Antibacterial drug discovery: is it all downhill from here?

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ABSTRACT

There has been a marked decline in the industrial research aimed at discovering novel antibacterial agents, including new drugs that target resistant organisms. While this decline may reflect past cyclical changes that often affect resource allocation at pharmaceutical companies, this decline is occurring at a time of increasing levels of antibacterial drug resistance and meagre pipelines of new agents that are active against them. There are multiple reasons for this decline, although few are unique to antibacterial drug discovery research. These include: lack of industry productivity, increasing size of clinical trials, increased generic competition and other pressures on drug pricing, a crowded and confused marketplace and industry consolidation. And while many (if not most) large companies and biotechs have exited the field or severely curtailed their research, others have made it a point to continue their efforts, citing both the unmet medical need and a large and apparently growing market. Despite the fact that some companies have remained engaged, the view here is that the current level of industrial effort is insufficient to sustain a healthy flow of new and better agents that are needed to counter the imminent threat of bacterial drug resistance. Therefore, a clear and urgent need for finding ways to improve the level and quality of industrial research in this area is apparent.

Keywords antiinfective drug discovery, resistance, industry productivity, drug pricing, generic competition

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RESISTANCE MATTERS

The increase in the levels of antibacterial drug resistance in serious human pathogens has been well documented and oft repeated to the point of cliché. Numerous studies [1–4] have shown that the frequency of multidrug-resistant isolates is increasing in US hospitals and throughout the world. For severely ill, hospitalised patients, therapeutic efficacy is important to ultimate morbidity and mortality, and therefore, to the overall cost of care; however, there have been very few studies concerning the actual costs of antibacterial resistant infections. For many of these pathogens, especially among the Gram-negative bacteria, options for therapy are becoming extremely limited and, while reports of mortality to pan-resistant infections are mainly anecdotal, it will not be long before they are easily quantifiable, meaning that we are already too late in the discovery and development of novel antibiotics.

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A BRIEF HISTORY OF ANTIBACTERIAL DRUG DISCOVERY

The pharmaceutical industry owes much of its early prosperity to the discovery of antibacterial agents. The identification of these virtually miraculous, life-saving drugs and the manufacture of related analogues have obviously benefitted to society. Early antibacterial agents discovered were the sulfonamides, penicillin and streptomycin, and these were rapidly followed by tetracyclines, isoniazid, macrolides, glycopeptides, cephalosporins, nalidixic acid and other molecular classes culminating in rifampicin which was marketed in the late 1960s. It is worth noting that, despite its discovery in 1928, it required a consortium of five pharmaceutical companies (Abbott, Lederle, Merck, Chas. Pfizer and ER Squibb & Sons) and the US Department of Agriculture to develop and produce penicillin in the 1940s, mainly as part of

the war effort during the Second World War. The cephalosporins became popular during the 1970s, with several 'second' and 'third' generation products entering the marketplace by the mid-1980s. Coincident with the growing market dominance of the third generation cephalosporins was the emergence of the pandemic of multiply resistant *Streptococcus aureus* infections in US hospitals [5] and *Streptococcus pneumoniae* in the community [6]. At that time, in the early 1980s, the pharmaceutical industry began scaling back on their antibacterial drug discovery efforts with approximately half of large US and Japanese pharmaceutical companies ending or curtailing their efforts [7,8]. Yet antibacterial drug discovery efforts did continue at many major European and US pharmaceutical companies through the 1990s and these efforts led to the introduction of quinupristin-dalfopristin (Synercid®) and linezolid (Zyvox®), both targeting Gram-positive pathogens, to the marketplace in 1999 and 2001. Linezolid is the first of a new class (oxazolidinones) of antibacterial agents to be marketed since rifampicin. But since 1999 the industry has once again pulled back from anti-infective research in an even more concerted manner, with 10 of the 15 largest companies ending or curtailing their discovery efforts. While this was occurring the industry has been experiencing a series of mega-mergers leading to large-scale consolidation. Five modern pharmaceutical companies (Pfizer, GlaxoSmithKline, Novartis, Bristol-Myers Squibb and Aventis) actually are comprised of 32 progenitor companies, all in business as recently as 1980 (Fig. 1); many of those 32 companies had their own antibacterial groups, so consolidation alone has resulted in a major decrease in the hunt for novel antibacterial agents.

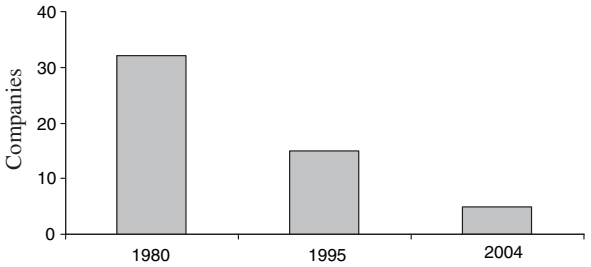

Fig. 1. Contraction of the pharmaceutical industry with time, indicated by the number of companies that now form Pfizer, GlaxoSmithKline, Novartis, Bristol-Myers Squibb and Aventis.

