Arcolo Road, Collegeville, Pennsylvania 19426, USA, and Evelyn J. Ellis-Grosse (formerly of Wyeth) is at e2g Biopharmaceutical Counseling, 994 Skelp Level Road, Downingtown, Pennsylvania, 19335 USA. Wyeth is a co-sponsor of this focus. e-mail: brenner1@wyeth.com or evelyn@e2gconsulting.com

The health and drug industry context

The increasing prevalence of antimicrobial-resistant organisms has led to a public health crisis[1–4]. The World Health Organization (Geneva), various regulatory agencies and many infectious disease experts have drawn attention to this crisis and the unmet medical need that has arisen[5,6]. In a 2003 report from the Institute of Medicine (Washington, DC) entitled "Microbial Threats to Health," antimicrobial resistance was considered the paramount threat of the 21st century[7]. Similarly, in its July 2004 policy report, "Bad Bugs, No Drugs: As Antibiotic R&D Stagnates, a Public Health Crisis Brews," the IDSA proposed legislative and other federal solutions to this emerging public health problem[8]. The proposal offered specific potential legislative solutions and administrative recommendations, such as the formation of an independent expert commission to study and stimulate anti-infective R&D efforts, the use of supplemental intellectual property protections and other potential statutory incentives.

A recent follow-up review by the Antimicrobial Availability Taskforce (AATF) of IDSA has highlighted the urgent need for newer agents. This article identifies numerous high priority organisms as targets for which antimicrobial development is needed[9]. The resistant organisms that have been identified are primarily from the hospital setting. Even so, increasing resistance has also been observed in patients in the community with little or no previous healthcare contact. Such resistant bacterial organisms include methicillin-resistant *Staphylococcus aureus* (MRSA), both virulent and invasive types, vancomycin-resistant *Enterococcus* spp. (VRE), extended spectrum β-lactamase (ESBL)-producing *Escherichia coli* and *Klebsiella* spp., *Pseudomonas aeruginosa* and multidrug resistant *Acinetobacter* spp.

The continued emergence of these resistant organisms complicates already serious infectious disease problems and presents significant global treatment challenges. Therapeutic options to combat these resistant pathogens continue to decline. Currently available antibiotics are often of limited use because of bacterial resistance to these agents, a limited spectrum of activity (e.g., efficacy against either Gram-positive or Gram-negative organisms alone) and associated safety concerns. Thus, the need for new antimicrobial products, particularly those with novel mechanisms of action, continues to grow.

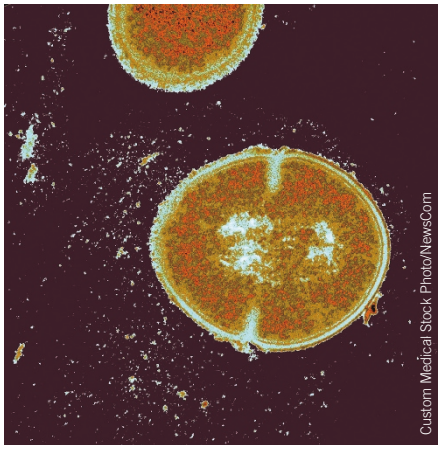
At the same time, research and development in antibiotics has declined dramatically since early 2000 (refs. 10,11). Spellberg *et al.*[10] report that FDA approvals of new antibacterial agents decreased by 56% between 1998 and 2002 as compared to the period from 1983 to 1987. A study completed in 2004 (ref. 11) notes that of the world's 15 largest pharmaceutical companies and 7 largest biotech firms, only 7 new antimicrobial products were in development.

The decline in development of antimicrobials, specifically by the larger pharmaceutical firms, can be attributed to many factors, including costs associated with antibiotic development, clinical trial challenges, limited market share potential compared with other treatment populations (antibiotic treatment durations are shorter than those of chronic treatment or lifestyle products), the shortened product-life due to likely development of resistance, expert recommendations to preserve antibiotics and the restrictions of use placed upon new antibiotics entering the therapeutic armamentarium. The changing/evolving global regulatory environment has also played a role in this decline.

