Impact of antibiotic restrictions: the pharmaceutical perspective

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ABSTRACT

The development of new antibiotics is dependent on their performance in economic models that favour products with large markets, high levels of potential sales and low development risks. There is a trend toward more severe and more widespread market restrictions for the use of antibiotics, ostensibly to control resistance, though they may be enacted through the control of drug budgets. The restrictions reduce the potential earnings of new antibiotics. In addition, more stringent regulatory procedures increase development costs and risk. As a consequence, compared with drugs for other diseases, particularly chronic diseases, antibiotics perform poorly in economic decision models and are therefore less likely to be selected by pharmaceutical companies for continued development. Overall, this creates a conflict between the twin objectives of controlling resistance through antibiotic restriction and addressing resistance clinically through the introduction of new agents. Ultimately, this may lead to the accelerated loss of efficacy for currently available agents, as we become more dependent on them. Moreover, the new agents that we need to maintain our current levels of health will be lacking in pharmaceutical pipelines. Antibiotic resistance is inevitable; the development of new antibiotics is, however, under threat. Unless the market conditions can be economically rebalanced to encourage innovation and investment, or new models of pharmaceutical development can be applied to this area, the number of companies with active antibiotic research programmes will continue to fall. Just as we should not be complacent regarding the development of resistance, we should not be complacent in assuming that the antibiotics of tomorrow will be there when we need them.

Keywords Antibiotic resistance, pharmaceutical development, pharmaceutical regulation, rational antibiotic prescribing, review

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INTRODUCTION

In the 1960s and 1970s, there was a general belief, though it now seems naïve, that we had won the war against infectious diseases. Smallpox had been eradicated, measles had been conquered (at least in the developed world) and there was an expectation that further vaccines would become available that could manage other common infections. Antibiotics had reduced the complications and mortality associated with infectious diseases to levels that could not have been imagined even a generation before.

This complacency was general, not restricted to the pharmaceutical industry, and reflected in the medical, political and social thinking of the time.
last decade has also reduced the number of single companies involved. However, a number of prominent companies actively decided to stop investing in antibiotic R&D relatively recently. In 2001, Eli Lilly and Bristol-Myers Squibb stopped work on developing new antimicrobial drugs. Not only does this threaten the development of new drugs against existing drug-resistant pathogens, it also undermines our capacity to respond rapidly to the threat of emerging infectious diseases.

There is no doubt that, in the past, many pharmaceutical companies invested considerable resources in antibiotic R&D with exceptional results. By the early 1970s, 11 distinct antibiotic classes and more than 270 antibiotics had been brought into clinical use [1]. So what has changed? In the face of ever increasing resistance, and a growing need for novel agents, why has R&D in this area faltered?

This article will examine some of the reasons why antibiotic research has been cut back and why it is becoming an increasingly philanthropic area of investment for drug companies, as barriers to developing, registering and marketing new agents erode commercial interests. It will also look at some of the measures that could be introduced to stimulate renewed investment in this area of therapy.

**ECONOMICS OF DRUG DEVELOPMENT**

The costs of bringing a new pharmaceutical product into clinical use are staggering. For example, in 2001, the Tufts Center for the Study of Drug Development estimated the average cost to develop a new prescription drug as US $ 802 million, nearly 3.5 times the cost of developing a new drug in 1987 [2]. The US Department of Health and Human Services provided an even higher estimate based on 2002 data: US $ 1.7 billion represented an increase of 55% over 5 years. Based on these numbers, even Eli Lilly’s blockbuster product, Prozac, which earned approximately $ 21 billion in total [3], would only provide enough income to launch a maximum of 12 new products, not counting the costs of products that fail during development and general overheads.

With more sophisticated whole cell screening techniques and early assays for compounds that not only have activity, but also drug-like properties, choosing those compounds that have the greatest chance of clinical success is becoming more reliable. Thus, there is the potential for a more ‘front-loaded’ model of drug development. It has been estimated that a 10% improvement in predicting failures before clinical trials could save $ 100 million in development costs per drug [4]. However, whether we will see a ‘biotechnology payback’ of this sort is still unclear as the capital investment in these more sophisticated techniques is substantial [5]. Thus, although such innovations may reduce some of the risk of late failure, they may not impact on the overall cost of bringing a new antibiotic to market. For the foreseeable future, it is likely that costs will continue to rise and greater efforts are needed to seek out innovative approaches to antibiotic development.

