Despite increasing resistance among clinically important gram-negative and gram-positive pathogens to many common antibacterial agents, many large pharmaceutical companies are showing decreased interest in this product area that is so critical to public health. This downturn in antibacterial discovery and development, in turn, is leaving us vulnerable to emerging resistance, particularly to recently arrived vancomycin-resistant *Staphylococcus aureus* and multiply resistant, gram-negative bacilli for which we do not have adequate antimicrobial therapy in the United States.

We believe that such pathogens represent a public health threat whose urgency deserves both regulatory and legislative relief. Dealing with this threat could provide opportunities for larger companies to regain a strong presence in this area. However, action should be taken soon before critical expertise disappears.

**Urgent Need for Antibiotics Reflected in Resistance Data**

Focus Technologies of Herndon, Va., maintains a database that includes results from 65 million antimicrobial susceptibility tests—or 2.6% of all isolates tested per year—on cultures ordered by clinicians in various locations throughout the United States. Only 27 bacterial taxa account for 95% of clinically encountered organisms, and *Staphylococcus aureus* accounts for 16% of all clinical isolates. Almost 40% of clinical isolates include those with potential for multiple drug resistance, and 20% of clinical isolates are, in fact, multiply resistant (see table). Meanwhile, the frequency of multidrug-resistant isolates from blood cultures is also increasing.

For many of these pathogens, especially gram-negative bacteria, options for therapy are becoming extremely limited. Therefore, the need for better treatments for these infections, particularly in hospitals where resistance is immediately life threatening, is growing more urgent.

Historically, the pharmaceutical industry owes much to the discovery that some microbial secondary metabolites can serve as antibotics. Identifying these life-saving compounds and subsequently developing related analogs provided benefits to humankind and the pharmaceutical industry. Among the early compounds from the golden age of antibiotics are sulfonamides, penicillin, and streptomycin. Soon after this first wave came the tetracyclines, isoniazid, macrolides, glycopeptides, cephalosporins, nalidixic acid, and a variety of other molecular classes.

Progress was so heady that, by the late 1960s, some experts considered infectious diseases nearly conquered. Since then, however, new cycles of discovery, development, and marketing of antibacterial compounds continue to occur—albeit irregularly. For example, the cephalosporins became the rage during the 1970s, with multiple second- and third-generation compounds entering the marketplace by the mid-1980s.

Then, despite an emerging epidemic of multiply-resistant *S. aureus* infections in U.S. hospitals and similarly resistant *Streptococcus pneumoniae* infections in U.S. communities, the pharmaceutical industry began pulling back on...
their discovery efforts in antibacterial drugs. Approximately half of the U.S. and Japanese pharmaceutical companies either ceased or decreased their antibacterial research efforts, according to a 1989 survey by George Miller of Blanca Pharmaceuticals, Mountain View, Calif.

Antibiotic Development Efforts Continue to Fluctuate

Nonetheless, antibiotic discovery efforts continued in many major pharmaceutical companies through the 1990s. For example, quinupristin-dalfopristin (SynercidR) and linezolid (ZyvoxR), both targeted towards gram-positive pathogens, were introduced in 1999 and 2001, respectively. Linezolid represents the first new class—oxazolidinones—of antibacterial agents to be marketed since rifampicin. Efforts to bring these new drugs to market were stimulated in part by the threat of multiply resistant *S. aureus* in hospitals around the world and the emergence in the 1990s, mainly in the United States, of pan-resistant *Enterococcus faecium*.

However, since 1999 and during a period of major consolidation, the pharmaceutical industry again pulled back from anti-infectives research, posing an important public health risk over the next decade that should be dealt with in an urgent manner. The current state of affairs is a cause for serious concern. The number of new antibacterials in development has been in steady decline since the 1980s, based on surveys of annual reports from a number of large companies (Fig. 1). In 2002, out of 89 new medicines emerging on the market, no new antibacterial drugs were approved. Since 1998, only seven new antibacterials have been approved. Current annual reports for leading pharmaceutical companies (Merck, Pfizer, GlaxoSmith Kline, Bristol-Myers Squibb, Aventis, Abbott, AstraZeneca, Lilly, Hoffmann-LaRoche, Johnson & Johnson, and Novartis) list only 4 new antibacterials in the drug pipeline out of 290 agents listed (or 1.38% of the products in development).