The antibiotic regulatory environment

The major regulatory agencies recognize the growing need for new antibiotic agents, but few changes have been made to improve the regulatory regime and foster development in this area. Global regulatory agencies, such as the FDA, the European Medicines Agency (EMEA)/Committee for Medicinal Products for Human Use (CHMP) and the Japan Pharmaceutical and Medical Devices Agency (PMDA; Tokyo), continue to update their respective guidelines focusing on antibiotic development[12–14]. Changes in these guidelines, for example, provide for shortened development times for narrow or niche indications. But for general development, these guidelines have the reverse effect; they result in more stringent requirements on safety and efficacy, which need to be enforced to develop products with broad indications that are commercially viable.

The United States. The FDA first introduced an antibiotic-specific guideline to the public in 1977 (ref. 15). This guideline covered both general development issues and indication-specific clinical trial details. The information was further updated in 1992 when the FDA issued the "Points to Consider, Clinical Development and Labeling of Anti-Infective Drug Products"[16]. This document gave both agency reviewers and industry an understanding of the minimal requirements necessary for the clinical development of routine antimicrobial products. In 1998, the FDA issued draft guidelines dealing with both general considerations and indication-specific guidelines. It was this 1992 document along with the 1998 draft guidelines that guided development for these agents until early 2000.



Trial design for testing antibiotics that target drug-resistant bacteria (such as antibiotic-resistant *Enterococcus* sp. pictured here ×30,000) is an ongoing problem for drug sponsors and regulators.

As early as November 2002, the FDA indicated publicly that it would try to facilitate antimicrobial development through a series of new guidance documents[17]. These documents would provide specific guidance for targeted development of agents to treat small or niche populations, such as those with resistant organisms or bacteremia. These documents have yet to be issued, however.

Europe. In the 1990s, antimicrobials-specific European guidelines were developed with the expansion of the EMEA/CHMP and the growing popularity of the centralized approval process. The centralized approval process has helped harmonize drug requirements within the European Union (EU) and its current 25 member states. The process has also provided an opportunity for earlier pan-EU feedback on development programs. This, however, has not removed the specific uncertainties that exist within infectious disease research.

For example, there is complexity with clinical trial conduct and the differences (real or perceived) within an individual country's standard of clinical care. Challenges also exist regarding regulatory and clinical acceptance of comparator selection used in the pivotal trials, differences in resistance patterns and the need for specific types of new agents, as well as differing regulatory approaches with regard to benefit/risk and unmet medical needs. The centralized EU guidelines are general guidelines and are not specific to any indication.

The "Note for Guidance: Evaluation of Medicinal Products Indicated for the Treatment of Bacterial Infections" was initially developed in Europe in 1997 and subsequently updated in October 2004 (ref. 13). Significant changes in the 2004 version of the guidelines include considerations for approaches to develop new therapies for the treatment of niche populations, such as difficult-to-treat or resistant pathogens. Although the guidance does provide specific information on how to register a product with limited data, these narrow indications do not provide the return on investment or other benefits required to support big pharma investment, thus adding additional roadblocks to antimicrobial research.

Latin America and Asia. Difficulty with clinical trial recruitment owing to a variety of issues[18], including patient unwillingness to participate, time and significant cost in the United States and western EU countries, pose additional challenges that require clinical development to be truly global. In this context, clinical trials have migrated to such regions as India, China, Japan, Latin America, Africa and other Asian counties. Although these regions have differing standards of care and are still developing an adequate infrastructure for supporting clinical trials, patient interest is high because local state-funded healthcare is limited. With new countries coming into the clinical-trial, drug-development arena, regulatory requirements for drug registration within these countries are evolving[19].

However, these challenges can be used as an advantage when added to a regulatory submission strategy. Many regions typically require country-specific or local information, including safety, efficacy, susceptibility data and pharmacokinetic factors. As such, expanding country selection and enrolling patients from these regions can accomplish several tasks for a drug's registration, including the following: first, local safety, efficacy and pharmacokinetic data; second, local susceptibility data on clinical isolates obtained from the regions; and third, expanded recruitment of patients that could result in shorter trial time lines.

For most countries within Latin America and Asia, antibiotic drug approvals can be obtained using data generated from the global clinical database. If the countries participated in the trial (even with limited enrollment), a subanalysis of local information (regional patient experience) may also be requested. Even so, some countries provide very specific guidelines on the development of antimicrobial agents, and these must be taken into consideration early in a program to minimize duplication of the clinical trial work

required to support regulatory submissions and approvals.

