

# Where have all the antibiotic patents gone?

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**Patent and regulatory hurdles combined with low returns on investment are stifling antibiotic R&D in the pharmaceutical industry.**

Since the discovery of penicillin by Alexander Fleming in 1929, many bacterial infections that were once fatal have become treatable with antibiotics. Although Fleming never patented penicillin, virtually every newly discovered antibiotic since 1929 has been patented. These include erythromycin, vancomycin, rifamycin, clarithromycin, ciprofloxacin and azithromycin. The vast majority of patents related to antibiotics are assigned to pharmaceutical and biotech companies. However, recent years have witnessed a marked slowdown in the development of new antibiotics. Accordingly, there are fewer patent applications filed with the US Patent and Trademark Office (USPTO) for new antibiotics, and fewer patents issuing from these applications. This article examines some of the reasons why there is less antibiotic research and suggests some solutions that may alleviate this problem.

major pharma companies are still players in the antibiotics market, it seems that they are losing interest in these drugs. A 2004 study reported that out of more than 506 drugs in development, only five were new antibiotics<sup>1</sup>. We have updated this analysis using company websites, annual reports and information available at the website of the US Food and Drug Administration (FDA) and other sources. Since 1998, only nine antibiotics or new uses of old antibiotics have been approved by the FDA, and only six antibiotics are in phase 2 or phase 3 clinical trials (Table 1). In contrast, there are approximately 313 non-antibiotic drugs in phase 2 or phase 3 trials. Moreover, of the approved antibiotics, only four are truly novel: that is, either exhibiting a new mechanism of action or exhibiting a structure different from that of antibiotics already on the market.

Of the companies examined, only eight seem to be currently conducting antibiotic R&D: Pfizer, Merck, Johnson & Johnson, GlaxoSmithKline, Wyeth, Bristol-Myers Squibb, Sanofi-Aventis and Schering-Plough. Of these, Pfizer is the leader, having obtained FDA approval for three antibiotics since 1998. Of the three, only two represent new mechanisms of action: Eraxis (anidulafungin) and Zyvox (linezolid). The third antibiotic is an extended-release formulation of an oral suspension of an existing drug, Zithromax (azithromycin). Currently, Pfizer has two antibiotics in phase 2 or phase 3 trials. In addition, since 1998, only four other companies—Merck, Wyeth, Bristol-Myers Squibb and Sanofi-Aventis—have obtained approval for any antibiotics. These data strongly imply that pharma companies are developing fewer antibiotics in comparison with other therapeutic categories.

## Shifting research priorities

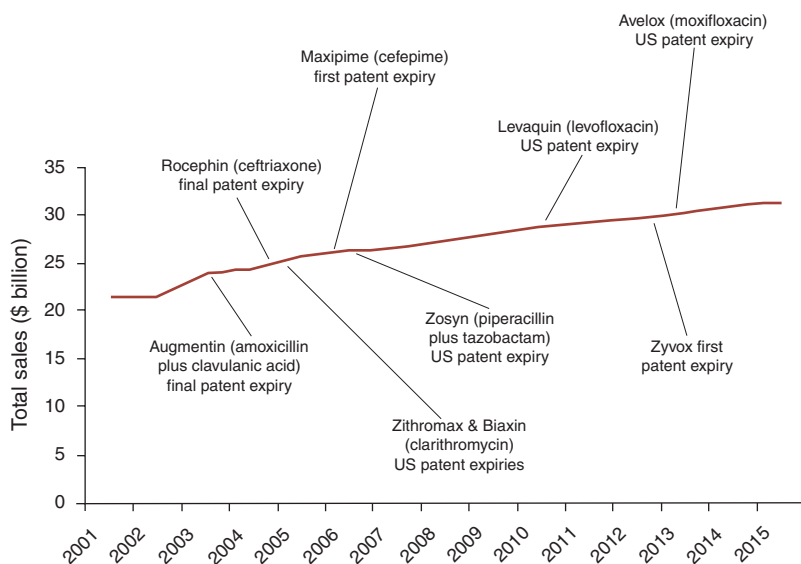
One possible reason for the slowdown in antibiotic research may be the advances in healthcare that have prevented the occurrence of epidemics requiring new antibiotics. At the same time, there are still no satisfactory treatments for many chronic diseases such as arthritis and cancer, and for some relatively recent diseases, such as AIDS. Faced with relatively little societal pressure to develop new antibiotics, companies have shifted their resources to developing other, more profitable drugs.

