Antibiotic dealmaking poised for resurgence

A commercial environment reinvigorated by improved fundamentals—increased regulatory flexibility and the emergence of exciting new scientific opportunities and innovative business models—has set the stage for a resurgence in the antibiotics space that has already led to an uptick in early-stage venture investment and strategic partnerships.

BY CHRIS MORRISON

The rise of antibiotic-resistant infections portends a public health disaster that has regulatory agencies and governments rolling out the red carpet for antibiotic drug developers. Recent estimates suggest that deaths attributable to antimicrobial resistance could hit 10 million per year by 2050—substantially more than are caused by cancer (*Review on Antimicrobial Resistance*, December 2014, http://amr-review.org/). Yet the development scene is anything but crowded.

Antibiotics research and development (R&D) remains far from the pharmaceutical industry's top anti-infectives priority and has been a relatively barren area, thanks to a dearth of new compound classes in the pipeline and a historical lack of commercial incentives—such as the fact that the best antibiotics tend to be reserved for crucial uses, rather than used broadly, to reduce the emergence of resistance. But new incentive structures, along with attentive and consistent regulatory action promised by initiatives such as the 2012 Generating Antibiotic Incentives Now (GAIN) Act in the US, may combine with recent scientific advances and the tail end of the current biotech bull market to reignite interest in the space.

The treatment of acute bacterial infections is unlikely to ever rival the treatment of chronic viral infections such as hepatitis C as Big Pharma's most lucrative anti-infective target. But while it is doubtful that a Sovaldi-like mega-blockbuster will emerge on the antibiotic scene, New Jersey-based Merck & Co.'s December 2014 $9.5-billion acquisition of Massachusetts-based Cubist Pharmaceuticals illustrates the appetite for late-stage clinical and commercial assets, several of which may be ripening in the pipelines of the biotech industry. What is more, multiple antibiotics players have pulled off impressive initial public offerings (IPOs) during the current window, illustrating renewed investor interest in the space.

The handful of new antibiotics that have made it to market in the past 18 months also offer signs of commercial encouragement. One, Avycaz (a combination of the third-generation cephalosporin ceftazidime with avibactam, a beta-lactamase inhibitor) from London-based AstraZeneca and Dublin-based Actavis (now Allergan), was approved in February 2015 on the basis of just two phase 2 studies to treat complicated intra-abdominal infections and complicated urinary tract infections. Avycaz' story highlights how the sector's improved fundamentals—the US Food and Drug Administration (FDA)'s newfound flexibility and the potential for early commercial success—set the stage for a resurgence that has already led to an uptick in early-stage venture investment and strategic partnerships.

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Antibiotic headwinds

If the field can prolong this momentum, it will qualify as quite a turnaround. Antibiotics R&D faced "a tremendous headwind" over the past 10 or 15 years, says Paratek Pharmaceuticals president and chief medical officer Evan Loh, who, before joining that Massachusetts-based antibiotics-focused biotech, had for more than a decade led the development of antibiotics such as Tygacil (tigacycline) at Wyeth and then Pfizer. A poor reimbursement climate and a lack of clarity and formal guidance at the FDA around clinical trial standards helped to drive large companies away from the space toward more lucrative markets with more predictable regulatory and commercial pathways. So much so that California-based Achaogen CEO Kenneth Hillan, on a panel at this year's Biotechnology Innovation Organization annual conference discussing the dire threat of antimicrobial resistance, went as far as to say that "fundamentally, [antibiotics] don't make sense for pharmaceutical companies."

That well-documented exodus from antibiotics R&D meant, says Loh, that "the innovation burden fell to small companies like Paratek," which like Achaogen is one of a handful of biotech companies shepherding new antibiotics through late-stage clinical trials (**Table 1**).

Until recently, though, the path for biotechs was challenged by poor capital environments, which led to the current paucity of late-stage antibiotics in the industry pipeline.

However, a renewed sense of urgency about the development of antibacterials, due to the global antimicrobial resistance crisis, together with reinvigorated regulatory and policy efforts to confront the crisis have coincided with biotech's financial boom of the past few years and the emergence of exciting new scientific opportunities. This state of affairs has resulted in a venture community that is now paying attention to antibiotics.

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For example, Paratek has entered phase 3 studies with its lead candidate omadacycline in acute bacterial skin and skin structure (ABSSSI) and community-acquired bacterial pneumonia (CABP) and, since going public via reverse merger with Transcept Pharmaceuticals in 2014, has raised more than $163 million to move toward registration. A second antibiotic in late-stage development at Paratek, sarecycline, is partnered in the US with Allergan.

Incentives GAINing momentum

The GAIN Act, which became law in 2012 as part of the FDA Safety and Innovation Act, gives the FDA authority to confer special status on antibiotics that treat serious and life-threatening infections. This Qualified Infectious Disease Product (QIDP) status grants automatic priority review (an 8-month review compared to the FDA's standard 12-month review) and an extra five years of market exclusivity. The FDA has bestowed the designation on dozens of antibiotic candidates, and several QIDP-designated products have been approved.

