

Executive Summary

Many public health experts and officials consider the emergence and spread of antibiotic resistance as one of, if not the, paramount public health threat of the 21st century. While not a new phenomenon, the emergence and spread of antibiotic-resistant bacteria has reached a state of crisis unlike anything modern healthcare has ever contended with. While most resistant microbes continue to emerge in the hospital setting, physicians and epidemiologists are finding more resistance outside of the hospital environment among people who have never had any previous healthcare contact. In the hospital setting, the number of patients who are dying from untreatable bacterial infections continues to grow.

The antibiotic market has seen only 2 new classes of antibiotics over the past 30 years:

1. The oxazolidinones: Pfizer's Zyvox (linezolid) was the first of this new class of synthetic antibiotic compounds. Approved by the FDA in 2000, growth in the use of Zyvox is among the fastest in the market, second only to Cubicin. Sales totaled about \$944 million in 2007, a 21% increase over 2006.
2. The cyclic lipopeptides: Cubist's Cubicin (daptomycin) is the first of the cyclic lipopeptides, a natural class of compounds. Approved by the FDA in 2003, use of Cubicin is growing at a faster rate than any other antibiotic. Net sales totaled \$290.4 million in 2007, representing a 53% year-over-year increase.

What has caused the current crisis situation? Industry experts interviewed for this report pointed to 3 interrelated factors: (1) the exodus of pharma from the field through the 1980s and 1990s and the loss of knowledge and expertise in antibiotic R&D which ensued, (2) the continual emergence and spread of new antibiotic-resistant bacterial strains, and (3) the difficult economics of antibiotics.

Resistance is a practically inevitable evolutionary response to the selective pressures exerted by antibiotics. Every new antibiotic eventually comes up against newly evolved strains of bacterial cells no longer susceptible to the drug's once-potent effects. Even Pfizer's Zyvox and Cubist's Cubicin have already created new drug-resistant infectious bacterial strains, especially Zyvox because of its longer time on the market.

Antibiotics are short-course therapies intended for acute or semi-acute conditions, not life-long chronic conditions, which translates to limited returns on investment (relative to other therapeutic areas). Added to this is the fact that most new antibiotics almost immediately become drivers of the evolution, or development, of resistance as soon as they become introduced to medical care and the marketplace. Knowing this, and for good reason, efforts continue to be directed toward imposing restrictions on antibiotic usage. However, this also has the unfortunate effect of reducing the potential earnings—a strong disincentive for companies relying on the blockbuster model of pharmaceutical development to become involved with antibiotic R&D.

Combating resistance will require a multi-pronged approach: one focused on prevention and the more judicious use of antibiotics, but one also focused on the discovery and development of not just new antibiotics, but new antibiotics with novel potential to inhibit bacterial growth, reproduction, and resistance—either through novel mechanisms of action or through the inhibition of new targets. Several companies featured in this report are pursuing the discovery and development of new antibiotic compounds. However, far too many of the new compounds are simply improved analogues of already existing compounds, which means that they probably won't be presenting much of a challenge to the bacterial world with respect to combating resistance. By one estimate (Echols 2006), large pharma have only 13 antibiotic compounds in the developmental pipeline, and most of those compounds are in a single antibiotic class: the oxazolidinones.

Dealing with the economic realities of antibiotic development and commercialization will require a shift away from the blockbuster model and one toward niche-market products, such as single-indication antibiotics. While some companies are clearly benefiting from blockbuster earnings today and others expect to do the same with future product launches, the industry has seen a tremendous influx of small pharma players who neither expect nor demand blockbuster returns on their antibiotic R&D investments. While some of these companies have picked up old antibiotic research programs discarded by large pharma players no longer involved in antibiotic R&D, others are

starting from scratch (e.g., with technologies developed in university laboratories). And while many of the smaller players intend, as part of their business plan, to partner with larger companies for production and commercialization purposes, others aim to develop their own internal sales and marketing force.

While the problem calls for a new way of conducting science and business, there is no right new way. Scientists and industry leaders are taking as many different approaches as there are companies. For example, while some have abandoned genomics-based high-throughput screening (HTS) technology of the 1990s (e.g., GlaxoSmithKline), others have embraced it with the realization that it is one component of a larger, integrated system of drug discovery and development (e.g., AstraZeneca). While some companies continue to pursue blockbuster products (e.g., Replidyne), others seek niche-market products (e.g., also Replidyne). While some companies seek, or have sought, their fortune with synthetics (e.g., Merck), others have looked to nature (e.g., Novozymes). While some small pharma companies seek already discovered compounds tossed aside by large pharma (e.g., Cubist), others identify themselves as discovery companies (e.g., Rib-X). Still others seek novel types of antibacterial compounds (e.g., NovaBay) or ways of contributing to the antibiotic development process (e.g., InterMed).

Roadmap of this Report

Chapter 1 explores the factors driving the field forward and the challenges and opportunities for both large and small pharma. Chapter 2 provides an overview of 3 key challenges to antibiotic drug discovery. Chapter 3 highlights select compounds in clinical development for both Gram-positive and Gram-negative bacteria. Chapter 4 explores the economic and regulatory realities of antibiotic R&D. This report is based on expert interviews (see Chapter 5 for transcripts of select interviews); survey results (see Chapter 6); materials presented at Cambridge Healthtech Institute's 2nd Annual "The Challenge of Antibacterial Drug Development" conference, which was held at the Hilton San Diego Resort (San Diego, CA) on April 23–24, 2008; and information gathered from the peer-reviewed scientific literature.