Although many large companies have either diminished or eliminated their research efforts in antibacterial drug discovery, some, including Johnson & Johnson, Merck, Novartis, and Pfizer, as well as a number of biotechnology companies, remain in the field. This doggedness is based on the perception that resistant pathogens will continue to proliferate, that older drugs will select for new resistances, that the medical need is an important one and that, therefore, commercial opportunities still exist. For some companies, a feeling of social responsibility is another factor contributing to decisions to continue pursuing antibiotic development.

Several other factors have influenced decisions about whether to continue anti-infective research and development. For instance, industry officials consider unmet medical needs in terms of the patients who might be treated by a new product, how the new product would be differentiated from others that compete for the same population group, how such a new product would be priced, the investment that might be required in bringing such products to market, and the eventual recovery of development costs through sales.

Further, because of increasingly stringent requirements by regulatory agencies in the areas of manufacturing, safety, and efficacy in product development, the pharmaceutical industry is shouldering a rising cost burden for each product brought to market. These costs might exceed $800 million per drug, according to an estimate from several years ago by Joseph DiMasi of the Tufts Center for the Study of Drug Development in Boston, Mass. These up-front costs force the industry to set strict priorities for discovery and development activities, favoring those products with the greatest potential return on investment.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Overall %</th>
<th>% Multiresistant*</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>S. aureus</em></td>
<td>16.2</td>
<td>6.5</td>
</tr>
<tr>
<td>CoNeg staphylococci</td>
<td>9.4</td>
<td>6.6</td>
</tr>
<tr>
<td><em>Enterococcus faecium</em></td>
<td>0.9</td>
<td>0.6</td>
</tr>
<tr>
<td>Enterobacteriaceae&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3.4</td>
<td>1.7</td>
</tr>
<tr>
<td>Pseudomonas, Acinetobacter, Stenotrophomonas, and Burkholderia spp.</td>
<td>8.9</td>
<td>5.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>38.8</strong></td>
<td><strong>20.4</strong></td>
</tr>
</tbody>
</table>

<sup>a</sup>Resistant to more than two antibiotics (usually of differing classes) to which a species is typically susceptible.

<sup>b</sup>Includes *K. pneumoniae*, *S. pneumoniae*, *E. cloacae*, and other members of the *Enterobacteriaceae*.
Setting Priorities for Drug Development: Complex, Sometimes Subjective Procedures

Pharmaceutical and biotechnology companies will be investing approximately $40 billion to discover and develop therapeutic products across all health areas in 2004. While this amount surpasses the total budget for the National Institutes of Health by about $15 billion, many valuable, medically significant research and development (R&D) projects cannot be adequately supported. In determining where to direct these resources, companies use several methods to guide decision making.

For example, one such tool involves calculating the Net Present Value (NPV) of a particular project after projecting expenses and revenues from the anticipated commercial product while discounting for the potential investment value of the money that will be spent in executing the project. NPV is also usually “risk-adjusted” — the rNPV — to account for increased risks associated with projects at earlier stages. Moreover, risks are different depending on factors such as the therapeutic target and type of compound. Notably, antibacterial agents at all stages of development through phase III clinical trials are considered to have a relatively low risk compared to projects in other therapeutic areas, according to Ronald Johnson and his colleagues at BioGenetic Ventures in Bellevue, Wash.

Thus, a candidate antidepressant entering clinical trials has a rNPV of $720 million, compared to $100 million for a candidate injectable antibacterial agent that targets gram-positive bacteria. Because the projected return on investment for such an antibacterial agent is typically lower than that for drugs to treat other kinds of diseases, any increased stringency in clinical trial design, which increases costs, will lead to a lower rNPV projection for antimicrobial products and further disadvantage them when companies set R&D priorities.

Not all companies rely on NPV calculations. Other financial tools include determining the compounded annual growth rate of the marketplace and estimating peak year sales. Some companies set a minimum peak sales figure, such as $200 million or $500 million, to determine whether to develop a particular product and reject those projects whose expected peak sales fall below that figure.

In general, an oral antibiotic that would be used for treating community-based infections is more likely to receive favorable status than an injectable agent for treating infections caused by vancomycin-resistant enterococci. However, both these antibiotics would receive a lower priority than would a drug for treating depression.

One important caveat for these or other marketing analyses is that these projections are done without clinical data to assess the efficacy of candidate drugs. Rather, they are based on sales data for similar products, an idealized “target product profile,” and responses of physicians to what these drug might do. Because drugs often are used very differently when they reach the market, these premarket, target product profiling procedures can lead to major disparities between analysis and experience — thus undercutting the validity of the process for setting priorities within the pharmaceutical industry, or at least showing how subjective it can be.