WHY STAY IN?

While many large companies have either diminished or eliminated their research efforts in antibacterial drug discovery, some, including Johnson & Johnson, Merck, Bayer and Pfizer (as well as a few biotechnology companies) have elected to remain in the field. This persistence is based mainly on the existing, profitable franchises these companies have in the antibacterial drug market, but also upon the (accurate) view that resistant pathogens will continue to emerge and disseminate. Therefore, it is reasoned, there remains both an unmet medical need and a commercial opportunity in the future, although perhaps not to the same extent as for some other therapeutic areas.

WHAT DOES IT TAKE TO DEVELOP A NEW DRUG?

In determining research priorities pharmaceutical companies consider the unmet medical need, and the potential patient population that may be treated by a new product, how that new product would be differentiated from competition, the price that a new product would fetch in different markets (especially developed countries), the investment that would be required to bring product to market, and the costs to promote the new drug. Because of increasing requirements by regulatory agencies in the areas of manufacturing, safety and efficacy for product development in general, the pharmaceutical industry is bearing an ever higher cost burden for each product brought to market. To illustrate: the number of patients enrolled in clinical trials for each new drug application (NDA) in the 1981–84 period averaged 1321, that number had more than tripled to 4237 by 1994–95 [9], with the trend continuing ever upward since. Combining this with postmarketing commitments (i.e., additional, required clinical studies even after a drug makes it to the market) and ever more restrictive labelling (severely constraining how a drug can be used or whether its expense can be reimbursed), many (if not most) approved drugs never recoup the investment required to bring them to the market. The latest Tufts Center survey indicates that these costs exceed US $800 m [10] and may even be approaching $1 bn. Therefore, pharmaceutical companies have been ever more cognisant of the market potential for each new medication and prioritise accordingly.

CLINICAL TRIALS AND TRIBULATIONS

Both the greatest unmet medical need and the projected market growth are in the area of hospital-based infections and parenteral drugs. Clinical trials for parenteral products, however, especially those targeting specific resistant pathogens, are quite expensive, with at least 600–1000 patients per trial at costs of $5 000 or more per patient [11]; and multiple indications (and therefore multiple trials) are required for market viability. The International Committee on Harmonization (ICH) has put forth proposed guidelines requiring an increase in stringency for the active comparator, noninferiority trials used for registration of most antibacterial agents. The FDA then notified some companies that the stringency of the trials required for registration would be increased along the lines suggested by the ICH, thus dramatically increasing costs and time to market for antibacterial drugs. Taken together with the challenges discussed above this caused many within industry to question the relative value of antibacterial drug discovery. In consultation with the Pharmaceutical Manufacturer's Association (PhRMA) and the Infectious Diseases Society of America (IDSA), the US FDA has somewhat revised its views on the level of stringency for all possible applications of antibiotics [11]. However, little has been actually done to motivate companies to develop novel agents that are active against resistant pathogens. What is needed is for sponsors to have a clear understanding in the review process of what an acceptable drug profile would be, in terms of both safety and efficacy, prior to the start of Phase III pivotal studies. This would undoubtedly result in more compounds being tested in proof of concept studies (e.g., Phase II) but fewer, yet higher quality, agents being tested in the large Phase III studies. To date, the regulatory authorities have not been able to formulate clear guidance on what it would take to bring a novel antibacterial, with activity towards resistant strains, to the market. Indeed there has been much talk about the regulatory review times as an important issue for industry. Faster review times by regulatory authorities are always well appreciated by the industry but they are really not the issue. As pointed out by the former Commissioner of the FDA, Dr Mark McClellan, drugs spend only approximately 10% of their time under regulatory review in the period from discovery to marketing. Instead, the real problem is the demand for more and 'higher quality' data that require longer and more expensive clinical testing, well before the filing of new drug applications, which results in time lines that erode the patent life and commercial viability of a new agent.

It has been suggested that while big pharmaceutical companies will not find and develop novel antibacterial drugs, biotech companies will pick up the slack. Biotech companies, however, have to date had a poor record in discovering novel antibacterial agents and many of these companies have simply ceased to exist. Some biotechs, like Cubist, actually are developing drugs, like daptomycin (which was discovered at Eli Lilly), originally found by large pharmaceutical companies. As Cubist discovered, however, it is really just as expensive to develop a narrow spectrum, niche (and therefore less profitable) antibiotic like daptomycin as it is to develop a broad spectrum (and probably more profitable) antibiotic. In general, biotechs rely on large companies to provide the funding for the large Phase III pivotal clinical trial studies. With fewer large companies in the field, and even fewer large companies to do business with due to consolidation, it is not clear whether the large industrial entities will be there to partner such projects.

