

Chapter 1

ANTIBIOTIC RESEARCH AND DEVELOPMENT: AN INDUSTRY IN TRANSITION

The current crisis in antibiotic research and development (R&D)—an industry pipeline with few late-stage candidates up to the task of combating the emergence and spread of novel, drug-resistant bacterial strains—is a challenge that must be met. It is a public health (some might argue moral) imperative. The Infectious Diseases Society of America sounded the alarm very loudly in its famous *Bad Bugs, No Drugs* report a few years back (IDSA 2004). Based on a year-long study of the recent decline in antibiotic R&D, which involved interviewing stakeholders from all sectors (i.e., from government to private industry), the IDSA concluded that while the biological inevitability of resistance and government inaction are both significant contributing factors to the current crisis, calming this crisis will necessarily revolve around industry effort:

“Based upon past successes, the pharmaceutical and biotechnology industries are clearly best situated to take the lead in developing new antibiotics needed to treat bacterial diseases. As such, industry action must become the central focus of an innovative federal public health effort designed to stimulate antibiotic R&D.”

The challenge of resistance requires not just a new way of doing business (which it does, and which much of this report explores). It also requires a better scientific understanding of the biology of resistance. This report highlights steps currently being taken in both directions (i.e., business and science) by both large and small pharma. Chapter 1 begins by exploring current major drivers of the industry; reasons for the exodus of large pharma from the field and opportunities being seized by those that stayed; and the challenges and opportunities for new, small pharma competitors.

1.3. Economics of Antibiotics: Contrary to Popular Opinion, Antibiotics Can Be Lucrative

“It has been reasoned that it makes more commercial sense to treat chronic conditions requiring years of therapy rather than curing disease with short courses of treatment. The use of this pharmaceutical industry calculus has long been the rationale for the chronic under-resourcing of antibacterial research programs (not to mention anemic public funding for studying pathogenic bacteria and antibacterial drug resistance), but this actually flies in the face of commercial and public health realities. Not only are infectious disease therapeutics the second-largest source of revenue for pharmaceutical companies (behind cardiovascular drugs), with antibacterial drugs taking the lion’s share, but there are no fewer than six branded products garnering over \$1 billion annually, this despite fierce generic competition. No other area of therapeutic focus can boast this level of commercial, not to mention therapeutic, success.”

- Steven J. Projan (Projan 2002)

Despite the general perception that antibacterial sales are not large, global sales are actually quite significant and several antibiotics have reached blockbuster status. For example, GlaxoSmithKline’s (GSK) Augmentin, a combined beta-lactam/beta-lactamase inhibitor, brought in about \$1 billion in 2007. Of course, as with any pharmaceutical, patent expirations and eventual generic competition limit the lifetime of blockbuster returns. For example, GSK’s anti-bacterial sales declined 1% in 2007, compared with 2006 sales, to a total of £1,330 million, or about \$2.7 billion, because of increased global generic competition. But the same could be said of any blockbuster drug, and it is difficult to deny that Augmentin and other once-branded blockbuster antibiotics were worth the effort.

The question, of course, is whether the blockbuster business model is still viable—a question explored in more detail in Chapter 4. Clearly, many companies think so, as experts interviewed for this report alluded, including even single-indication antibiotics. At the same time, many experts and companies are realizing that the potential earnings from smaller-than-blockbuster drugs can be significant, worthwhile, and perhaps more viable in the long term.

Blockbuster or not, the need for novel antibiotics—with novel mechanisms of action—has not been this pressing since the mid-1900s (when antibiotics were first discovered and developed), not just because

Chapter 2

THE DIFFICULT SCIENCE OF ANTIBACTERIAL DISCOVERY

“Most alarming of all are diseases where resistance is developing for virtually all currently available drugs, thus raising the specter of a post-antibiotic era. Even if the pharmaceutical industry were to step up efforts to develop new replacement drugs immediately, current trends suggest that some diseases will have no effective therapies within the next 10 years [i.e., 2012!].”

