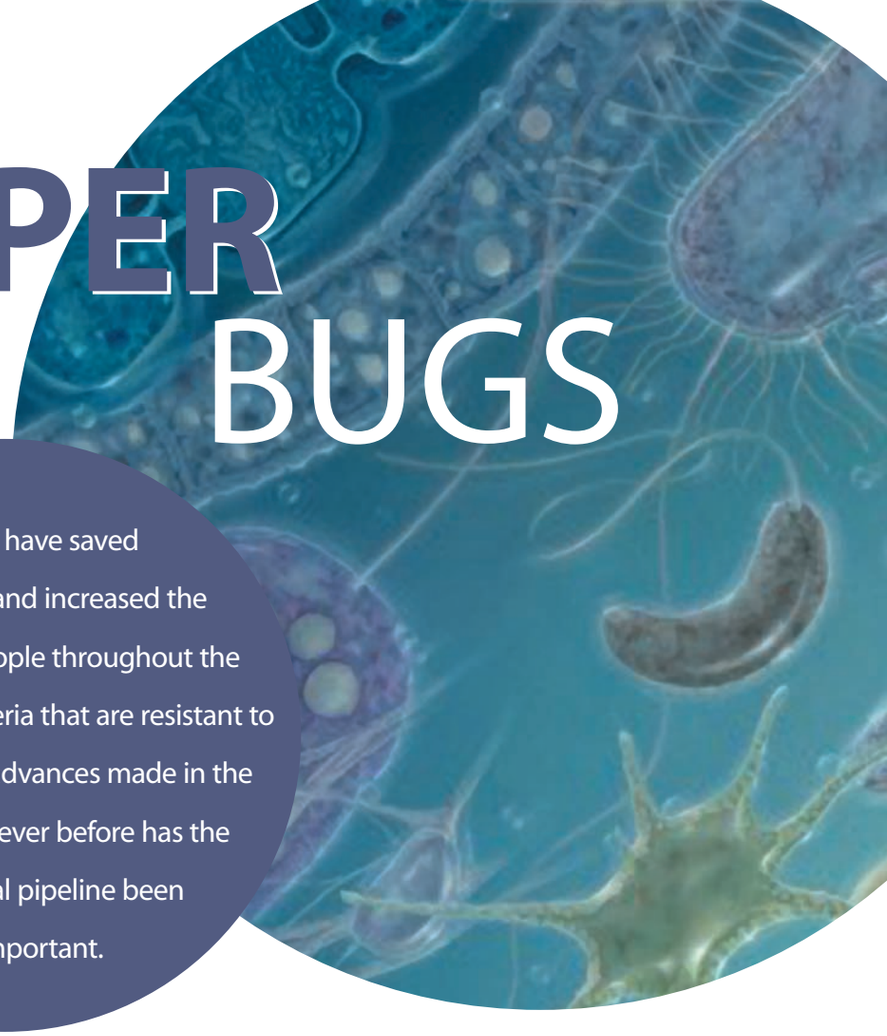
BY CYNTHIA BORDA

SUPER BUGS



Antibiotics have saved millions of lives and increased the quality of life of people throughout the world. Now, new bacteria that are resistant to drugs threaten the advances made in the last half century. Never before has the pharmaceutical pipeline been more important.

Bacteria have proven to be resourceful organisms. They are so resourceful that the widespread use of antibiotics in recent years has enabled bacteria to adapt and develop resistance to currently marketed treatments.

Antibiotics stop infection and the spread of infection, yet they also eventually decrease in effectiveness because of mutations of the pathogen. In fact, more than 70% of the bacteria that cause hospital-acquired infections are resistant to at least one of the antibiotics most commonly used to treat them, according to the National Institute of Allergy and Infectious Diseases.

Drug-resistant infections have become a serious health concern. MRSA, or methicillin-resistant Staphylococcus aureus, caused more than 94,000 life-threatening infections and almost 19,000 deaths in the United States in 2005, according to the Centers for Disease Control and Prevention (CDC).

The proportion of drug-resistant infections has been growing. According to CDC data, MRSA infections accounted for 2% of the total number of staph infections in 1974; in 1995 the rate was 22%; and in 2004 it was 63%.

"There is a continued expansion and progression of resistant pathogens that common empiric treatments no longer cover," says Barry Eisenstein, M.D., senior VP of scientific affairs at Cubist Pharmaceuticals Inc. "Some of these pathogens, for example, MRSA, have emerged in the community, which means emergency departments are now treating infections with drugs that no longer work against these pathogens. This leads to increased treatment failures, including death."