Japan is another region that has become very important in drug development, especially antimicrobials, because of its large patient population and its potential market share. Japan has developed a guideline for antimicrobial product development. This guideline provides very specific information regarding the types of studies, indications and local data that are required for approval in Japan[14].

In addition, the International Conference on Harmonization (ICH), a consortium of global regulatory agencies working to provide global drug development guidance, provides very specific guidance with respect to the requirement to support products that do not demonstrate differences (safety, efficacy and pharmacokinetics) in ethnicity[20]. Although most antibiotic agents show no discernible difference among ethnicities, Japan has historically required local data to support product approvals.

Challenges associated with regulation

Guideline changes that occurred in early 2000 in the United States and the EU have had a profound impact on the pharmaceutical industry's incentives to invest in research and development in this area. The changes related to the evidence needed to differentiate a new antibiotic from existing treatments (the delta issue or noninferiority trials) and the need for multiple pivotal trials to support an application (registration). More recently, the ways in which regulatory agencies determine breakpoints (data related to an antibiotic's effect and its correlation with clinical efficacy) have also become a concern.

The delta issue. The most striking issue in the changing landscape is what has become known as 'the delta issue'. Instead of a placebo comparison, clinical trials for antibiotics intended to treat serious infections require the use of an active control (an already approved agent) to ensure that enrolled patients are receiving viable therapy[21]. To have a successful outcome, trials are required to demonstrate that the investigational therapy is no worse than the control agents. These types of studies are known as 'noninferiority trials'[22,23].

Specific statistical criteria are applied to these studies to determine the numbers of patients that need to be enrolled to demonstrate that the products are noninferior. Factors influencing this are expected cure rates, the risk the company is willing to take regarding a false negative (power), expected differences in cure rates between the investigational drug and the control therapy and the difference allowed in the lower end of the confidence interval to demonstrate noninferiority. The delta issue has been highlighted by industry and supporting organizations to be of particular importance because it has a direct impact on the number of patients enrolled in a clinical trial, thus contributing to cost and time.

The FDA's 1992 "Points to Consider" guidance[16] provided a sliding scale for antibiotic trials based on the expected cure rates of the infection type being studied. Ultimately, this implied that the more difficult-to-treat infections, such as the current resistant pathogens and those that will inevitably emerge, for which one would expect lower cure rates, would require fewer patients and have greater margins to demonstrate noninferiority. Historically, studies for these types of infections would require a 15% delta (lower end of the confidence interval ≥ -15). In early 2000, both the US and EU agencies changed this requirement to a more stringent 10% delta. Although this may seem like a small change, from a clinical trial perspective, this can significantly increase the requirements for study size and patient recruitment, resulting in substantial increases in the costs and time associated with completion of the clinical phase of development[24].

It should be noted that agency expectations on the delta were imposed on industry with the ultimate goal of protecting public health by providing further assurance of a drug's potential impact. What could not be anticipated was the impact (or perceived impact) that this change has had on corporate investment into the antibiotic sector of development[8]. The FDA has since stated that there is no single approach to noninferiority margins for drugs, and it has allowed sponsors the opportunity to discuss this in the context of the complete data package. This approach, though collaborative, provides additional uncertainty about drug approval standards.

Registration. The Food, Drug and Cosmetic Act, the US law by which the FDA regulates drugs in the United States, calls for "adequate and well-controlled clinical trials" to support approval of a product for a specific indication[25]. In traditional drug development terms, this language translates into at least two 'pivotal' trials to support registration. The purpose of these two clinical trials is to have one trial confirm the results of the other, thereby reducing the probability of outcomes associated with false positives.

As antibiotics are used to treat various types of infections, the registration process requires the threshold of 'studies' to generally be applied to each of the pursued indications. As such, a product requesting registration for three different indications may have to go through six separate pivotal trials to support the registration. Although this burden of proof is the same for other disease states, the requirements to secure multiple indications for an anti-infective are critical to retain a scientific advantage, expand the potential patient populations and thus expanded sectors of use in the market.