Antibiotic Product Developers Face Serious Scientific Challenges

Even though the prospects for antimicrobial products entering development may be better than are those for other therapeutics, antibacterial agents in particular face other challenges that can put them at a disadvantage. First, the scientific challenge is a significant one. For example, despite about a decade of impressive progress in bacterial genomics, there are no promising antibacterial agents in clinical development and none on the market derived from this technology. The expectation that 10

Table 2. Recent history of antibiotic research

<table>
<thead>
<tr>
<th>Period</th>
<th>Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>1989</td>
<td>50% of U.S. and Japanese large Pharma report that they have halted or decreased antibiotic discovery efforts.</td>
</tr>
<tr>
<td>1990</td>
<td>VRE outbreak plus worsening MRSA; some companies renew and expand research efforts</td>
</tr>
<tr>
<td>1990s</td>
<td>Consolidation leads to fewer large Pharma companies.</td>
</tr>
<tr>
<td>1999</td>
<td>Quinupristin-dalfopristin approved</td>
</tr>
<tr>
<td>2000</td>
<td>Roche spins off anti-infective discovery</td>
</tr>
<tr>
<td>2001</td>
<td>Linezolid, member of the first new antibiotic class in 35 years, is approved</td>
</tr>
<tr>
<td>2001–2</td>
<td>Bristol-Myers Squibb, Lilly, and Wyeth halt anti-infective discovery; GlaxoSmithKline and Abbott downsize anti-infective effort. Aventis announces intention to spin off their anti-infective group.</td>
</tr>
</tbody>
</table>
years of work in a technologically promising area would yield products is probably unfair. Indeed, the discovery, development, and manufacture on a large scale of sulfonamides and penicillin required decades of concerted efforts. Scientifically, we are still learning how to use genomics, proteomics, structure-based design, high-throughput screening, and combinatorial chemistry to identify antibacterial drug candidates. The first versions of such agents are not of the same quality of antibacterial agents that benefited from more than 50 years of traditional approaches to optimizing performance. However, the newer, target-based drug discovery approach is starting to pay off. For instance, several inhibitors of peptide deformylase are being evaluated clinically, while other novel inhibitors of fatty acid biosynthesis are at an earlier stage of development.

Antibiotic Product Developers Also Face Several Economic Challenges

Companies interested in developing antibacterial agents are faced with a paradox because of how rapidly and inexorably resistance can develop. Thus, use of antibacterial drugs leads to bacterial resistance that, in turn, leads to a need for additional antibiotics, which also eventually select for new resistance phenotypes. A growing awareness of the relationship between antibiotic use and emerging resistance has led to efforts to decrease use, which could decrease the market potential for new drugs.

Although substantial, the antibacterial marketplace has grown slowly for the past few years, hovering near $26 billion per year in overall sales. Market projections vary—ranging as high as $37 billion per year by 2007, according to IMS Health, Fairfield, Conn., to a more modest $28.9 billion by 2008, according to Datamonitor America, New York, N.Y. The market for antibiotics is divided between community sales for mainly orally available drugs and the hospital marketplace, which is dominated by parenterally administered agents. The community market accounts for almost 70% of the antibacterial sales, with parenteral agents accounting for the remainder. Most “blockbuster” antibiotics, those with greater than $500 million annual sales, are sold in the community market, although a few parenteral agents, such as ceftriaxone and piperacillin-tazobactam, exceed this sales figure in the hospital marketplace.

Although many patients are treated with generic antibiotics, more than 80% of the total antibacterial sales represents branded products. However, an unusually large number of important products—that is, those accounting for from $500 million to almost $2 billion in annual sales—will soon lose patent-based exclusivity in major markets during the next 5 to 10 years. Even though such events have not always resulted in significant market contractions, the looming prospect of market perturbations may discourage some companies from staying in or entering this field.

The presence of many effective and safe therapies, some generic, poses another set of challenges for companies hoping to bring forward new products, even in the face of emerging resistance. The difficulties are especially challenging in the community setting, where a strong marketing presence is essential. The hospital arena, where the need for new products is greater, also presents significant marketing hur-

![Figure 1](https://example.com/figure1.png)

New antibacterial agents approved in the United States per 5-year period from 1983 to 2002.
dles because of the number of products already available and the ever-increasing cost pressures on hospital pharmacies.

Further constraining the perceived future market for novel antibacterial agents is the fear that agents with activity against drug-resistant strains might be held in reserve until they are desperately needed. Fueling this concern is the fact that both quinupristin-dalfopristin and linezolid, which are agents that target resistant gram-positive bacteria, to date apparently have fallen short of the market share and sales levels that had been anticipated for them.