Economic considerations are now the most common reason for terminating drug development, ahead of efficacy and safety [5]. This is not just an issue for antibiotics. Although R&D costs have been rising by about 8% per year overall, the numbers of new drugs receiving regulatory approval continues to fall. In 1995, the Food and Drug Administration (FDA) received approximately 40 applications for new molecular entities; by 2003 this had fallen to approximately 25 and an even more dramatic decline has been seen in applications for new biologics [6]. In addition, the expiry of patents on some of the most profitable drugs ever developed has affected most of the large pharmaceutical companies over the last 10 years, reducing certainty concerning future revenue streams [7]. The potential for developing ‘blockbuster’ drugs in the future is also decreasing as drug therapies become more diversified. As a consequence, pharmaceutical development decisions are likely to become more risk averse.

**Net present value**

Net present value (NPV) is a figure used for evaluating an investment decision and is widely used in the pharmaceutical industry to determine the viability of specific products and to compare investment strategies. Using this model, economic costs and benefits of a development programme are estimated according to current values. In short, it describes the relationship between the
projected costs of the project and the potential returns in terms of cash flow.

An NPV > 0 means that the project will be of benefit to the company; a sensitivity analysis can be run to determine the range of NPVs for different scenarios, such as first to market vs. second, and whether a specific indication is achieved. Monte Carlo simulations are now generally used to create a picture of the combined risks at different points in the development process through several thousand scenarios [8]. Thus, an element of risk assessment is incorporated and, in the case of pharmaceuticals, this also includes the likelihood of obtaining regulatory approval. Fig. 1 shows the basic relationship between NPV and the potential for marketing approval.

Antibiotic restrictions impact NPV by reducing the potential profit. Increased regulatory hurdles may also shift acceptable projects into more marginal projects by increasing development costs and by reducing the chances of a successful registration in the indications needed to obtain a satisfactory return on the investment (Fig. 1).

Resistance also has an impact on NPV. An agent to which resistance will develop rapidly, due to cross-resistance with existing antibiotic classes, through inadequate dosing, a low genetic barrier to resistance or overuse in ‘reservoir’ populations, such as children in day care and nursing home residents, will have a shorter useful clinical lifespan than an agent for which antimicrobial activity is preserved over a longer period (Fig. 2). Thus, to maximise NPV, it is in the interests of pharmaceutical companies to minimise the emergence and spread of antimicrobial resistance; this is counterintuitive to the popular belief that pharmaceutical companies are focused on selling as much product in as short a time as possible.

Of course, the length of patent protection is also an issue here. It may appear that there is little to be gained commercially by preserving the useful life of an antibiotic past the end of the patent-protection period. However, for successful antibiotics, companies will often try to preserve their franchise through life-cycle management options, such as high-dose or extended-release formulations. In some cases, if the antibiotics offer substantial clinical benefits, these life-cycle extensions can be more profitable than the original formulations, although peak sales are likely to be lower.

Importantly, it should be remembered that NPV is used to compare projects, both within the antibiotic pipeline and across the entire portfolio. Not all leads can be progressed, and there is considerable competition for resources among projects. As mentioned previously, drug development is an expensive business, and pharmaceutical companies must necessarily pursue

![Fig. 2. In terms of net present value (NPV), maintaining antibiotic efficacy is in the interests of pharmaceutical companies.](image-url)
those projects that have the greatest NPV and lowest relative risk of failure. Unfortunately, compared with drugs for chronic conditions, antibiotics perform poorly with regard to NPV. A typical NPV for an antibiotic would be 100, vs. 300 for an anticancer drug, 720 for a neurological drug and 1150 for a muscular-skeletal drug [9]. Any drug with an NPV < 100 is unlikely to be progressed by a large pharmaceutical company, so antibiotics really are on the borderline. Even if an antibiotic makes it past the selection stage and into development, it may well be scheduled as a lower priority than other competing drugs in the portfolio. In this way, a company seeks to maximise NPV across the whole portfolio over a given time.

