ANTIBIOTICS YO-YO

Companies score big deals but still **STRUGGLE** with regulatory authorities

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IT'S BEEN A TURBULENT few years for companies developing antibiotics. Several late-stage drug candidates have suffered setbacks, and companies claim the regulatory environment has become confusing at best. But the Food & Drug Administration is beginning to offer more clarity on data it needs to approve new antibiotics. And as more development programs reach late-stage trials, biotech firms with promising drugs are finding partners ready to pay big bucks for them.

Since October 2009, AstraZeneca, Forest Laboratories, Novartis, and Cubist Pharmaceuticals have each spent hundreds of millions of dollars for access to antibiotics that have produced good data in Phase II or III clinical trials. Industry watchers hope the spate of deals will accelerate the launch of new weapons against dangerous infections. In recent years, superbugs, or bacteria resistant to current antibiotics, have stymied physicians and sent researchers in search of better drugs.

Finding novel antibiotics outside currently approved compound classes is notoriously difficult (C&EN, April 14, 2008, page 15). Only two new classes—oxazolidinones and lipopeptides—have been introduced since the 1970s. As a result, many big firms have abandoned antibiotics research in favor of more lucrative markets. Although virtually all big pharma companies were active in antibiotics 20 years ago, today, only Pfizer, AstraZeneca, GlaxoSmithKline, and Novartis appear to have substantial internal R&D programs.

The regulatory climate recently has emerged as an even bigger hurdle than discovering a drug that works. Although clinical trials for antibiotics are short, developers contend that FDA and European regulators keep changing their minds about the proof they need to approve a drug.

As a result, failures outweigh successes among the antibiotic drug candidates seeking FDA approval. The agency nixed four of the six antibiotics that came before it in the past two years, points out David Shlaes, president of Anti-Infectives Consulting.

"Some of those drugs didn't deserve to be approved, but others were the victim of moving goalposts," says Shlaes, who consults for a range of companies developing antibiotics. In other words, although a company and FDA agree upon a protocol for a Phase III trial, by the time the trial is complete, the agency says it wants different data.

For example, in response to Targanta Therapeutics' New Drug Application (NDA) for oritavancin, a semisynthetic glycopeptide, the agency returned a laundry list of issues with the data and asked for a new Phase III trial.

Other companies have also faced delays and expensive new trials after choosing a clinical pathway that didn't jibe with what FDA now expects. For small firms that thought they were near the goal line, a request for a new Phase III trial can be devastating. After Targanta heard from FDA, the firm shed 75% of its workforce and eventually sold itself to Medicines Co.

FDA views developing new antibacterials as "an important health issue," says Edward Cox, director of FDA's Office of Antimicrobial Products. But at the same time, the agency argues that companies need to keep pace when new developments occur in their field. "When there are significant changes in our understanding of the science, as has occurred in some disease areas over the past several years, we cannot ignore this new scientific information, and we may need to change our advice," Cox says.

BUT EVEN AMID a rocky regulatory environment, antibiotics are still among the most straightforward drugs to develop. Once researchers find a chemical family that works against bacteria in vitro, development largely entails finding the family members that are safe and have the right pharmacokinetics in humans. Furthermore, because clinical trials can be short, drug development is often relatively inexpensive.

"The fantastic thing with antibiotics is that at the end of Phase I, you know everything," says Guy Macdonald, chief executive officer of Tetraphase Pharmaceuticals. "In most therapeutic areas, it takes you to the end of Phase III to find those things out."

And because most of the antibiotics being developed today are for serious infections requiring hospitalization, companies don't generally have to invest in big sales teams to get their products out. Finally, because antibiotics are typically administered for only a few days or weeks and often under life-or-death circumstances, they are unlikely to be affected by pricing pressures due to health care reform.

Those pluses seem to be outweighing the minuses for the companies that have committed to antibiotics. In addition, the spate of drug development deals suggests a healthy appetite in recent months among larger firms for promising treatments.