Infectious disease research differs from research for other disease states in that product development focuses more directly on affecting the organism within the host. Resistance to an antibiotic typically develops during the product's life cycle and is rarely observed during clinical trials. In addition, there is little or no well-controlled clinical data on resistant organisms of public health concern that are available during registration. As such, infectious disease is a therapeutic area that could benefit from the use of additional research tools, such as pharmacokinetic/pharmacodynamic (PK/PD) modeling.

The FDA and EMEA, as well as other agencies and leading experts, have noted the value of PK/PD modeling and simulation in drug development and in the regulatory review process[13,26]. In April 2004, a workshop cosponsored by the FDA recognized the utility of PK/PD modeling in facilitating dose selection and quantitatively predicting microbiologic outcomes in antimicrobial drug development. Even so, it was also noted that PK/PD relationships derived from nonclinical studies should be validated in well-controlled clinical trials[27]. The utility of PK/PD modeling in antimicrobial drug development is promising, but its acceptance by regulatory agencies in lieu of larger clinical trials remains to be seen[28,29].

Susceptibility testing criteria. The most recent challenge emerging in the regulatory environment is antimicrobial susceptibility testing, or what is known as 'breakpoint determination'. Breakpoints are data derived from an antibiotic's effect on a specific organism and the correlation to clinical outcome. Breakpoints are used by microbiology laboratories to provide physicians with information on the antibiotic susceptibility of a certain organism isolated from a patient's culture. Breakpoints ultimately affect treatment decisions as they enable physicians to select an antibiotic to maximize the likelihood of treatment success.

As part of the regulatory approval process, health agencies assign breakpoints to a product based on a detailed and an integrated review of safety, efficacy, microbiology and PK/PD information. Approved breakpoints are provided in the product labeling. In addition,

breakpoint determinations have also been evaluated by local (country-specific) committees. These committees include local experts given the responsibility to assess susceptibility data provided by the sponsor in support of the breakpoint process. In addition, the committees monitor and compare overall resistance epidemiology and the development of resistance as an individual product matures in the marketplace. As numerous health agencies and requisite country committees review data packages, their review techniques and data interpretation preferences have created multiple sets of differing breakpoints assigned to a product. In Europe, this problem was more complex because of the potential of different breakpoints in many countries within the same geographic region. The added uncertainty of harmonized breakpoints and the complexities of maintaining them place additional demands on drug sponsors.

To address this issue in Europe, the EMEA/CHMP and the European Committee on Antimicrobial Susceptibility Testing (EUCAST) have agreed on a procedure in which a single set of breakpoints are assigned throughout the EU that are identical to those contained in the approved product labeling. This procedure includes EUCAST during the drug approval process and allows breakpoint review to take place as part of the drug approval process.

The situation in the US on the other hand is less clear. As part of the drug review process, the FDA is the legal entity that determines product breakpoints, which are then included in the product labeling. In addition, another group of experts, the Clinical Laboratory Standards Institute (CLSI), produces and maintains laboratory standards manuals that are used by microbiology laboratories to guide susceptibility testing. The CLSI manual provides the guidelines used by the laboratory to perform and report susceptibility data. These standards are used by agencies to determine certification for conducting such testing. Therefore, microbiology laboratories feel obligated to follow CLSI guidelines.

Traditionally, after approval of a product, companies subsequently present data to CLSI for inclusion in the CLSI manuals. Recently, however, because of the potential difference in reviewing techniques and data interpretation preferences, there has been a higher likelihood that breakpoints assigned by the FDA may not match those assigned by CLSI. This results in a dichotomy between what microbiology laboratories use as standards and what a drug company has in its product label and can present to a physician. Such differences may ultimately result in confusion at the clinic and/or laboratory, which could affect patient care. Industry has identified this as an issue and the hope is that in the immediate future an approach to breakpoint setting, which provides a single review of data and a unified breakpoint assignment, will exist as it now does in the EU.

Conclusions

The challenges confronting antimicrobial drug development are well understood. Although the threat to public health continues to receive considerable attention, little action is taking place to provide relevant incentives to industry to continue to invest in research and development in this sector.

Unlike researchers in other areas, antibiotic developers are fortunate in having development guidelines specifically tailored to their infectious disease indication. These come from special interest groups—including the IDSA and the European Society of Clinical Microbiology and Infectious Disease—and indication-specific guidelines from government agencies, it is clear that regulatory oversight lacks clarity in key areas.