- World Health Organization (WHO 2002)

“The growing resistance problem is the result of a multiplicity of drivers. It is often emphasized that a number of these drivers fall under the general headings of inappropriate use and overuse of antibiotics. However, it is also important to recognize that the development of antibiotic resistance is an inevitable process, and one that some bacterial species are particularly well adapted for.”

- AJ O'Neill, University of Leeds, Antimicrobial Research Centre & Institute of Molecular and Cellular Biology (O'Neill 2008)

Many scientific and industry leaders consider the current antibiotic resistance crisis the beginning of a re-entry into the “pre-antibiotic era.” In reality, we are on the verge of entering a “post-antibiotic era” since, unlike the bacterial strains that existed decades ago, as Dr. Prabhavathi Fernandes, CEO and president of Cempra Pharmaceuticals (a start-up firm in Morrisville, NC) wrote in a historical commentary published in *Nature Biotechnology* in 2006: “In reality, the situation will be far worse because today’s bacterial strains are not only resistant to commonly available antibiotics, but more importantly may also have acquired virulence genes. As a result, even commonly occurring bacteria have been transformed into invasive and toxin-producing pathogens” (Fernandes 2006). Of course, if the WHO projection—that there will

- Advanced Life Sciences' cethromycin (a ketolide antibiotic)
- Arpida's iclaprim (a diaminopyrimidine antibiotic)
- Inimex Pharmaceuticals (a novel antibacterial approach)
- Novozymes (antibacterial peptides)
- Profos (phage proteins)
- Targanta Therapeutics' oritavancin (a glycopeptide antibiotic)
- Theravance's telavancin (a glycopeptide antibiotic).

Table 3.1. Snapshot of the Late-Stage Antibacterial Pipeline

Company	Product	Drug Class	Gram Positive or Gram Negative?	Hospital or Community?	Current Status
Advanced Life Sciences (license from Abbott)	Cethromycin	Ketolide	Gram positive	Community	Has completed 2 pivotal Phase III trials; preparing for NDA submission.
Arpida	Iclaprim	Dihydrofolate reductase inhibitor	Gram positive	Hospital	"Rolling NDA" nearly complete as of February 2008.
Basilea and Johnson & Johnson	Ceftobiprole	Cephalosporin	Gram positive & Gram negative	Hospital; initial indication is for patients with cSSSI, including diabetic foot infections	Has completed Phase III trials. Received an approvable letter from the US FDA in March 2008 regarding its NDA, which was submitted in May 2007.
Cerexa (a wholly owned subsidiary of Forest Laboratories)	Ceftaroline	Cephalosporin	Gram positive & Gram negative	Hospital	Two Phase III trials in cSSSI were initiated in February 2007. In January 2008, Forest and Novexel (Paris, France) announced a development, manufacturing, and commercialization agreement for the co-administration of ceftaroline with Novexel's beta-lactamase inhibitor NXL104.
Oscient	Ramoplanin	Glycopeptide	Gram positive	Community; niche indication: <i>C. difficile</i> -associated disease	Has completed Phase II clinical trial and has received a Special Protocol Assessment for Phase III clinical trial.

Continued

4.3. Challenges from a Biotech Perspective

On the other hand, the fact that big pharma companies are leaving (or have left) the arena makes it more difficult for biotech companies to find partners of sufficient size and with the marketing and sales strength to guarantee broad distribution. Finding a marketing partner is by no means the only option for biotech companies able to get their product that far, but it is one that many companies do consider. Others develop their own internal marketing and sales division.