Cubist paid $92.5 million for privately held Calixa Therapeutics. The biotech firm was conducting Phase II trials on a combination cephalosporin and β-lactamase inhibitor that works against gram-negative infections. Novartis agreed to pay up to $485 million for the rights to Paratek Pharmaceuticals' PTK0796, a broad-spectrum antibiotic.

AstraZeneca bought the French biotech firm Novexel for $350 million. Forest, which was already working with Novexel on a drug that combines experimental com-

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PESKY PATHOGEN Several drugs to combat gram-negative bacteria, such as *Pseudomonas aeruginosa,* are in the pipeline.

pounds from both companies, will ultimately pay AstraZeneca half the purchase price to partner on both drug candidates.

Notably, all of the firms that scored big pharma deals at the end of 2009 had compounds in mid- or late-stage trials to treat complicated skin infections, an indication of where the regulatory dust seems to be settling. "In skin and soft tissue, there's the potential for approval," Shlaes says.

Some of the deals vindicate drug candidates that faced their share of challenges. Paratek's PTK0796 was originally licensed to Bayer in 2003. It was picked up by Merck & Co. in 2006, only to be dropped before being scooped up by Novartis. The broad-spectrum tetracycline derivative, now in Phase III trials for treating skin and soft tissue infections, was designed to improve the activity and safety of tetracycline. Importantly, the drug can be given both intravenously and orally, an advantage because patients who start on an IV in the hospital can continue treatment at home.

Novexel, meanwhile, was created in 2004 after Sanofi-Aventis decided to end anti-infectives research. A group of Sanofi chemists had been working to boost the activity of cephalosporins, which are prone to degradation by β-lactamase enzymes created by the bacteria they target, explains Kenneth Coleman, Novexel's chief scientific officer. The end result was NXL104, a small-molecule β-lactamase inhibitor touted as having broader activity than previous enzyme inhibitors. Novexel now has two programs that combine NXL104 with cephalosporins.

Meanwhile, in November 2009, Novexel's NXL103, a combination of the streptogramin antibiotics linopristin and flopristin, started Phase II trials as a treatment for acute bacterial skin and soft tissue infections.

"The FDA anti-infectives division is in danger of regulating itself out of business and us out of antibiotics."

ONE NEW PLAYER is also trying to keep alive a drug candidate that struggled during a period of changing regulatory demands. A five-member venture capital syndicate formed a company called Durata Therapeutics to commercialize dalbavancin, a lipoglycopeptide it acquired from Pfizer in December 2009.

At the time, Pfizer had all but abandoned development of the drug after a protracted period of back-and-forth with FDA. Dalbavancin was one of two key assets—the other was the antifungal anidulafungin—that prompted Pfizer to pay a whopping $1.9 billion for Vicuron Pharmaceuticals in 2005.

Dalbavancin hit a string of roadblocks. The drug was viewed as highly attractive for its once-weekly dosing profile, and FDA had already given it priority review status. Vicuron expected approval by early 2006, but the agency instead asked Pfizer to provide data showing its drug was as effective

as existing antibiotics. The company finally withdrew NDAs for dalbavancin in both the U.S. and Europe in 2008.

Despite Pfizer's challenges, Durata executives believe a clear path to approval exists for dalbavancin. "We acquired the asset because it was so advanced, with more than 1,000 patients having gone through clinical trials," says Ron Hunt, a member of Durata's board. And because clinical trials for antibiotics are relatively short, the drug could be on the market in just a few years.

The investors in Durata include firms with significant experience backing antibiotic developers: Sofinnova Ventures was a lead funder of Novexel; Canaan Partners and New Leaf Venture Partners backed Cerexa, which Forest bought in 2006 for $580 million for access to ceftaroline; and Canaan and Domain Associates funded Calixa.

Although financial terms of the deal were not disclosed, Hunt, who's also managing director of New Leaf, notes that the bulk of the cash raised to form Durata was to pay for clinical development rather than the rights to the drug.

Durata plans to initiate a Phase III trial that involves between 600 and 1,000 patients. Like others in antibiotics, Durata is focusing on serious skin infections. The deal with Pfizer included enough active pharmaceutical ingredient and finished drug product to get through the trial. The new company will need to secure a manufacturing relationship when it comes time to file an NDA.