A tool commonly used in the prioritisation and fallibility of market research is the Net Present Value (NPV) calculation [12]. The NPV is a determination of the value of a given project after projecting expenses and revenues into the future and discounting for the potential investment value of the money that will be spent in executing the project. NPV is usually 'risk-adjusted' (the rNPV) with increased risk associated with projects at earlier stages; risks are different depending on factors such as the therapeutic target and type of compound. Antibacterial agents that enter development at all stages of development through Phase III clinical trials have a relatively low risk compared with projects in other therapeutic areas [13]. By way of example, a hypothetical project entering clinical trials for a novel antidepressant has been calculated at one company to have a rNPV of $720 m compared with $100 m for a novel injectable antibacterial targeting susceptible and resistant Gram-positive bacteria. But if an increase in clinical trial size or a post-marketing commitment is factored in,

because of changes in the regulatory process, the rNPV would drop relative to most other projects (therefore the imposition of the 'infamous' 10 per cent delta rule (see below), rather than the previously defined less stringent delta, would result in an rNPV of $35 m, ranking the project near the bottom of most companies' projects).

However, NPVs are calculated according to the rather inexact science of market research and they often fail to take competitive drug discovery programmes into consideration (rather, benchmarking based on currently marketed products). Given the fallibility of the assumptions used to calculate NPVs, most companies also take other factors into consideration, such as peak year sales and compounded annual growth rates. Some companies set a minimum peak sales figure (e.g., $200 m or $500 m) and reject projects based on projected peak sales less than that figure. In terms of prioritisation of projects, a community-based oral antibiotic would receive a more favourable status than an injectable agent to treat only vancomycin-resistant enterococci. Still both of these would receive a lower priority than a drug to treat depression. However, because sales projections are made before hard clinical data are available, the reality of how a drug is used once it reaches the market often bears little resemblance to the target product profile; these disparities are the rule more often than the exception.

UNIQUELY CHALLENGED

While antibacterial projects entering clinical development have better rates of success than those in other therapeutic areas [13,14], antibacterial drug discovery faces unique challenges. First, the scientific challenge is a significant one. Although nearly 15 years after the emergence of the field of bacterial genomics, there are no promising antibacterial agents in clinical development or on the market derived via this technology. Perhaps it is unfair to expect that a decade and a half of work in a novel technological area would give rise to first generation agents that are superior to current agents that have been optimised over the last 60 years. Indeed, target-based drug discovery for novel antibacterials confronts another unique problem: even a relatively narrow-spectrum agent would have to be active, not against a single molecular target, but a family of targets that are similar but far from identical. Recent publications, however, suggest that target-based drug discovery is starting to pay off. Inhibitors of peptide deformylase [15] are entering clinical development and novel inhibitors of fatty acid biosynthesis have been described [16].

Perhaps even more vexing is the 'antibiotic paradox'. As we have seen, the rise of multiply-resistant *S. aureus* infections led to increased usage of vancomycin, but after a period of heavy use, strains of staphylococci resistant to vancomycin have emerged. This is an example of what can be termed 'Levy's Law of Antibiotics'. Use of antibacterial drugs leads, perhaps inevitably, to bacterial resistance, which increases the need for new antibiotics, which would then select for new resistance phenotypes [17]. The awareness of the relationship between use and emerging resistance has led to efforts to decrease, even restrict, antibiotic use, and therefore decrease the positive influence of resistance on the market and decrease market potential.

At $26 bn, the antibacterial marketplace is large, but has been growing at an increasingly modest rate over the past four years. What is clear is that the market for parenteral (injectable) antibiotics (most often used for serious, hospital infections) is growing faster than for oral antibiotics most commonly used for community-acquired infections although the parenteral market is only about 30% of total sales. More than 80% of the total antibacterial sales represent branded products as opposed to generics, demonstrating a surprising resistance to generic competition in this area. Several major ($500 m to almost $2 bn annual sales) products, however, are about to lose exclusivity in the major markets over the next 5–10 years, if not sooner, due to challenges of patent validity. This increased amount of generic competition may well lead to a significant market contraction; but perhaps it is more the fear of market contraction; rather than the commercial reality of an expanding market, that has further discouraged some companies.