Sales of antibacterials will likely increase by almost **$3 BILLION TO $25.5 BILLION IN 2011.**

Kalorama Information

MARKET IMPACT

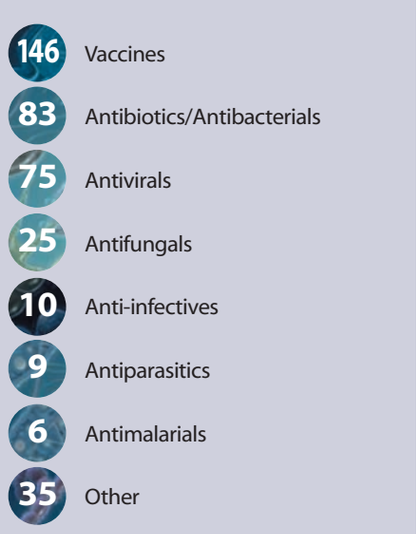
Worldwide, the anti-infective market is expected to grow to more than $45 billion by 2012, according to research by Arrowhead Publishers. This growth will be driven by the uptake of newer antibacterial agents such as glycopeptides and carbapenems, which demonstrate resistance to MRSA and vancomycin-resistant Enterococcus (VRE).

According to the Arrowhead report, pharmaceutical companies will continue to develop new generations of antibacterial agents — cephalosporins, macrolides, and quinolones. In addition, a number of new drug classes, such as dihydrofolate reductase inhibitors (DHFR), are under evaluation for their effectiveness in multidrug resistant organisms.

Kalorama Information researchers estimate that the market will grow 2.5% from 2006 to 2011. Sales will likely increase by almost $3 billion to $25.5 billion in 2011.

In 2006, antibacterial drugs accounted for an estimated $22.6 billion in revenue, accord-

MEDICINES IN DEVELOPMENT FOR INFECTIOUS DISEASES



Source: Pharmaceutical Research and Manufacturers of America, Washington, D.C. For more information, visit phrma.org.

ing to Kalorama. This is, however, a decline of 1.8% from 2004. According to Kalorama Analyst Melissa Elder, the decline is due to a shift in sales from branded products to generic products resulting from recent patent expirations.

"The penicillins and cephalosporins have been negatively impacted in this market, and they are having a difficult time remaining on top," Ms. Elder says. "Newer products, which show less resistance, have taken their place with physicians. Few branded products in this segment currently hold much weight. Products such as Augmentin and Zosyn remain the only brands to have a significant market share. And Augmentin sales continue to slide because of generic competition, while sales of Zosyn remain steady."

Product sales in the quinolone and miscellaneous segments were responsible for the highest growth and will continue to play a key role in fueling the market, according to the Kalorama report.

INFECTIOUS DISEASE PIPELINE

The Pharmaceutical Research and Manufacturers Association's 2007 Infectious Disease Report states that there are 146 vaccines to prevent diseases from staph infections to pneumococcal infections; 83 antibiotics; and 75 antivirals for treating such viruses as hepatitis, herpes, and influenza in clinical trials or awaiting approval from the Food and Drug Administration.

Despite what appears to be a substantial cadre of new products in the pipeline, a Pharmacor report from January 2007 finds the late-stage antibacterial pipeline is not keeping up with the increasing need for novel agents to target drug-resistant bacteria.

The Pharmacor report finds that the late-stage pipeline is skewed toward products targeting the crowded market of resistant Gram-positive infections, but the true commercial opportunity may lie in novel classes in earlier stages of development.

"The cost of development has hampered research and development efforts into antimicrobials, prompting large companies to seek out contract research services, an industry that is growing at exceptional rates," Ms. Elder says. "More complex products have been shown to require larger amounts of investment."

According to Decision Resources analysts, developing new drug classes remains a challenge in antibacterial R&D. In the past decade, only two entirely new antibacterial classes have been introduced to the market: oxazolidinones and lipopeptides.

Although companies have found some success with spin-offs of existing classes, such as the ketolides and glycylcyclines, experts emphasize that agents with entirely novel mechanisms of action are needed.

"One of the most complex issues for smaller companies is that the regulatory environment is becoming murkier and more challenging," says Susan Froshauer, Ph.D., president and CEO of Rib-X Pharmaceuticals Inc. "We have serious value-creation goals and budget drivers from our investors and, therefore, need to operate with defined timelines. An uncertain regulatory environment slows down progress. I suspect that the regulatory environment will stabilize as more discussion unfolds during advisory meetings in the months ahead, but in the meantime, trial design discussions with the regulatory agency can take some time."

Despite the barriers, there are a few products showing promise. Astellas Pharma US and Theravance Inc. received an FDA approvable letter in October 2007 for Arbelic (telavancin) for use in treating complicated skin and skin structure infections (cSSSIs) caused by Gram-positive bacteria, including MRSA.

Arbelic also is in Phase III development for the treatment of hospital-acquired pneumonia, including patients with ventilator-associated pneumonia caused by Gram-positive bacteria.

Another lipoglycopeptide in the pipeline is oritavancin, which is being developed by Targanta Therapeutics Corp. Phase II and III trials have shown promise against MRSA and vancomycin-resistant pathogens, such as enterococci and staphylococci.

There are two next-generation cephalosporins being investigated. Ceftobiprole is being developed through a collaboration between Basilea Pharmaceutica and Johnson & Johnson Pharmaceutical Research & Development. It is a broad-spectrum cephalosporin that has demonstrated positive results in two Phase III trials in cSSSIs.