Merck's Cubist acquisition came only days before the biotech announced FDA approval of Zerbaxa (the novel cephalosporin ceftolozane combined with the existing beta-lactamase inhibitor tazobactam) to treat adults with complicated intra-abdominal infections; this was the fourth antibiotic approved in 2014 under the FDA's QIDP designation. It was also Cubist's second approval of the year: Sivextro (tedizolid) was approved in June to treat ABSSSI infections. Durata Therapeutics of Illinois received approval for Dalvance (dalbavancin), its own ABSSSI drug, in May and in October 2014 was acquired by Actavis for $675 million plus earn-outs. New Jersey-based The Medicines Company's ABSSSI drug Orbactiv (oritavancin) was approved in August 2014.

Although QIDP status may speed review and prolong an asset's potential commercial lifespan, a drug kept in reserve or used sparingly may have limited impact on a company's top line. In Europe, the Innovative Medicines Initiative's DRIVE-AB program was launched in late 2014 to test new antibiotics reimbursement models. Current legislation winding through Congress in the US, the so-called 21st Century Cures Act, includes provisions for approval of antibiotics for limited use based on ever-smaller datasets—effectively creating an orphan drug–like environment around certain therapies for drug-resistant infections—as well as improved reimbursement for antibiotics covered by Medicare (formerly a separate bill known as DISARM). Whether or not the Cures bill emerges as law—as of early October it had cleared the House of Representatives but remained in the Senate—it is clear that better reimbursement for antibiotics has taken a place alongside streamlined regulation as a key industry incentive.

Pharma returns?

Merck, The Medicines Co. and Allergan have all been joined by a few other large companies in returning to the antibiotics space. Paris-based Sanofi in early 2014 set up a research unit to look for new antibiotics, as part of a natural products center of excellence. Swiss company Roche has struck multiple antibiotics partnerships over the past two years, including a January 2015 deal with Tokyo's Meiji Seika Pharma for a phase 1 beta-lactamase inhibitor; an April 2014 alliance with Massachusetts-based Spero Therapeutics; and a February 2014 discovery and development deal with UK-based Discuva.

And interest extends beyond traditional antibiotics. Companies including Merck and AstraZeneca's Gaithersburg-based MedImmune division are making progress with antibodies directed against bacterial toxins. In early 2015, AstraZeneca spun off most of its early-stage antibiotics R&D into a new biotech, Entasis, which so far remains wholly owned by AstraZeneca. And in late September 2015 Merck announced that pivotal data for its antibody bezlotoxumab against toxins released by the Gram-negative bacteria *Clostridium difficile* showed that the drug reduced rates of infection recurrence.

Along with these advances, there have also been clinical setbacks. In September 2015, Tetraphase announced that its phase 3 IGNITE2 trial of eravacycline—which tested an intravenous-to-oral transition therapy for the treatment of complicated urinary tract infections—had failed to hit its primary endpoint. IGNITE1, which tested the drug candidate as an intravenous therapy only, had previously met its primary endpoint in complicated intra-abdominal infections in December 2014. The drug, which carries the FDA's QIDP designation, could potentially get reviewed at the FDA with the single positive trial, though Tetraphase has yet to comment on its strategy pending discussions with the agency. The trial results sent the company's shares down by about 80%, suggesting that investors were not optimistic.

On the other hand, the fact that Tetraphase's market value was so high to begin with suggests that investors had incorporated more than a modest takeout premium into the company's value,

Table 1. Selected unpartnered, QIDP-designated late-stage biotech antibiotics.

Drug candidate	Company	Clinical stage	Indication
Omadacycline	Paratek Pharmaceuticals	Phase 3	ABSSSI and CABP
Delafloxacin	Melinta Therapeutics	Phase 3	ABSSSI
Plazomicin	Achaogen	Phase 3	cUTI
Solithromycin	Cempra	Phase 3	CABP
Eravacycline	Tetraphase Pharmaceuticals	Phase 3	cUTI

ABSSSI, acute bacterial skin and skin structure; CABP, community-acquired bacterial pneumonia; cUTI, complicated urinary tract infection. Source: company reports.

underscoring the interest—or at least perceived interest—of pharmaceutical acquirers.

That same sentiment may be helping antibiotics biotechs raise tremendous sums from the public markets, alongside companies pursuing immuno-oncology targets and technology platforms like gene therapy. For example, in September 2015, Austria-based Nabriva raised $93 million in an IPO only months after its $120 million mezzanine round, to fund development of its antibiotic portfolio.