Incentives have been discussed publicly at FDA Anti-Infective Advisory Committee Meetings as well as public workshops headed by the FDA. Most of the ideas that provide true financial incentives would require a change in US legislation, and thus have not progressed over the past few years.

Although financial incentives cannot be provided by regulators, several agencies have created avenues to foster collaboration during development and streamline the review process, but the effect of these initiatives has yet to result in industry commitments. One example is 'fast track' designation in the United States. This designation is assigned to a compound intended to fulfill an unmet medical need during the development phase and provides more frequent interactions between the FDA and industry. In addition, the parallel scientific advice procedure provides the opportunity to get FDA and EMEA advice through the same procedure to try to harmonize global development issues[30]. Agencies have also provided incentives regarding agency review times through priority/accelerated review mechanisms.

It will take commitment from both industry and regulatory agencies to ensure that a global situation of untreatable pathogens does not become reality. The delivered promise for new guidelines and additional incentives, as well as a commitment from major pharmaceutical companies, will be critical in the acknowledgement that resistance is not a passing trend but more a permanent attribute in an ongoing fight against infectious diseases.

1. Powers, J.H. *Clin. Microbiol. Infect.* **10** (**Suppl 4**), 23–31 (2004).
2. Weber, J.T. & Courvalin, P. *Emerg. Infect. Dis.* **11**, 791–792 (June 2005).
3. Commission of the European Communities. Communication from the Commission on a Community Strategy Against Antimicrobial Resistance (European Commission, Brussels, Belgium, 2001).
4. World Health Organization. WHO Global Strategy for the Containment of Antimicrobial Resistance (WHO, Geneva, 2001).
5. Nordberg, P., Monnet, D.L. & Cars, O. Antibacterial Resistance. Background Document for the WHO Project: Priority Medicines for Europe and the World—a Public Health Approach to Innovation (WHO, Geneva, 2005). <http://mednet3.who.int/prioritymeds/report/index.htm>
6. Norrby, S.R., Nord, C.E. & Finch, R. *Lancet Infect. Dis.* **5**, 115–119 (2005).
7. Smolinski, M.S., Hamburg, M.A. & Lederberg, J. (eds.). *Microbial Threats to Health: Emergence, Detection, and Response* (Institute of Medicine, Washington, DC, 2003).
8. Task Force on Antimicrobial Availability. *Bad Bugs, No Drugs: As Antibiotic R&D Stagnates, a Public Health Crisis Brews* (Infectious Diseases Society of America, Alexandria, Virginia, July 2004). <http://www.idsociety.org/pa/IDSA_Paper4_final_web.pdf>
9. Talbot, G.H. *et al. Clin. Infect. Dis.* **42**, 657–668 (2006).
10. Spellberg, B., Powers, J.H., Brass, E.P., Miller, L.G. & Edwards, J.E., Jr. *Clin. Infect. Dis.* **38**, 1279–1286 (2004).
11. Livermore, D.M. *Clin. Microbiol. Infect.* **10** (**Suppl 4**), 1–9 (2004).
12. US Food and Drug Administration. *Guidance for Industry: Developing Antimicrobial Drugs—General Considerations for Clinical Trials* (FDA, Rockville, Maryland, July 1998). <http://www.fda.gov/Cder/guidance/2580dft.pdf>
13. European Medicines Agency/Committee for Proprietary Medicinal Products. *Note for Guidance on Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections* (EMEA/CPMP, London, October 2004). <http://www.emea.eu.int/pdfs/human/ewp/055895en.pdf>
14. Japan Pharmaceutical and Medicine Safety Bureau, Evaluation and Licensing Division. *Guidelines for the Clinical Evaluation of Antibacterial Drugs* (PMSB/ELD, Tokyo, August 1998).
15. US Food and Drug Administration. *Guidelines for the Clinical Evaluation of Anti-Infective Drugs (Systemic Adults and Children)* (FDA, Rockville, Maryland, September 1977). <http://www.fda.gov/Cder/guidance/old047fn.pdf>
16. US Food and Drug Administration. *FDA Points to Consider—Clinical Development and Labeling of Anti-Infective Drug Products.* (FDA, Rockville, Maryland, October 1992). <http://www.fda.gov/cder/guidance/ptc.htm>
17. Blaser, M.J. & Bartlett, J.G. Letter to Acting Commissioner of Food and Drugs Administration. (September 28, 2006). <http://www.idsociety.org/Template.cfm?Section=Home&Template=/ContentManagement/ContentDisplay.cfm&ContentID=17039>
18. Getz, K.A. A swift predominance of ex-US sites. *Applied Clinical Trials Magazine,* December 1, 2005. <http://www.actmagazine.com/appliedclinicaltrials/article/articleDetail.jsp?id=261633>
19. Bakhle, D. *Global Clinical Trials in India—Challenges and Opportunities. Business Briefing Pharmatech* (Touch Briefings, London, 2003). <http://www.touchbriefings.com/pdf/17/pt031_r_4_bakhle.pdf>
20. International Conference on Harmonization. *ICH Harmonized Tripartite Guideline. E5: Ethnic Factors in the Acceptability of Foreign Clinical Data.* (ICH, Geneva, February 1998). <http://www.ich.org/cache/compo/475-272-1.html#E5>
21. Temple, R. & Ellenberg, S.S. *Ann. Intern. Med.* **133**, 455–463 (2000).
22. International Conference on Harmonization. *ICH Harmonized Tripartite Guideline. E9: Statistical Principles for Clinical Trials* (ICH, Geneva, February

