

# Antibiotics—an investment worth making?

Ralph E Christoffersen

**Antibiotics markets are huge and the need for new classes of antibiotics is great, but the risks give investors pause.**

**D**emand for new and more effective antibiotics continues to grow, particularly as bacterial resistance to existing antibiotics spreads. Moreover, the development of new anti-infectives should, by most measures, lend itself to continued biotech investment by venture capitalists. Clinical endpoints are generally clear and the markets for individual drugs are both large enough for substantial returns and small enough to limit competition from big pharma.

Yet, although a number of antibiotic companies have been created over the past 15 years, including several with successful exits, the dangers from new regulatory, political, scientific and clinical trends are increasing. The result is likely to be greater caution by venture capital investors.

## The market

On first consideration, investing seems to be an obvious opportunity. The market for antibiotic drugs is huge. In 2005, worldwide sales of oral antibiotics totaled \$25.0 billion (**Fig. 1**), including US sales of \$8.5 billion (\$7.0 billion for adults and \$1.5 billion for children). The area also continues to grow at a significant rate, with adult and pediatric prescriptions growing 8.5% and 10.8%, respectively, in 2005.

In addition, development of antibiotic resistance has emerged as a significant medical challenge (especially methicillin-resistant *Staphylococcus aureus*, or MRSA). Virtually every antibiotic on the market today is subject to development of resistance to its effectiveness by bacterial mutation, and the need for new classes of antibiotics that the bugs haven't seen



Antibiotic ventures—still a sufficiently attractive prospect for investors to touch?

is high. Unfortunately, only three new classes of antibiotics have been discovered in the past 50 years. Two of the new classes (oxazolidinones and cyclic lipopeptides) have specific products approved for use, and another new class has been identified recently (platensimycin), but the need for new classes remains great. In addition, the use of microbes as agents of bioterrorism has created an even greater need for new antibiotics.

Thus, there is little risk that there will not be an adequate market for successfully developed new antibiotics. These could include any and all new analogs of existing antibiotics, new classes of antibiotics that may avoid or delay antibiotic resistance and antibiotics to combat microbes used by terrorist organizations.

## Rules for approval and use

The appropriateness of using antibiotics and the rules for developing them are well established. From the invention of penicillin in the

early twentieth century to today, it has been recognized that bacterial infections are not always cleared by innate immunological processes. However, many antibacterial drugs have been shown to be safe and effective ways of treating, and usually curing, bacterial infections.

Furthermore, rigorous processes have been developed for determining whether candidate antibacterial drugs are safe and effective. These include guidelines published by the US Food and Drug Administration (FDA) in 1998 ([http://www.access.gpo.gov/nara/cfr/waisidx\\_98/21cfr314\\_98.html](http://www.access.gpo.gov/nara/cfr/waisidx_98/21cfr314_98.html)), historical records of FDA antibiotics approvals that provide examples of implementation of the FDA guidelines and recommendations for use of antibiotics in practical situations by such prestigious agencies as the Sinus and Allergy Health Partnership (Washington, DC, USA), the American Academy of Pediatrics (Elk Grove Village, IL, USA) and the Infectious Disease Society of America (Alexandria, VA, USA).

In addition, before pivotal trials, the FDA usually agrees with a company, in writing, about the protocols and clinical endpoints that will be acceptable for approval. In other words, the rules for antibiotics development and the ways in which antibiotics are to be used are well established and provide a clear pathway for developing new antibiotic compounds. Thus, regulatory risk should not be expected to be a significant deterrent to developing new antibiotics, if the development plan is agreed upon in advance with the regulatory agency.

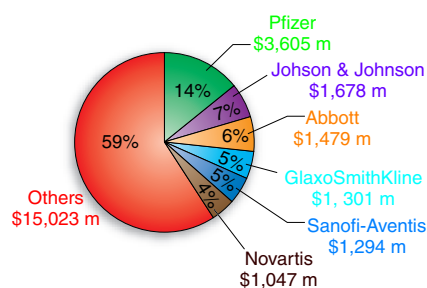
## Unambiguous endpoints

Preclinical and clinical endpoints are quickly obtained and are quantitative and relatively unambiguous. When considering a new potential antibiotic product, several cell-culture assays and animal models to measure efficacy are available that have been validated and are known to be predictors of the drug's activity in humans. Basically, the drug either kills the bug or not, and subsequent questions deal only

*Ralph Christoffersen is a General Partner at Morgenthaler Ventures, 4430 Arapahoe Avenue, Suite 220, Boulder, Colorado 80303, USA.*

*Morgenthaler is an investor in Replidyne, Inc., and Christoffersen is a member of the Board of Directors of Replidyne.*

*e-mail: rchris@morgenthaler.com*



**Figure 1** The antibiotics market is over \$25 billion in size, although much of it comprises generic sales. Source: Commercial insight: antibacterials (Datamonitor/IMS Health, London, December 2006).

with safety and the most appropriate dose and treatment schedule.