SOLVING THE PROBLEM

There is much that can be done to re-engage industry in antibacterial research. Such solutions have been proposed in recent discussions among PhRMA, the FDA and the IDSA [11,18]. Included among these are providing clearer guidelines for the development of novel antibacterials as

discussed above and taking a more imaginative approach to clinical trials design which would allow for smaller trials. Other potential solutions, including extension of product exclusivity, will require legislative initiatives. It is also incumbent upon the pharmaceutical industry to become more efficient in its drug discovery and development processes. Many have already quietly but radically changed their business models to address this. But, perhaps most critical of all, it is necessary for the academic community to improve the study of bacterial physiology and resistance because, to put it simply, you cannot build a good house on a rotten foundation.

CONCLUSIONS

Coincident with the increase in the number of multidrug resistant bacterial infections has been a diminution in the quantity and quality of industrial antibacterial research, resulting in a very dry pipeline of new antibacterial drugs. The reasons for this decline are many, including industry consolidation combined with decreased productivity of research and development efforts, increased regulatory requirements, decreased respect for intellectual property, and the perceived potential for contraction in what already is the most crowded and confused pharmaceutical market. The resulting perfect storm is already having dire consequences for patients who have untreatable infections while public, private and political concerns have shown little inclination to act. Drugs discovered today will take longer than a decade to reach clinical practice under today's regulatory regime. Therefore, as the situation becomes more dire, the prediction here is that draconian and expensive infectious disease control measures will become *de rigueur* in many hospitals, and agents with compromised utility and safety will be employed in our desperation to deal with this underappreciated crisis.

REFERENCES

1. Archer GL. Why do we REALLY need antibacterial drugs. *ICAAC Annual Meeting*, Chicago 2003: Abstract 1123.
2. Wenzel RP, Sahm DF, Thornsberry C, Draghi DC, Jones ME, Karlowsky JA. In vitro susceptibilities of Gram-negative bacteria isolated from hospitalized patients in four European countries, Canada, and the United States in 2000–01 to expanded-spectrum cephalosporins and comparator antimicrobials: implications for therapy. *Antimicrob Agents Chemother* 2003; **47:** 3089–98.
3. Livermore DM, James D, Reacher M, *et al*. Trends in fluoroquinolone (ciprofloxacin) resistance in enterobacteriaceae from bacteremias, England and Wales 1990–99. *Emerg Infect Dis* 2002; **8:** 473–8.
4. Bromiker R, Arad I, Peleg O, Preminger A, Engelhard D. Neonatal bacteremia: patterns of antibiotic resistance. *Infect Control Hosp Epidemiol* 2001; **22:** 767–70.
5. National Nosocomial Infections Surveillance, Report: data summary from October 1986–April 1996. *Am J Infect Control* 1996; **24:** 380–8.
6. Crook DWM, Spratt BG. Multiple antibiotic resistance in *Streptococcus pneumoniae*. *Br Med Bull* 1998; **54:** 595–610.
7. Shlaes DM, Levy S, Archer G. Antimicrobial resistance: new directions. *Am Soc Microbiol News* 1991; **57:** 455–8.
8. Lederberg J, Shope RE, Oaks SC Jr, eds. *Emerging Infections. Microbial Threats to Health in the United States*. National Academy Press 1992.
9. Peck C. Drug Development: Improving the Process. *Food Drug Law Journal*, 1997, 52.
10. DiMasi JA. New drug development in the United States from 1963 to 1999. *Clin Pharmacol Ther* 2001; **69:** 286–96.
11. US Food and Drug Administration. Labeling requirements for systematic antibacterial drug products intended for human use. 21 CFR Part 201 Docket; 00N-146, 2003.
12. Stewart JJ, Allison PN, Johnson RS. Putting a price on biotechnology. *Nature Biotechnol* 2001; **19:** 813–7.
13. Keim KL, Calcagno J, Leventer SM, Harris HW. Unlocking the value of failed CNS trials. *Curr Drug Dis* 2003; **3:** 29–33.
14. DiMasi JA. Risks in new drug development: Approval success rates for investigational drugs. *Clin Pharmacol Ther* 2001; **69:** 297–307.
15. Hackbarth CJ, Chen DZ, Lewis JG *et al*. N-alkyl urea hydroxamic acids as a new class of peptide deformylase inhibitors with antibacterial activity. *Antimicrob Agents Chemother* 2002; **46:** 2752–64.
16. Payne DJ, Miller WH, Berry V, *et al.* Discovery of a novel and potent class of FabI-directed antibacterial agents. *Antimicrob Agents Chemother* 2002; **46:** 3118–24.
17. Levy SB. The Antibiotic Paradox: *How the Misuse of Antibiotics Destroys Their Curative Powers*, 2nd edn. Cambridge, MA, Perseus Publishing, 2002.
18. US Food and Drug Administration, IDSA, /PhRma/FDA, *Working Group Meeting* 2002; November 19–20. Available at: http://www.fda.gov/cder/present/idsaphrma/default.htm.