A review of some of the largest pharmaceutical firms reveals that the pipeline of new antibiotics is fairly scarce. Although the

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**Table 1 Antibiotic development at selected major pharmaceutical companies**

Company	New antibiotics or new uses of old antibiotics approved since 1998	New antibiotics approved since 1998	Number of antibiotics in phase 2 trials or beyond	Approximate total number of drugs in phase 2 trials or beyond
Pfizer	3	2	2	16
Merck & Co.	1	1	1	26
Johnson & Johnson	0	0	1	18
GlaxoSmithKline	0	0	1	34
Wyeth	1	1	0	12
AstraZeneca	0	0	0	24
Bristol-Myers Squibb	1	0	0	8
Sanofi-Aventis	2	0	0	31
Novartis	0	0	0	41
F. Hoffmann-La Roche	0	0	0	16
Abbott Laboratories	0	0	0	7
Eli Lilly & Co.	0	0	0	13
Schering-Plough	1	0	1	13
Bayer	0	0	0	4



**Figure 1** Antibacterial sales forecasts from 2005 to 2015, and key patent expirations. The patent expirations of some of the leading antibacterial drugs will inevitably lead to further incursion into the market by generic drugs. Although the degree of generic incursion following patent expiration tends to vary considerably between different countries and also between individual products, most brands experience declining sales following the launch of cheaper copies. Source: Datamonitor. Report: Commercial Insight: Antibacterials, December 2006.

**A raised utility bar**

Although it seems that antibiotic R&D has become a low priority for many pharma and biotech companies, another possibility for the decline in the number of patent applications being filed and issuing may be the US patent process. In order to obtain a US patent, an invention must be new, useful (namely, possess ‘utility’) and nonobvious. In response to the criticism that prior utility guidelines were too liberal, in January 2001 the USPTO issued new guidelines<sup>2</sup>. Although these guidelines were stated to be applicable to all inventions, specific examples were included for biotechnology and large generic chemical applications.

Under the new guidelines, an examiner is required to review an application to determine whether or not the applicant has asserted a “specific” and a “substantial” utility for the claimed invention. If an asserted utility is specific and substantial, the examiner must determine whether or not the asserted utility would be “credible.” For example, patent applications claiming recombinant proteins that assert that such proteins are useful for treating certain types of bacterial infections may be receiving rejections for lacking utility.

**Regulatory hurdles**

Another factor contributing to the low number of antibiotics in the R&D pipeline may be the significant time and cost involved in discovering and developing a new drug and obtaining marketing approval from the FDA. According to the Tufts Center for the Study of Drug

Development, the cost of developing a new drug rose from \$231 million in 1987 to about \$802 million in 2001, with one of the major reasons for the increase being the rising cost of clinical trials<sup>3</sup>. Some antibiotics may be subject to particular scrutiny by the FDA because certain antibiotics, such as grepafloxacin, have been found to cause cardiac problems, such as the prolongation of the QT interval, which is a measure of the time between the start of the Q wave and the end of the T wave in the heart’s electrical cycle. QT prolongation is known to cause ventricular tachyarrhythmia, which can cause sudden cardiac death<sup>4</sup>. If a new antibiotic is found to cause QT prolongation during preclinical testing, millions of dollars in additional R&D costs will be needed if the antibiotic is to have any chance of receiving FDA approval.

The risks inherent in developing new antibiotics are further demonstrated by two recent cases. The first surrounds Sanofi-Aventis’s Ketek (telithromycin), which was approved by the FDA in 2004. In June 2006, an FDA official warned that Ketek might cause severe liver damage, blurred vision, loss of consciousness and even death. Moreover, the official stated that there was no evidence that Ketek worked any better than any of the other, safer drugs already on the market<sup>5</sup>. Although Ketek is still on the market, this incident underscores the risks companies face in developing new antibiotics.