1998). <http://www.ich.org/cache/compo/475-272-1.html#E9>
23. International Conference on Harmonization. *ICH Harmonized Tripartite Guideline. E10: Choice of Control Group and Related Issues in Clinical Trials.* (ICH, Geneva, July 2000). <http://www.ich.org/cache/compo/475-272-1.html#E10
24. US Food and Drug Administration, Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research. *Guidance for Industry. E9 Statistical Principles for Clinical Trials* (FDA, Rockville, Maryland, 1998). <http://www.fda.gov/cder/guidance/ICH_E9-fnl.pdf>
25. Federal Food, Drug, and Cosmetic Act, Chapter V—Drugs and Devices Subchapter A, Drugs and Devices, Section 505. <http://www.fda.gov/opacom/laws/fdact/fdtoc.htm>
26. US Food and Drug Administration. *Guidance for Industry. Population Pharmacokinetics* (FDA, Rockville, Maryland, February 1999). <http://www.fda.gov/cder/guidance/1852fnl.pdf>
27. US Food and Drug Administration. *Antimicrobial Resistance & Drug Development: FDA/IDSA/ISAP Working Group Presentations and Transcripts* (FDA, Rockville, Maryland, May, 2004). <http://www.fda.gov/cder/drug/antimicrobial/FDA_IDSA_ISAP_Presentations.htm>
28. Bradley, J.S., Dudley, M.N. & Drusano, G.L. *Pediatr. Infect. Dis. J.* **22**, 982–992 (2003).
29. Metlay, J.P., Powers, J.H., Dudley, M.N., Christiansen, K. & Finch, R.G. *Emerg. Infect. Dis.* **12**, 183–190 (2006).
30. US Food and Drug Administration. *General Principles EMEA-FDA Parallel Scientific Advice Meetings Pilot Program* (FDA, Rockville, Maryland, May, 2004). <http://www.fda.gov/oia/pilotprogram0904.html>

The biotech company view

Roger Echols

The current state of antibiotic drug development can at best be described as a process in transition. First, the larger pharmaceutical companies, with a few notable exceptions (e.g., Basel-headquartered Novartis), have withdrawn from major discovery efforts to identify new classes of drugs needed to address the growing problem of antimicrobial drug resistance. This trend is likely to continue because treatment with antibiotics is generally short, rendering antibiotics less profitable than drugs used for chronic conditions.

Fortunately, small biotech companies (some of which were spin-offs from the global pharmaceutical companies) have been able to attract the capital investment to continue the quest for new antimicrobial drugs. There is a small window during which discarded discovery research programs may be continued and result in meaningful new products. An early example was the development of Cubicin (daptomycin), which was discovered by Eli Lilly (Indianapolis, IN, USA) but developed and marketed by Cubist Pharmaceuticals (Lexington, MA, USA).