Different companies also have different risk tolerances and different objectives in terms of diversification across several disease areas vs. specialisation in a few. The heritage of the company is also a factor. A company that has had substantial involvement in antibiotics in the past is likely to be one of the last to leave this area, possibly even after it has ceased to be a major part of the business of that company.

**IMPACT OF REGULATORY ISSUES**

Regulatory guidance can have a pivotal effect on the progress of R&D. Not only do regulatory agencies set the criteria by which new drugs are evaluated, they also determine the parameters within which they can be marketed. A key example of the impact of regulatory guidance on antibiotic development in particular is illustrated by the 2001 announcement by the FDA and the European Agency for the Evaluation of Medicinal Products (EMEA) regarding changes in the requirements for clinical trials.

A new antibiotic is required to show noninferiority to a currently registered agent in clinical trials. The FDA and other agencies had previously used a sliding-scale approach to determining noninferiority, with the lower limit of the 95% confidence interval (CI) (or one-sided 97.5% CI) for the experimental drug being less than 10–20% lower than the reference drug, which was termed the delta value. The delta value used depended on the anticipated cure rates and number of evaluable patients expected for that indication; for antibiotics, it was typically 15%. However, the FDA had two main concerns regarding this approach. Firstly, the FDA believed that the selection of successively less effective comparator agents results, over time, in the presumed ‘equivalence’ of statistically and clinically inequivalent products (termed ‘bio-creep’) [10]. Secondly, the recognised effectiveness of certain products changes with time, because of alterations in resistance patterns and the development of new knowledge [10]. As a consequence, the FDA and the EMEA recommended a change in the delta value to 10%. This may seem a small change, but it threatened to severely curtail or even halt R&D in antibiotics.

The problem is that such a change more than doubles the number of patients required for clinical trials [11]. Already, increases in the costs of running phase II and III clinical trials are largely responsible for the huge increase in the cost of bringing a drug to market seen over the last 5–10 years [6]. The cost of running these larger trials and the length of time that they would require pushes the overall expense of developing a new antibiotic to a level that cannot be justified economically. For example, reducing a delta value from 15% to 10% would result in an NPV of 100 being reduced to approximately 35 [9]. Furthermore, this delays the availability of new agents.

In addition, for indications that are relatively uncommon, such as meningitis, recruiting the necessary number of patients with a delta of 10% would take many years and require the involvement of many different centres across the globe. The infrastructure for conducting such a trial would have to be put in place, adding to costs and delays. Moreover, the comparator at the start of such a long trial may not be the ‘standard’ therapy at the end of the trial – making the results less relevant.

These changes resulted in a number of antibiotic programmes being put on hold, and are also credited with causing at least two pharmaceutical companies to withdraw from antibiotic development entirely. In February 2002, the FDA responded to these unwanted policy effects by convening a meeting with the Pharmaceuticals Research and Manufacturers of America and the Infectious Diseases Society of America [12]. The outcome of this meeting was that an across the board delta value of 10% was dropped in favour of a more case-based approach, taking into account the indication, projected efficacy and comparators, while maintaining safety and valid-
ity [12]. In practice, the FDA has a great deal of input into comparator regimens and thus is in an ideal position to manage these issues. This meeting averted a crisis and drug development resumed in most cases, although there were some enduring casualties, such as the antibiotic research programmes of Eli Lilly and Bristol-Myers Squibb, as well as delays in the development of new products, such as tigecycline. In addition, there remains a degree of uncertainty regarding the requirements for clinical assessment, which may tip the balance against investing in antibiotic development.

**IMPACT OF ANTIBIOTIC RESTRICTIONS**

Restrictions on antibiotic prescribing are becoming more common at all levels of decision making within healthcare structures (Fig. 3). For example, in Belgium, a campaign to reduce antibiotic prescribing included downward pressure through a position paper in a professional journal, and a letter to family practitioners and pharmacists. In addition, family practitioners received feedback on their prescribing habits. Simultaneously, upward pressure was generated through patient education initiatives, such as booklets and leaflets, television and radio advertising/features, a website and a press conference [13].