Human clinical trials are short (antibiotic treatment courses typically are 5–14 days), endpoints are unambiguous and safety issues are minimized because of the acute treatment setting. And, under official guidelines for non-inferiority trials, patient recruitment is straightforward and easy. From an investment perspective, this means that the scientific and clinical risk can be evaluated rapidly (in contrast with, for example, the time needed for preclinical and clinical trials of treatments of chronic diseases), thus minimizing the time to failure (or maximizing internal rate of return if successful) and removing scientific and clinical uncertainty. This can become an important criterion for investment, when placed into the context of desired returns from venture capitalists to limited partners within a five- to six-year investment horizon.

### Pharma's retreat

Several major pharmaceutical companies have decided that antibiotic products do not meet the 'blockbuster' criteria for sales and, because of this and other factors, have left the marketplace. Antibiotics, for the most part, have annual sales in the <\$1 billion category, and a competitive label for an antibiotic to be used by general practitioners as well as in hospitals will usually need several indications (four or more). The latter requirement means that multiple clinical trials, two per indication, will be needed, making the total product-development costs quite high. As a result, the decision of several major pharmaceutical companies, including Sanofi-Aventis (Paris) and Bayer (Leverkusen, Germany), has been to exit the antibiotic field.

However, if a biotech company could either develop an internal marketing and sales organization or find a commercialization partner adequate to serve the market for the product,

a new antibiotic with sales in excess of \$100 million would be viewed as a major success. Furthermore, the exit of major pharmaceutical companies from the space has both reduced the competition for market share for biotech companies and increased the number of senior executives with antibacterial development and marketing expertise available to the biotech community. For example, Replidyne (Louisville, CO, USA) was able to attract very senior persons with many years of experience from Bristol Myers Squibb (New York) and Abbott (Abbott Park, IL, USA) to lead their antibiotics' clinical development and commercialization. Thus, the available market niche for biotech companies with new antibiotics seems to be substantial.

### So what's the problem?

In the US, the regulatory climate is currently dominated by political influences and lack of leadership, resulting in retrospective changing of regulatory policies and significant additional costs for drug development. Although the FDA has not published even draft changes to the published 1998 guidelines for antibiotics approvals, recent FDA actions seem to have been influenced by two sets of arguments, one scientific and one political.

First, some question whether anti-infectives work at all for diseases that are usually self-limiting such as influenza and bronchitis. To answer the question, some within the FDA propose use of either placebo-based clinical trials or 'superiority' trials to demonstrate efficacy of antibiotics rather than the current standard of 'non-inferiority' trials. A 2003 anti-infectives advisory committee to the FDA, for example, recommended that clinical trials for drugs to treat bronchitis should be done as superiority trials. Opponents to this point of view argue that antibiotics have been shown conclusively to be valuable in treating, and usually curing, diseases such as bronchitis and question the need for change and, indeed, the ethics of placebo-control testing.

Second, questions of scientific fraud surrounding trials of Sanofi Aventis' antibiotic Ketek (telithromycin) have intensified existing public suspicions about drug companies' clinical trials and attracted the attention of Congress<sup>1</sup>. 'Tighter controls' have become the political watchword and have overlapped with the academic pressure for 'purer' testing. The situation has not been helped by the absence of an appointed leader of the FDA. At the very least, a severe lack of regulatory clarity has resulted.

For example, the FDA approved Levaquin (levofloxacin; Ortho-McNeil, Raritan, NJ, USA) for acute bronchitis as recently as August 2005, on the basis of noninferiority clinical trials and the 1998 guidelines, and no changes have been made to any package inserts of antibiotics already approved for treatment of acute bronchitis on the basis of non-inferiority clinical trials. On the other hand, in recent actions, the FDA has changed course dramatically by declining to approve either Factive (gemifloxacin mesylate; Oscient Pharmaceuticals, Gaithersburg, MD, USA) in September or faropenem (Replidyne, Louisville, CO, USA, and Forest Laboratories, New York) in October on the basis of successful non-inferiority trials. These nonapproval letters resulted despite agreements between the FDA and the company sponsors before initiation of the trials that non-inferiority clinical trials would be acceptable for approval.

The prospective changes in regulatory guidelines and approval criteria are quite appropriate, especially those based on new scientific and clinical insights. However, the arbitrary retrospective changes without even draft guidance from the FDA, which have cost companies millions, are totally unacceptable, especially when political influences and lack of FDA leadership seem to have played a nontrivial role in the process. Such actions will surely have a chilling effect on the willingness of the investment community to make additional investments in new antibiotics.