Deals and investment

Big Pharma's interest in antibiotics is also evident in its corporate venture activity. Take tiny Macrolide Pharmaceuticals, for example. The Massachusetts start-up raised $22 million in its Series A in March 2015, and the deal was led by the Novartis Venture Fund, Gurnet Point Capital, Roche Ventures and GlaxoSmithKline's SR One. "I like to say that we talked to every chemist in Basel before we got that deal done," quips Macrolide co-founder and CEO Lawrence Miller, a reflection of both the interest among Big Pharma strategic venture funds as well as their level of due diligence. The fundraising environment is "substantially different" from when Miller was raising money for Tetraphase, his previous antibiotics biotech startup, a decade ago. "There's no question that antibiotics are back in favor."

Macrolide is based on the "spectacularly good" chemistry platform developed by Harvard University professor Andrew Myers that will allow the company to synthesize "virtually any macrolide we can conceive of," says Miller. Gram-negative bacteria, he notes, have been largely resistant to macrolide antibiotics, but the biotech's platform will enable it to develop compounds that will partially or completely erase that resistance—infections caused by Gram-negative bacteria, which possess an outer lipopolysaccharide membrane that often thwarts intervention by antibiotics, are a key area of research. The company's first round of financing should allow it to progress to investigational new drug (IND) stage, and it is likely that Macrolide will announce "at least one partnership" in the next 6 to 12 months, he says.

Prabhavathi Fernandes, founder, president and CEO of Cempra Pharmaceuticals, says that real deal value, particularly for companies with late-stage assets, is likely to be tied to regulatory and commercial success. Cempra has priority review and fast-track designation from the FDA for its lead antibiotic solithroymcin—the former as part of the compound's QIDP status. "We're focused on delivering the best product to patients," she says. "There's always money to be made if you have a great product." Eventually Cempra will need partners—definitely in Asia, Europe and other 'rest-of-world' territories, and Fernandes doesn't rule out that such a partner may help Cempra market solithromycin in the US as well. And though she's skeptical of the so-called resurgence in antibiotic interest among the industry's largest companies, she notes that a partner doesn't need to be an antibiotics powerhouse. "Who are the biggest users of macrolides? Pulmonary doctors in hospitals. So it's possible that the companies that may be interested [in solithromycin] may already have a COPD drug, or an asthma drug," she says. "It's not necessary to have an anti-infective sales force" *per se*.

Indeed, Merck's acquisition of Cubist fits well with its focus on acute-care hospital products, explains executive director of business development for antibiotics Eric Warren, and "gives us momentum" as well as the impetus to backfill the company's antibiotics pipeline. The Big Pharma is "going after that space aggressively," he says. According to Warren, within the antibiotic piece of that market, Merck is working to help address gaps in the treatment of Gram-negative antibiotic-resistant infections via internal R&D, strategic investments and dealmaking in therapeutic and diagnostic areas. "There have been a lot of companies approaching us with early-stage assets," he says. "We're in discussions with many. There's definitely renewed interest."

Spero raised $30 million in its June 2015 Series A, in a round that included Merck's Research Ventures Fund and lead investor Lundbeckfond Ventures, alongside existing investors SR One, Atlas Venture and others. In July 2015, Merck made another investment in antibiotics through its separate Global Health Innovation Fund, as the sole investor in a $6 million financing of publicly traded infectious-disease diagnostics company OpGen. Spero's lead program is a potentiator, which essentially clears a path for a macrolide drug through the protective lipopolysaccharide membrane that surrounds Gram-negative bacteria. When combined with existing antibiotics for Gram-positive bacteria, the potentiator can increase the drugs' effects by 10,000-fold in Gram-negative bugs, says Spero co-founder and CEO Ankit Mahadevia. "Adding our potentiator can take a drug with no Gram-negative activity and create a market-leading drug," he says. The first compound from Spero's potentiator program should hit the clinic in 2016, though Mahadevia declines to say which macrolide the company plans to pair with it. The company's second program is the subject of its Roche deal. That collaboration targets the *Pseudomonas aeruginosa* transcription factor MvfR, which regulates production of that bug's virulence factors. In July, the companies said Spero had been awarded its first milestone payment under the deal.

Nodding to the recent Tetraphase clinical failure, Mahadevia acknowledges that the antibiotics space "will have blips like any other field, but that hasn't impacted the fundamentals because of the serious unmet need and the better regulatory environment," he says. "What's more, any reimbursement scheme that rewards breakthrough innovation, like value-based pricing, should reward the kind of drugs that Spero and other start-up antibiotic players are developing." Spero's proposition will be "solid and credible," Mahadevia says, noting that it's possible to have a great dialog from a public health perspective when you're "selling drugs that if you don't take them, you can die."

Chris Morrison is a freelance analyst, editor and writer who reports on the biotechnology and pharmaceutical industry.

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> **LAWRENCE MILLER, CEO OF MACROLIDE PHARMACEUTICALS**

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