Basilea also is conducting Phase III clinical

DR. BARRY EISENSTEIN
Cubist Pharmaceuticals

There is now the diversion of resistant pathogens that common empiric treatments no longer cover. **THE END RESULT IS AN INCREASE IN MORTALITY.**

UNDERSTANDING DRUG RESISTANCE

Primary to the defenses of bacteria are their complex outer structures: the "capsule," the "cell wall," and the "cytoplasmic membrane." It is these structures that first protect the bacteria from foreign compounds, like antibiotics.

In general, bacteria become resistant to antibiotics by using three major strategies. The first is to prevent the drug from reaching its target. Some bacteria accomplish this by having a "double-membrane" layer to retard the entry of the compound into the cell. Other bacteria simply expel the drugs from inside the cell using pumps located in the membrane.

The second strategy bacteria employ to become drug resistant is to produce enzymes that physically alter the antibiotic so that it can no longer bind to its cellular target.

The third strategy is to physically alter the cellular target (the ribosome) so that an antibiotic can no longer bind and inhibit its function. Bacteria can use any combination of these methods to resist the action of antibiotics, rendering them therapeutically ineffective.

DNA mutations that allow bacteria to become antibiotic resistant occur as a natural consequence of the bacteria duplicating their DNA. Such mutations typically occur infrequently, but because bacteria can reproduce every 20 minutes, mutations are much more common than in human cells.

In addition to random mutation, bacteria are often able to exchange their DNA with one another thereby transferring resistance determinants to their antibiotic-sensitive neighbors. By employing these strategies, bacteria have virtually assured themselves of ways to develop resistance to the antibiotics in use today.

Source: Rib-X Pharmaceuticals Inc., New Haven, Conn. For more information, visit rib-x.com.

studies of ceftobiprole for the treatment of hospital-acquired pneumonia.

Ceftobiprole is currently under review with the FDA, with the European Medicines Agency, and Health Canada for cSSSIs. Upon approval, the product will be marketed by Ortho-McNeil Inc. in the United States and Janssen-Cilag in Europe and Asia.

Ceftaroline, which is being developed by Forest Laboratories, is another broad-spectrum cephalosporin to receive FDA fast-track review for cSSSIs caused by MRSA.

Further in the pipeline are products from both Rib-X Pharmaceuticals and Cubist.

"Our most advanced programs target MRSA, but we also are closely looking at multidrug resistant Gram-negative organisms as well," Rib-X's Dr. Froshauer says. "We have potent molecules that are tightly bound to the bacterial ribosome, and this suggests that higher levels of bacterial resistance may be tolerated before a drug becomes resistant."

Rib-X's technology platform is based on the high-resolution crystal structure of the 50S subunit (the large subunit) of the ribosome.

One product is RX-3341 (WQ-3034 or ABT-492), a quinolone antibiotic with broad-spectrum activity against MRSA and other Gram-positive pathogens resistant to other quinolones. Rib-X has an agreement with Japan-based Wakunaga Pharmaceutical Company to develop and commercialize the product worldwide. The product is about to enter Phase III studies in an IV formulation.

Rib-X also has an agreement with Molecular Biology of the Medical Research Council of London to explore the high resolution crystal structure of the full 70S ribosome recently determined by MRC's ribosome scientist.

Cubist is conducting Phase II development of Cubicin in high-dose short duration and a Phase II comparative dose study in prosthetic joint infections. ✦

The estimated number of people developing a serious MRSA infection in 2005 **WAS 94,360. ABOUT 18,650 PEOPLE DIED** during a hospital stay related to an MRSA infection.

Centers for Disease Control

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.

THE ANTIBACTERIAL MARKET

MARKET DRIVERS

- The increasing prevalence and diversity of bacterial resistance to an antibiotic or class of antibiotics will fuel a continuous need for novel therapies that are unaffected by existing resistance mechanisms.
- The hospital Gram-positive market is set to expand significantly. Generic vancomycin is the current patient-share leader for treating hospital-acquired infections (HAIs) caused by drug-resistant Gram-positive pathogens.
- Therapeutic antibodies (TAs) represent a new approach to the treatment of bacterial infections, including those caused by MRSA. Because TAs will command a significant price premium and will be used in combination with antibiotic therapy, they will have an additive effect on the market.

MARKET LIMITERS

- The patents of several key antibiotic products will expire over the next 10 years. Generic erosion of these products will be the most significant constraint on antibiotic sales.
- Despite the increasing incidence of community-acquired infections caused by drug-resistant pathogens, U.S. managed care organizations will likely restrict the use of premium-priced branded products in favor of equally safe and effective lower-priced generics.
- In the hospital setting, formulary and infection control officials will limit the use of both advanced-generation compounds from existing classes and innovative agents from novel drug classes. Agents from novel drug classes will face restricted use because infection control officials will want to limit the development of resistance and preserve their activity.

Source: Decision Resources, Waltham, Mass. For more information, visit decisionresources.com.

DR. SUSAN FROSHAUER
Rib-X Pharmaceuticals

THE MOST COMPLEX ISSUE FOR SMALLER COMPANIES DEVELOPING ANTIBACTERIALS IS THE REGULATORY ENVIRONMENT, which is becoming murkier and more challenging.

Experts on this topic

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