Regulatory Hurdles and Moving Goalposts: The Need for Clearer Regulatory Guidelines

While the economic challenges may not be as daunting for small pharma as they are for large pharma, the regulatory challenges are more so. Other than resistance, one of the greatest challenges many antibiotic companies currently face is the need for more regulatory clarity regarding drug-approval standards. Without clear approval standards, the already significant risk associated with investing in a product that is already considered a risky investment becomes impossibly large. In the CHI survey accompanying this report (see Chapter 6), when asked what the greatest challenge to antibiotic development is, the greatest proportion of respondents (44.4%) indicated “The emergence of resistance during clinical development.” The next most popular answer (25.9%) was “Lack of clear regulatory guidelines.”

The first antibiotic-specific guidelines were introduced in 1977.

Historically, antibiotic R&D has been a relatively straightforward endeavor in the sense that drug developers have known what their goal was—develop a product for the treatment, if not cure, of bacterial infections. Furthermore, they knew how to do it—follow the regulatory guidelines. The first antibiotic-specific guidelines were introduced in 1977. They provided general regulatory guidelines as well as some details for indication-specific clinical trials. In 1992, the guidelines were updated, and details for minimum requirements necessary for the development of antimicrobials were spelled out in the FDA publication, “Points to Consider: Clinical Development and Labeling of Anti-Infective Drug Products.” In 1998, new draft guidelines were published, again dealing with both general development issues and indication-specific details. The 1998 guidelines were the last antibiotic-specific regulatory guidelines provided by the FDA. In addition to the older 1992 and 1998 published guidelines, drug developers have had access to a long historical record of antibiotic regulatory action and plentiful examples of regulatory recommendations and industry responses to

Chapter 5

COMPANY PORTRAITS AND EXPERT INTERVIEWS

This chapter contains 5 interviews with senior scientists and executives from companies involved in different stages of antibiotic or antibacterial R&D:

1. NovaBay (early stage)
2. Rib-X (early stage)
3. Replidyne (late stage)
4. Cubist Pharmaceuticals (“small pharma” company with a product on the market)
5. AstraZeneca (“large pharma” company with a product on the market)

5.1. Interview with Ron Najafi, PhD, Chairman and CEO, NovaBay Pharmaceuticals, Emeryville, CA

NovaBay is a publicly traded biopharmaceutical company focused on developing innovative product candidates for the prevention of a wide range of infections in both hospital and community environments. NovaBay has 35 employees, including 15 who hold PhDs and 2 who hold MDs. More than half of NovaBay’s employees are involved with R&D activities.

Cambridge Healthtech Institute (CHI): Tell me a little bit about NovaBay’s history– how the company was founded, how it has developed over time, and what its priorities and goals are today.

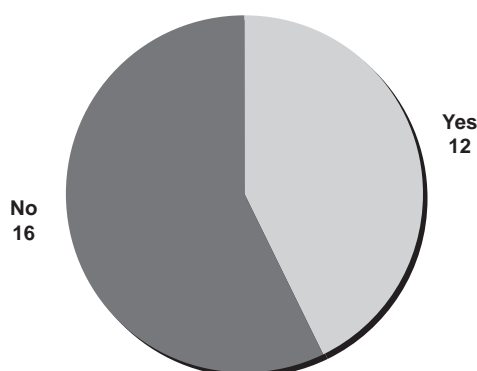
Dr. Ron Najafi: NovaBay began in 2000 with my interest in the chemistry of chlorine and ways of producing a stable form of hypochlorous acid, which is probably the most potent antimicrobial

6.5. Antibiotic Products

Slightly less than half of the respondents (42.9%) are from organizations involved with product launch (Figure 6.11).

Figure 6.11. Organizational Involvement in Product Launch

Has your organization been involved, or will it be involved, in product launch?



$n = 28$

Source: Insight Pharma Reports Antibacterial R&D Survey—March–April 2008

The numbers could simply be an artifact of the survey pool. Yet the fact that most respondents (80.8%) are affiliated with organizations that have yet to launch an antibiotic/antibacterial product might also reflect the recent renewed interest in this field and the entrance of many small pharma and biotech companies (Figure 6.12).