Ultimately, however, the big pharma pipeline of discarded programs will also dry up and it is unclear whether biotech will be capable of independently discovering novel antibiotic classes and bringing them to market. An unofficial tally of new chemical entities of antibacterials presented at the recent Interscience Conference on Antimicrobial Agents and Chemotherapy meeting[1] identified 27 from small biotech companies and only 13 from larger pharmaceuticals firms (most of which were from a single class, oxazolidinones). This is in contrast to the same meeting held in Toronto in 1997, where 63 new antibacterial drugs were in early or later phase development, almost all of which were big pharma products.

The medical need for new antimicrobial drugs is driven by the continuing development of drug resistance to existing marketed agents. This medical need is augmented by the potential for rare infectious microbes to be exploited as agents of bioterrorism. The Infectious Diseases Society of America (IDSA; Alexandria, VA, USA) has identified specific target pathogens for which we need new therapeutic agents in their "Bad Bugs; No Drugs" white paper[2].

Regulatory requirements

For new anti-infective development to be an attractive business, a critical component for both investors and scientists is to have a clear understanding of the regulatory requirements for drug approval. In the early 1990s, IDSA was contracted by the US Food and Drug Administration (FDA) to provide detailed clinical trial guidelines for the more common bacterial infections. These guidelines were eventually published (although still as draft guidelines) in 1998 and have remained posted on the FDA website[3]. Similar guidelines were adopted by the European Medicines Agency (EMEA)[4].

The guidelines, however, are only a starting point and the FDA and to a lesser extent the EMEA actively engage in discussions with the sponsoring companies regarding the details of protocol design and study analysis. Sponsors can and usually do request formal meetings with the FDA to discuss their drug development plans and ask specific questions to which the FDA provides advice or guidance. However, until the establishment of the Special Protocol Assessment process by the FDA in 2003 (ref. 5), there was no binding agreement that would ensure that the advice received before initiating pivotal phase 3 trials would remain in force at the time the data were reviewed as part of the new drug application (NDA) submission.

Noninferiority

Until recently, the FDA has honored its agreements with companies with regard to development advice, unless new scientific evidence rendered irrelevant the assumptions upon which the agreements were established. Recent congressional criticism of the approval of Sanofi-Aventis' (Paris) Ketek (telithromycin), linked to a high incidence of adverse events and surrounding allegations over scientific fraud in a large safety study[6], has highlighted not only the safety concerns regarding that product but also the fact that FDA approval was based on clinical trials that were conducted using active control treatments rather than using a placebo control. These so-called noninferiority trials are designed to show that a new antimicrobial agent is no less effective than a standard-of-care control regimen.

Congressional letters to both the FDA acting commissioner and the US Government Administrative Office (Washington, DC) have questioned the legitimacy of drug approvals based on noninferiority studies[7,8]. Although the letters refer to International Conference on Harmonization (ICH) guidelines that are generic for all therapeutic drug classes, they do not acknowledge the medical and ethical problems of conducting placebo-controlled or active-controlled superiority studies in subjects with acute bacterial infections. The FDA's "Points to Consider" guidelines for the development of antibacterial drug products specifically raise the ethical problem of conducting placebo-controlled studies and conclude that the use of active-controlled, noninferiority clinical trials are appropriate for the development of antibacterial drugs[9].

To be fair, the FDA has been discussing in public forums the need to change the clinical development guidelines to address the efficacy uncertainties inherent in noninferiority studies; however, long-promised new guidelines have not been issued, even in draft form[10]. Two antibiotic submissions for acute exacerbation of chronic bronchitis were not approved in 2005 and recently, two products

Roger Echols is at Replidyne Inc., 1450 Infinite Drive, Louisville, Colorado 80027, USA.
e-mail: rechols@replidyne.com

have been rejected for the indication of acute bacterial sinusitis, largely based on the opinion that efficacy could not be demonstrated based on noninferiority studies[11,12].

Although superiority studies may be more robust in differentiating one treatment from another, proving an antibacterial drug is better than placebo still does not answer the question of whether or not the new agent is as good as or better than the current standard of care. For the FDA to suggest that 'new science' does not allow them to approve new antibacterial drugs based on noninferiority studies for certain indications is a bit disingenuous because all currently marketed antibacterial drugs have been approved on the basis of noninferiority study designs. A logical extension of the FDA's opinion would require the removal of the indications of acute exacerbation of chronic bronchitis or acute bacterial sinusitis and perhaps acute otitis media from the labels of all marketed drugs that currently have these indications.