Examples of the increasing stringency of antibiotic restrictions include the need for antibiograms (which are not usually available in primary practice) before prescribing (Greece), local guidelines leading to the omission of newer antibiotics from hospital formularies (UK), and quotas for generic substitutions and parallel imports (Germany). Such measures of high-level control are a paternalistic response to the need to encourage appropriate prescribing. Unfortunately, they completely circumvent the clinical interaction between the physician and patient, and make assumptions regarding medical need on a population basis that may not be justifiable at the level of the individual. The consequences of these interventions on clinical outcomes are scarcely investigated, although data are generally collected on their impact on drug budgets and antibiotic consumption.

There is therefore a direct conflict between the two aims of antibiotic management: on the one hand, to restrict the use of these agents to prevent the spread of resistance; and on the other, a call for the development of new agents to fight resistant strains. Market restriction stifles innovation and investment; fewer antibiotics are developed, leaving us more dependent on existing agents that may no longer be maximally effective. An increased dependency on a reduced number of antibiotics may also accelerate the development and spread of resistance to these agents. Overall, this creates a vicious circle, potentially resulting in an increase in the incidence of infectious complications and mortality, with a limited pharmacological response, and eventually leading us back to the conditions of the preantibiotic age (Fig. 4).

**OPPORTUNITIES FOR ENCOURAGING ANTIBIOTIC R&D**

Most articles on the need for new antibiotics criticise the pharmaceutical industry for not investing enough in the development of new agents. However, we should also remember that were it not for the investment of these companies...
in the past, we would be in a much worse position than we are today. In fact, between 1999 and 30 June 2005, there have been 11 new antibiotics approved by the FDA, i.e., new chemical entities, not reformulations or new indications (Table 1) [14]. In comparison, there have been 22 neurological products (including those for depression, psychiatric disorders, Alzheimer’s, multiple sclerosis, Parkinsonism, pain and migraine), 22 oncology products (including anti-emetics), 16 cardiology products (including cholesterol management drugs), nine drugs for use in diabetes, seven antiretrovirals, four products for respiratory indications and four nonhuman immunodeficiency virus (HIV) antivirals approved during this period. In addition, the majority of the new antibiotics registered were new classes, or new subclasses of an agent, and the remainder had significant advantages over earlier representatives of their class in terms of their antibacterial spectrum. In particular, the spread of methicillin-resistant *Staphylococcus aureus* in hospitals and now into the community has initiated a wave of new antibiotics with activity against this pathogen. Overall, the pharmaceutical industry has responded to medical need, despite the regulatory and market barriers. However, it is clear that antibiotic drug development is at the fringe of economic viability and this commitment is unlikely to persist as these barriers are progressively increased.

It is worth stating that no government has successfully discovered and developed an antibiotic, and it is unlikely that any public body would have the resources or technical ability to do this. Thus, we are essentially dependent on the pharmaceutical industry to provide us with new antimicrobial agents and there needs to be a dialogue between stakeholders on how this can best be achieved. Encouragingly, the pharmaceutical companies that have maintained antibiotic R&D, despite mounting disincentives, have done so partially because of a strong heritage in the area and a depth of expertise. A new impetus is needed to kick-start antibiotic R&D again and shift the perception of this therapy area from being a ‘nice to keep’ component to a ‘must have’ for these companies.

The options outlined below provide some examples of how antibiotic R&D could be encouraged and sustained. If we are serious about the need to preserve public health in the face of antibiotic resistance, the responsibility for the development of new agents needs to be assumed not just by pharmaceutical companies, but by other stakeholders, including governments, regulators and public health systems.

**Balancing incentives**

Balancing incentives are measures that compensate for the reduction in NPV caused by antibiotic restrictions and the increased risk due to regulatory requirements.

Allowing higher prices for new antibiotics is an obvious incentive that raises NPV. Based on the specific restriction policies and their perceived impact on sales (market penetration), a compensatory price could be agreed. A drawback of this approach is that prices are only currently discussed after regulatory approval has been granted; thus it would still represent an unknown risk. It may also be too inflexible should the environment change and it becomes necessary to use the new agents more widely.

Related to pricing is the possibility for guaranteed orders or national formulary inclusion for an antibiotic that has proved to meet a certain medical need. This would be particularly beneficial for serious, but uncommon, infections, allowing pharmaceutical companies to reduce projected future costs, thus boosting NPV, and anticipate future sales more accurately. However, these arrangements would have to be nonexclusive or have a time limit in order to avoid suppressing the development of suitable follow-on antibiotics to keep ahead of resistance development.