**Table 1 Private US biotech antibiotic companies since 1992**

Company	Year formed	Amount invested (\$ millions)
Achaogen (S. San Francisco, CA, USA)	2004	41
ActivBiotech (Lexington, MA, USA)	1996	63
Cerexa (Alameda, CA, USA)	2005	66
Elusys Therapeutics (Pine Brook, NJ, USA)	1998	53
Paratek Pharmaceuticals (Boston, MA, USA)	1996	78
Peninsula Pharmaceuticals (Alameda, CA, USA); acquired by Johnson & Johnson (New Brunswick, NJ, USA) for \$245 million in March 2005	2001	93
Rib-X Pharma (New Haven, CT, USA)	2001	120

**Table 2 Public US biotech antibiotic companies since 1992**

Company	Year formed	Initial public offering	Market cap as of 24 October 2006 (\$ million)
Advancis Pharmaceutical (Germantown, MD, USA)	1999	2003	133.5
Cubist Pharmaceuticals (Lexington, MA, USA)	1992	1996	1,222.0
Inhibitex (Alpharetta, GA, USA)	1994	2004	47.8
Oscient Pharmaceuticals (Waltham, MA, USA); merger of Genome Therapeutics (Waltham, MA, USA) and GeneSoft (S. San Francisco, CA, USA)	2004	NA	96.9
Replidyne	2000	2006	144.1
Vicuron; merger of Versicor (Fremont, CA, USA) and BioSearch Italia (Gerezano, Italy); purchased by Pfizer (New York) in June 2005 for \$1.9 billion	2003	NA	NA

NA, not applicable.

### Obstacles may prevent adequate returns

Markets may be large, but reimbursement policies, scientific hurdles and the lack of federal incentives to encourage research and development in the area may limit the ability to achieve adequate returns. Because nearly all new antibiotics are improved analogs of existing classes of antibiotics, many reimbursement agencies (especially outside the US) take the view that the new products are simply 'me-too' mimics of existing drugs and provide low reimbursement rates. Moreover, nearly 60% of the antibiotics market is already generic, thus increasing pricing pressures further. This endangers the ability of a company to recover costs and make a reasonable profit, and discourages investment in the area. At the same time, creating new classes of antibiotic therapeutics has turned out to be very difficult, despite an ever-expanding array of approaches for sampling bacterial diversity and the introduction of high-throughput screening of small-molecule libraries, microbial genomics and metagenomics, and even new types of combinatorial biosynthesis.

Another paradoxical problem has arisen in the area where the greatest need exists. Although MRSA resistance now represents a significant and increasing problem, especially in hospitals, research toward developing new antibiotics that are effective against MRSA (whether analogs of existing antibiotics or new classes of antibiotics) faces the danger that success may actually limit opportunities

to the point that the drug is not commercially viable. This is because so little is available in the antibiotic armamentarium for treatment of MRSA infections that hospital pharmacy and therapeutics committees may place any new agent with MRSA in the label (regardless of how broad the label is in addition to MRSA) on a list of restricted drugs, limiting its use to only those cases where MRSA has been definitively diagnosed.

Another complication relates to the small number of big pharma companies left in the antibiotics area; this means that it is difficult for biotech firms to find partners of sufficient size and scope who are capable of marketing an antibiotic intended for broad distribution to general practitioners. Although several new entrants have alleviated this problem somewhat, it remains a challenge for many biotech products in the antibiotics space.

Hope that encouragement of antibiotics research and development would be provided by the US government has been offered by several proposed initiatives, only to fail in their implementation. BioShield I was intended to provide federal incentives for bioterrorist antibiotic research and product development, but the rules implementing the law provide for reimbursement of expenses only after the FDA has approved the drug—hardly an incentive for venture capitalists and companies to spend millions at risk before FDA approval. BioShield II was intended to fix that problem but is still in congressional limbo.

### The bottom line

The combination of significantly increased regulatory risk and shrinking margins make it tough to argue for continued antibiotic investment. Despite the challenges, venture capital investment in antibiotics companies over the past 15 years or so has been remarkably robust (Tables 1 and 2). No fewer than 13 US companies were formed, with 6 of them becoming public companies during the period. More than \$500 million has been invested by venture capitalists in seven companies that remain private, and it is likely that a similar amount was invested in the companies that have become public. Given the average annual investment of nearly \$100 million in biotech antibiotic companies over a period of more than ten years, it is clear that venture capitalists believed this was a space that warranted investment.

Despite this investing history, the huge medical need and the very large potential markets, it is clear that a significant change has recently occurred in the landscape for antibiotics investment. The result of political meddling, lack of FDA leadership and inconsistency of regulatory policies, together with the difficulty of creating new classes of antibiotics to meet growing antibiotic resistance, has now made investing in antibiotics companies a tough sell. A few biotech companies pursuing clever strategies will probably find ways to success, but it won't be easy.

1. Anonymous. *Nat. Rev. Drug Discovery* **5**, 446–447 (2006).