Clinical endpoints

In addition to rejecting noninferiority study designs for certain clinical indications, the FDA has also questioned the validity of clinical assessment by the physician investigator as an appropriate (primary) endpoint for study analysis. They have proposed the use of patient- or parent- (in the case of pediatric infections) reported outcome measures (PROs) to evaluate the efficacy of antibacterial drug treatment[13].

Unfortunately, this new requirement only increases the risk that the study will fail to meet its predefined criteria for demonstrating efficacy because validated PROs do not exist for the acute infection indications for which they are to be used, for example, acute exacerbation of chronic bronchitis and acute otitis media. The time required to develop and validate such PROs is measured in years, especially considering they also need to be validated for each language for studies that are conducted globally.

Conclusions

Notwithstanding the academic and political discussions regarding study design, the absence of acceptable guidelines has the potential to paralyze future antimicrobial drug development. Both large pharma and small biotech companies need to be able to determine the potential risk for costly and lengthy development plans, and this calculation can be accomplished only with clear and constant regulatory guidelines. The leadership of the IDSA has recently addressed this lack of regulatory guidance in a letter to the acting commissioner[10].

We can only hope that these new guidelines, when they do appear, will not create insurmountable obstacles that further confound the development of new antimicrobial products. In the meantime, we can count on the fact that the increase in bacterial resistance to existing antibiotics will continue unabated and that treatment options for practicing physicians will dwindle.

1. Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) Meeting, September 27–30, 2006, San Francisco.
2. Task Force on Antimicrobial Availability. *Bad Bugs, No Drugs: As Antibiotic R&D Stagnates, a Public Health Crisis Brews* (Infectious Diseases Society of America, Alexandria, VA, July 2004). <http://www.idsociety.org/pa/IDSA_Paper4_final_web.pdf>
3. <http://www.fda.gov/cder/guidance/#clinical%20antimicrobial>
4. European Medicines Agency/Committee for Proprietary Medicinal Products. *Note for Guidance on Evaluation of Medicinal Products Indicated for Treatment of Bacterial Infections* (EMEA/CPMP, London, October 2004). <http://www.emea.eu.int/pdfs/human/ewp/055895en.pdf>
5. US Food and Drug Administration/Center for Drug Evaluation and Research. *Guidance for Industry for Special Protocol Assessment* (FDA/CDER, Rockville, Maryland, 2002). <http://www.fda.gov/cder/guidance/3764fnl.htm>
6. Anonymous. *Nat. Rev. Drug Discovery* **5**, 446–447 (2006).
7. Grassley, C. Letter to Andrew C. von Eschenbach, M.D. Acting Commissioner, Food and Drug Administration. (April 27, 2006). <http://www.finance.senate.gov/sitepages/grassley.htm>
8. Dingell, J., Grassley, C., Markey, E., Waxman, H. & Stupak, B. Letter to David M. Walker, Comptroller General of the United States. (September 6, 2006). <http://markey.house.gov/docs/health/09-06-06%20Letter%20to%20GAO.pdf>
9. US Food and Drug Administration. Points to Consider—Clinical Development and Labeling of Anti-infective Drug Products. (FDA, Rockville, Maryland, October 1992). <http://www.fda.gov/cder/guidance/ptc.htm>
10. Blaser, M.J. & Bartlett, J.G. Letter to Acting Commissioner of Food and Drugs Administration. (September 28, 2006). <http://www.idsociety.org/Template.cfm?Section=Home&Template=/ContentManagement/ContentDisplay.cfm&ContentID=17039>
11. Usdin, S. FDA's Superior Attitude. *BioCentury* **14**, A7–A10 (September 18, 2006).
12. Usdin, S. Antibiotic resistance. *BioCentury* **14**, A1–A6 (October 30, 2006).
13. US Food and Drug Administration. *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims* (US Department of Health and Human Services, Food and Drug Administration, Rockville, Maryland, February 2006). <http://www.fda.gov/Cder/guidance/5460dft.htm>