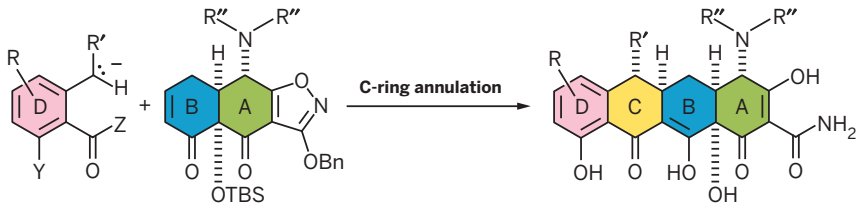
GIVEN THE recent interest by venture capitalists and big pharma, newer players are confident they will find partners or even go public to finance compounds that make it to Phase II.

Tetraphase, for example, hopes its technology will lead to more diverse tetracycline derivatives that attack a broad spectrum of pathogens. The company was founded in late 2006 to commercialize a chemistry platform that emerged from the lab of Andrew G. Myers, chair of the chemistry department at Harvard University.

Myers devised a fully synthetic route to tetracycline derivatives that enables chemists to make thousands of compounds with modifications at virtually any position on the molecule. Previously, tetracycline derivatives had been made through a semisynthetic route that enabled modifications only at the C-7 and C-9 positions. "The diversity was not great," says Joyce Sutcliffe, Tetraphase's senior vice president for biology.

A modification at the C-9 position endowed the dual IV- and oral-delivery characteristics of Paratek's PTK0796. Tetraphase scientists believe their ability for broader modification will permit even more control over the properties of tetracycline derivatives. In just two years, the company has synthesized more than 2,000 compounds and, importantly, is finding activity against the two main enzymatic resistance mechanisms used by bacteria.

In the future, companies are hoping to reach agreement with regulatory authorities over clinical trial protocols to enable their compounds to be developed for nonskin infections. It turns out that getting a drug approved for complicated skin infections does not guarantee approval for community-



TBS = *tert*-butyldimethylsilyl, Bn = benzyl

NEW ROUTE Tetraphase has expanded the diversity of tetracycline derivatives.

acquired pneumonia (CAP) and respiratory infections, areas where industry and FDA have had the most contentious interactions.

The regulatory environment for those indications "remains confused both in the U.S. and Europe, and that's the most charitable way to put it," Shlaes says. The situation was underscored just last month, when FDA told Theravance it would need a boatload of new data before it would review the company's NDA for telavancin, a lipoglycopeptide intended to treat CAP. The drug is already approved to treat serious skin and soft tissue infections.

The agency is considering clinical trial endpoints—a measure of efficacy—for CAP that some in the industry consider unduly difficult to reach. "FDA has brought out some recommendations the industry would consider unacceptable," Novexel's Coleman says.

In draft guidance on developing drugs for CAP that it issued last March, FDA goes to great length to address industry's biggest bone of contention: FDA's belief that mortality, or whether a drug improves survival in patients with CAP, can be used as the primary yardstick for success. FDA points out that it is not ethical to compare an antibiotic with a placebo for serious infections, leaving mortality as the best option—and the one used in historical studies—to demonstrate an antibiotic's efficacy. Industry, on the other hand, argues that because few patients with serious infections die, the mortality endpoint will require enormous patient pools, meaning trials will be endless and expensive.

Despite the impasse, development work continues. Novexel's NXL103 has completed a Phase II study to treat CAP, and Paratek says PTK0796 will begin a late-stage trial to treat pneumonia later this year. Tetraphase also plans to initiate a CAP trial down the road, Sutcliffe notes.

Still, at a December 2009 meeting of FDA's Anti-Infectives Drug Advisory Committee, Shlaes had strong words for the agency's stance on trials of antibiotics for pneumonia and respiratory infections. "The FDA anti-infectives division," he said, "is in danger of regulating itself out of business and us out of antibiotics." ■