Direct economic incentives have been applied to other areas of pharmaceutical development, most recently to stimulate the development of agents active against anthrax. These include tax incentives, one-off investments for capital expenditure and financial ‘rewards’ or ‘prizes’ for successful innovations. Tax credits on R&D investment may tip the balance in favour of retaining otherwise economically marginal research projects. Tax credits on sales spread the funding burden over the entire tax base, which is potentially more attractive to legislators [1].

Extending the period of patent protection would not only increase the NPV, but would also act as a further incentive for pharmaceutical companies to take a more long-term view in order to preserve...
# Table 1. New molecular entity approvals by the Food and Drug Administration for antibiotics between 1999 to 30th June 2005 [14]

<table>
<thead>
<tr>
<th>Antibiotic (class)</th>
<th>Company</th>
<th>Indication*</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tigecycline (glycycline)</td>
<td>Wyeth Pharma</td>
<td>Complications skin and skin structure infection</td>
<td>2005</td>
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<tr>
<td></td>
<td></td>
<td>Complicated intra-abdominal infection</td>
<td></td>
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<tr>
<td>Telithromycin (ketolide)</td>
<td>Aventis Pharma</td>
<td>Acute bacterial exacerbation of chronic bronchitis</td>
<td>2004</td>
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<td></td>
<td></td>
<td>Acute bacterial sinusitis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Community-acquired pneumonia</td>
<td></td>
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<tr>
<td>Rifaximin (rifamycin)</td>
<td>Salix Pharma</td>
<td>Traveller’s diarrhoea caused by noninvasive <em>Escherichia coli</em></td>
<td>2004</td>
</tr>
<tr>
<td>Gemifloxacin mesylate (fluoroquinolone)</td>
<td>LG Life Sciences Ltd</td>
<td>Acute bacterial exacerbation of chronic bronchitis</td>
<td>2003</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Community-acquired pneumonia</td>
<td></td>
</tr>
<tr>
<td>Daptomycin</td>
<td>Cubist</td>
<td>Complications skin and skin structure infection</td>
<td>2003</td>
</tr>
<tr>
<td>Ceftidoren pivoxil (cephalosporin)</td>
<td>TAP Pharm</td>
<td>Acute bacterial exacerbation of chronic bronchitis</td>
<td>2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pharyngitis/tonsillitis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Uncomplicated skin and skin structure infections</td>
<td></td>
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<td></td>
<td></td>
<td>Complicated intra-abdominal infections</td>
<td>2001</td>
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<tr>
<td></td>
<td></td>
<td>Complicated skin and skin structure infections</td>
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<td></td>
<td></td>
<td>Community-acquired pneumonia</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Complicated urinary tract infections including pyelonephritis</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Acute pelvic infections including postpartum endomyometritis,</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>septic abortion and postsurgical gynaecological infections</td>
<td></td>
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<tr>
<td>Eratapenem sodium (carbapenem)</td>
<td>Merck</td>
<td>Vancomycin-resistant <em>Enterococcus faecium</em> infections</td>
<td>2001</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Nosocomial pneumonia</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Complicated and uncomplicated skin and skin structure infections</td>
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<td></td>
<td></td>
<td>Community-acquired pneumonia</td>
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<tr>
<td>Linezolid (oxazolidinone)</td>
<td>Pharmacia &amp; Upjohn</td>
<td><em>Vancomycin</em>-resistant <em>Enterococcus faecium</em> infections</td>
<td>2000</td>
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<td></td>
<td></td>
<td>Nosocomial pneumonia</td>
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<td></td>
<td></td>
<td>Serious life-threatening infections associated with <em>vancomycin</em>-resistant</td>
<td>1999</td>
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<tr>
<td></td>
<td></td>
<td><em>Enterococcus faecium</em> bacteraemia</td>
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<tr>
<td>Quinupristin; dalfopristin (streptogramin)</td>
<td>Rhône Poulenc Rorer</td>
<td>Acute bacterial sinusitis</td>
<td>1999</td>
</tr>
<tr>
<td>Moxifloxacin (fluoroquinolone)</td>
<td>Bayer</td>
<td>Acute bacterial exacerbation of chronic bronchitis</td>
<td>1999</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Community-acquired pneumonia</td>
<td></td>
</tr>
<tr>
<td>Gatifloxacin (fluoroquinolone)</td>
<td>Bristol-Myers Squibb</td>
<td>Acute bacterial sinusitis</td>
<td>1999</td>
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<td></td>
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<td>Acute bacterial exacerbation of chronic bronchitis</td>
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<td></td>
<td></td>
<td>Community-acquired pneumonia</td>
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<td></td>
<td></td>
<td>Urinary tract infections, pyelonephritis and uncomplicated gonorrhoea</td>
<td></td>
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</tbody>
</table>