The second case relates to faropenem medoxomil, a novel antibiotic being developed

by Replidyne and Forest Laboratories. In December 2005, Replidyne submitted a new drug application for four adult indications, based on the results of eleven phase 3 clinical trials and a safety database of more than 5,000 patients treated with the antibiotic<sup>6</sup>. In October 2006, the FDA issued a ‘non-approvable’ letter recommending further clinical studies for all indications. Replidyne and Forest estimated that it would take at least two years to complete the additional clinical studies. Further, the FDA stated that for two of the indications, superiority studies may be needed. Whereas the current criterion used by the FDA for evaluating new antibiotics is non-inferiority (that is, the manufacturer must demonstrate that the new antibiotic is not inferior to currently available antibiotics), there seems to be a shift by the FDA towards a requirement of demonstrating superiority. Although superiority may be a better indicator of the usefulness of a drug, such a requirement may very well lead to even less research in the antibiotic field.

**Lost profits**

Other factors affecting companies’ decisions regarding antibiotic R&D programs include the difficulty in improving upon the efficacy of currently available antibiotics and the low return on investment compared with investing in the research of non-antibiotic drugs. Assuming the costs of developing antibiotics and other drugs are about the same, it is inherently more profitable to develop non-antibiotic drugs. Whereas one patient might require a full year of therapy for a chronically administered drug (such as an anticancer drug, antiarthritis drug, etc.), most antibiotic drugs are administered for about a week, and therefore, it would take 52 patients to achieve a similar financial return. In other words, from a commercial perspective, it is more profitable for companies not to engage in antibiotic research.

As with other therapeutic areas, the commercially successful development of some antibiotics is often a result of the discovery of a new use of an existing drug. However, companies may not be as likely to invest in the development of a drug for a new use, as patent protection for new uses is not as effective as for the drug itself. Although US patent laws allow one to obtain a patent for the discovery of a new use of an existing product, such patents are hard to enforce. Once the patent for the drug itself expires, generic companies are free to market generic versions for a fraction of the cost of the brand name compound (Fig. 1). Although there may exist a patent protecting a second indication for the

compound, pharma companies are unlikely to sue doctors who may still prescribe it for the second use. Additionally, because doctors and patients may often use a formulation approved for one use to treat another indication, pharma companies may not be inclined to develop a new dose, dosage form or brand name for a second use (which would have provided more effective protection). Therefore, there are fewer incentives for companies to invest in a product for a second use as compared with a new drug. One possible solution for this problem may lie in extending market exclusivity for the compound once a second use is approved.

### Conclusions

There seems to be less antibiotic R&D, and accordingly fewer patent applications being filed for antibiotics and even fewer patents issued. The reasons for this are wide-ranging and relate to both patent law and business

decisions made by pharmaceutical companies. Clearly, pharma are assigning a lower priority to antibiotic R&D programs or eliminating them altogether. Contributing factors include higher R&D costs associated with developing new antibiotics and then guiding these drugs through the FDA, difficulties in improving the efficacy and safety of new antibiotics, and difficulties in discovering new drugs effective against multiple strains of bacteria.

According to the Infectious Disease Society of America (IDSA), one of the main problems with currently available antibiotics is the rise in antibiotic resistance. In 2004, more than 70% of pathogenic bacteria were estimated to be resistant to at least one of the currently available antibiotics<sup>1</sup>. It is therefore crucial that new antibiotics be developed. Although there is no impending silver bullet, some of the IDSA's recommendations seem advisable, such as simplifying the FDA's approval process for antibiotics, granting priority antibiotics

accelerated review process at the FDA and providing financial incentives to companies engaged in antibiotic research. These incentives could include extending market exclusivity for antibiotics (especially when second uses are discovered) and providing longer patent term extensions to compensate for longer and costlier developments of antibiotics as compared to chronically used drugs.

1. Bad bugs, no drugs: as antibiotic R&D stagnates... a public health crisis brews (Infectious Diseases Society of America, Alexandria, Virginia, 2004).
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3. Tufts Center for the Study of Drug Development pegs cost of a new prescription medicine at \$802 million. <http://csdd.tufts.edu/NewsEvents/RecentNews.asp?newsid=6> (2001).
4. Fermini, B. & Fossa, A.A. *Nat. Rev. Drug Discov.* **2**, 439–447 (2003).
5. Harris, G. Approval of antibiotic worried safety officials. *New York Times* (19 July 2006).
6. FDA rejects Replidyne drug application. *Denver Business Journal* (23 October 2006).