In a more general sense, antibacterial products tend to be expensive to develop. Many companies prefer approval for at least three indications to assure a reasonable market. For parenterally administered products targeted against specific pathogens, clinical trials can prove expensive to conduct, typically requiring 300–500 patients per trial at costs as high as $35,000 per patient, according to an industry-government working group.

Regulatory Requirements Pose Cost and other Burdens

Regulatory requirements also affect costs for therapeutic products within the industry in general, but may sometimes put anti-infectives in an unfavorable position because of the prioritization process within industry noted above. Although faster regulatory reviews are always appreciated, they are really not the biggest burden for those developing antibiotics. Rather it is the demand for more and higher-quality data that require longer and more expensive clinical testing to acquire. Such efforts cut into the patent life and commercial viability of new agents.

In reviewing clinical trial designs, representatives of the Pharmaceutical and Research Manufacturers of America (PhRMA), the Infectious Diseases Society of America, and the Food and Drug Administration (FDA) recently agreed that reducing the cost burden of developing new antimicrobial agents will be required to stem the tide of companies leaving this area of R&D. In fact, in the FDA Public Health Action Plan to Combat Antimicrobial Resistance, approaches that streamline the regulatory process, including “clinical trials and enhanced preclinical studies (e.g., use of pharmacokinetics, and pharmacodynamics data) to help bring AR (antibiotic resistance) products (including drugs, vaccines, diagnostics and devices) to market as efficiently and rapidly as possible, while still assuring their safety and efficacy,” are specifically targeted.

Various approaches to relieving this problem are being considered. For instance, clinical trial size requirements could be decreased through creative trial design. In addition, two legislative proposals offer other incentives for retaining or bringing companies back into antibiotic R&D.

The first such proposal is termed the “wild-card” exclusivity extension. It would allow companies to extend exclusivity of another, marketed product in any therapeutic area, in return for a commitment to continue R&D of new antibacterial agents. For example, Eli Lilly might receive an extension for its antidepressant Prozac in exchange for approval of an antibacterial agent for resistance. An alternative legislative proposal, termed the “modified wild-card”
exclusivity extension, would be granted only for marketed antibacterial drugs. In this scenario, Augmentin, an antibiotic combination marketed by GlaxoSmithKline would receive some extension of exclusivity if the company delivers on antibacterial for resistance.

The intention of both these initiatives would be that the proceeds from the sales of these agents with extended patent lives would be funneled directly into R&D efforts for antibacterial agents. Other approaches that could contribute to solutions might include academic-industry collaborations similar to those that have been established to discover and develop therapies for tuberculosis, malaria, and other infectious diseases not accorded priority by industry. However, government-academic-industry collaborations of this type, which have led to successful development of antiviral agents, have yet to be of proven value for developing antibacterial agents.

Current Prospects for Industry Pursuing Antibiotic Development

Despite these challenges, several major pharmaceutical companies remain committed to antibiotic R&D, including Pfizer, Merck, Novartis, and Johnson & Johnson. Some observers argue that if big pharmaceutical companies stop working on antibacterial drugs, smaller biotechnology companies will do so. However, biotechnology companies also very much depend on attracting investors to fund such research. Moreover, companies find it easier to attract capital if they have products in development—the later the stage, the better.

Because the size of a potential market is less important for biotech companies than might be the case for large pharmaceutical companies, the drugs the biotechs develop can be targeted to smaller niches. However, the costs of clinical efficacy (phase III) trials are difficult to sustain even with funding from public markets. Therefore, large pharmaceutical companies often play an important role for biotech companies in shaping their strategies. Put another way, if large pharmaceutical companies are unlikely to invest in Phase III trials for antibiotics, it remains at least as difficult for biotech companies to attract funding for such activities.

An exception is the recent experience of Cubist Pharmaceuticals in Lexington, Mass. The company took the drug daptomycin (Cubicin®) through Phase III clinical trials without investments from a large pharmaceutical partner. Other biotechs may be following a similar path—for example, Vicuron of King of Prussia, Pa., with its antibiotic dalbavancin, and InterMune of Brisbane, Calif., with its drug oritavancin.

Sooner or later some pharmaceutical companies could find their late-stage development cupboards so bare that they again will be willing at early stages to invest in promising antibacterial compounds from biotech companies. However, the candidate products still must meet certain financial criteria, such as minimum projected peak sales—a condition that usually will preclude the licensing of agents being developed for only limited clinical indications.
SUGGESTED READING