*Initial indications on approval only are listed. Specific pathogens for each indication are not listed; refer to prescribing information.
antimicrobial efficacy in the face of resistance. Such changes would require new legislation, and may be opposed by generic manufacturers. However, generic manufacturers do not bear the risks of drug development. Also, patent extensions could be granted for specific indications or for additional indications that are investigated after the initial approval has been granted.

A variation on this idea is the ‘wild-card’ patent extension. In this model, a pharmaceutical company that brings a new and medically useful antibiotic to market could be granted the option of patent extension on any other approved product in their portfolio. This could mean a substantial additional income for a successful and established product. A drawback of extended patent protection is that the burden of funding is placed on patients and payers, rather than spread throughout society. As healthcare systems are under increasing financial pressure, this may be a politically and socially unattractive option [1].

Regulatory reform that would shorten the time to market would also act as an incentive. Even reducing the regulatory process by as little as 1 year would have a significant impact on the attractiveness of a drug development project. As the trend has been toward more stringent regulatory assessments and increased delays, this would require a considerable modification of outlook on the part of the regulatory bodies. However, the FDA has started to address this by introducing priority review, which reduces the time from 10 months to 6 months, for antibiotics that meet certain criteria for medical need based mainly on high prevalence, the seriousness of the infection and limited treatment options, among other things. Although this is a step in the right direction, it is more reactive to the current levels of resistance than proactive regarding future needs. The FDA has also been considering developing a new ‘critical path’ model to streamline drug development [6]. However, any improvements in this process are likely to be applied across the board to all therapy areas and would not realign the discrepancy between the NPV for antibiotics and those for drugs to treat other conditions.

New models of antibiotic R&D

The traditional model of a large R&D effort sustained by the profits of highly commercially successful compounds is no longer working for antibiotic drug development. On the one hand, as the only viable source of new antibiotics, pharmaceutical companies have an ethical responsibility to continue R&D in this area. On the other hand, companies must continue to be profitable to remain in business and have a responsibility to their shareholders to provide risk: return ratios on their investment comparable to other companies, both in the same sector and elsewhere. It is difficult to resolve these issues in an environment where higher risks and lower returns make antibiotic drug development an unattractive area for even the most committed of companies.

Although the notion that prioritising shareholder value over developing new antibiotics may seem economically hard-headed, it should be remembered that shareholders are bearing the risk of developing new pharmaceuticals and, if they are uncomfortable with that level of risk, they are perfectly free to invest in another pharmaceutical company or invest out of the sector altogether.

The problems that we now see in antibiotic development are not new to the pharmaceutical industry. The same issues of economic viability have held back R&D for rare diseases and for diseases associated mainly with the developing world. As a response to this, new models of pharmaceutical development have emerged that may provide a useful guide to future sustainable models of antibiotic development.

Orphan drug status is a strategy that has been applied to find and develop drug therapies for rare diseases. Although definitions of a ‘rare disease’ vary, the World Health Organization estimates that between 5000 and 8000 conditions qualify as a rare disease [15]. More than half of these are genetically related and would require intensive (and costly) efforts to identify and develop therapies. The Orphan Drug Act was introduced in the USA in 1983. The provisions of the Act require that the disease be present in <200 000 patients, and that the costs of R&D cannot be recovered within 7 years. Incentives for orphan drug development include 7 years of market exclusivity, regulatory fee waivers, 50% tax credit on clinical research, grants for clinical research, protocol assistance, priority regulatory review, and research grants for medical devices and medical food [15]. In 2000, similar orphan drug incentives were introduced in Europe [15].
Although market exclusivity may not be appropriate in the case of antibiotics, because of the need for follow-on agents as resistance develops, certainly a package of incentives to encourage R&D based on ‘public health’ needs would be a useful boost to antibiotic drug development.

Partnering agreements between smaller discovery companies, often in the biotechnology sector, and large pharmaceutical companies is another option. As more risk-averse large pharmaceutical companies withdraw from the antibiotic market, and as medical need evolves as a result of the development of antibiotic resistance, niches for smaller, more economically flexible companies are emerging. Small biotechnology companies are more tolerant of higher risk projects, but need further resources and expertise to develop products through clinical trials and into the marketplace. Once a project has reached ‘proof of concept’ stage, investment on the part of larger pharmaceutical companies is more forthcoming, as the risks of failure can be more accurately predicted. In-licensing of products in this way is likely to become more common. However, biotechnology companies still have to satisfy investors that antibiotics represent good long-term investment potential.

Public–private partnerships are a new model of pharmaceutical discovery and development that has been applied with encouraging results for diseases of the developing world. Organisations such as the Medicines for Malaria Venture and TB Alliance have radically improved the outlook for the development of new drugs to fight these diseases. The model roughly follows the normal pharmaceutical development plan with a ‘mini-portfolio’ of different leads being managed according to the relative risk:benefit ratio, but where the element of profit has been reduced or removed, although the cost of goods is an important consideration when trying to minimise prices. The public organisations often bear much of the cost of R&D, with the pharmaceutical partners providing facilities, infrastructure, and scientific, regulatory and manufacturing expertise, as well as covering overhead costs.

These partnerships often also include academic organisations involved in more basic research on disease processes. In fact, one of the major issues in drug development in recent years has been the widening gap between the fast pace of basic scientific research, particularly genomics, and the more sedate pace of drug development [6]. The linking process between these two aspects is often referred to as ‘translational research’. This describes research that tries to convert the advances in our understanding of genetic and biochemical processes, which may represent valid pharmaceutical targets, into screening assays against which large compound libraries can be rapidly tested for activity with the aim of identifying candidate drugs. These compound libraries and the large-scale ultra-high-throughput screening facilities are generally sited within large R&D pharmaceutical companies. Thus, public–private partnerships act as a catalyst to bring together drug targets and the means by which to identify possible candidate therapies, without requiring vast new capital expenditure and without exposing the pharmaceutical companies to a level of risk that cannot be economically justified. If we are truly in a crisis of antibiotic development, then this model is a proven strategy for encouraging innovation within a framework that allows new discoveries to be exploited pharmacologically with a risk profile that is acceptable to commercial pharmaceutical companies.

A recent model of pharmaceutical development challenges the necessity for commercial success in pharmaceutical development. The Institute for OneWorld Health was set up as the world’s first not-for-profit pharmaceutical company to investigate new therapies for neglected diseases prevalent in the developing world. Funding for this enterprise comes from a range of philanthropic sources. However, it must be remembered that funding bodies, just like shareholders, will be cautious of high-risk projects unless the need is acute and alternative approaches are lacking. Furthermore, the capital outlay required for antibiotic research is likely to be beyond even the most generous donations, and access to the R&D capabilities of pharmaceutical companies, particularly in the discovery phase, would still be required.

**CONCLUSIONS**

Resistance is inevitable if we use antibiotics at all. We must use antibiotics, but we must use them wisely. Policies that aim to manage resistance development and spread are being set every day. However, the consequences of these policies on resistance [16], as well as on clinical outcomes,
remain essentially unknown (see Price, this supplement, page 3).

Many pharmaceutical companies pulled out of antibiotics in the early 1980s, because of a lack of medical need. Today, as a result of increased market and regulatory barriers, the remaining companies working in this area are finding it increasingly difficult to justify continued research aimed toward antibiotic drug development. As it takes 8–12 years to bring a new pharmaceutical agent to market [17], we cannot afford to wait until we are in crisis. We understand so little about the dynamics of antibiotic resistance development in the community that predicting the next crisis is a hit and miss affair, and we need to spread our efforts for drug development across a range of potentially dangerous public health outcomes. Innovation and investment in antibiotic development has to be proactively encouraged to ensure that the next generation of antibiotics is not too little too late.

REFERENCES


