

Small companies play big role in search for superbug killers

By Sarah Owerhohle

March 23, 2017

Superbugs are quickly becoming a top health concern, yet there has been a roughly 30-year dry spell in antibiotic molecule discovery.

The World Health Organization attempted to boost the issue Feb. 27 with its first list of the world's deadliest pathogens — 12 superbugs that are becoming increasingly resistant to all existing forms of antibiotics. Several of the most lethal bacteria are gram-negative and can effectively keep some of the strongest existing antibiotics out through dual protective membranes.

Of the 40 antibiotics in clinical development for the U.S. market, 70% belong to existing drug classes, meaning that some bacteria have already found ways to resist related treatments and could quickly learn it again, according to a December 2016 analysis by the Pew Charitable Trusts.

The nonprofit research group calculated that of the 34 companies working on these drugs, only five rank among the top 50 big pharma companies. The rest are smaller companies with little revenue, making new molecule development difficult.

Big pharma has steadily exited the antibiotic space over the past decade, Allan Coukell, senior director of health programs for Pew Trusts, said.

“That’s been a long-term trend, driven both by that difficulty of finding new antibiotics, but also the economics of drug development, where the return tends to be much better on the investment in cancer drugs than in antibiotics,” he told S&P Global Market Intelligence.

Even without the pressure of new molecule development, the antibiotic market exists in a paradox. The more powerful an antibiotic is, the more precious it becomes to doctors, who will then prescribe it rarely to prevent resistance. An extremely effective antibiotic may see the light of day sparingly, generating very little revenue for its manufacturers.

Denmark-based Xellia Pharmaceuticals produces antibiotics through a stewardship program, repurposing older antibiotic molecules in new treatments. Executives say that

even with the use of existing treatments, the economics of the antibiotic market are challenging.

“The current business model in anti-microbial therapies is broken,” Aleksandar Danilovski, Xellia’s chief scientific officer and vice president of global R&D and regulatory affairs, said. “You have to put a lot of effort in trying to discover something which will then be used as a last resort.”

Lowering development costs

For Danilovski, pharmaceutical companies and payers need to change the way they think about targeted antimicrobial medicines, particularly those that work against superbugs. In a way, they need to be perceived almost on the level of orphan drugs or cancer therapies, he said.

Government bodies have worked to bring down clinical trial costs and expensive phase 3 trial requirements, which has alleviated some of the pressure, according to Carl-Åke Carlsson, CEO of Xellia.

“It’s not on the industry alone to try and solve this,” Carlsson said.

In the U.S., the Biomedical Advanced Research and Development Authority funds select pharmaceutical trials, and in July 2016 launched CARB-X, an accelerator program specifically for antibiotic-resistant bacteria research. The Generating Antibiotic Incentives Now Act, or GAIN, was passed in 2012 to extend the patent exclusivity by five years, giving companies more time to recoup costs.

In September 2016, the National Institutes of Health launched a cash prize to fund research. Coukell said that this is not traditionally the work that NIH funds, but it is also not the kind of work that companies are able to do themselves right now.

The future in synthetic antibiotics

One antibiotic company is attempting to step outside the typical antibiotic model entirely. Australia-based Recce Ltd., named for the local shorthand for a reconnaissance mission, is developing a synthetic antibiotic that the chairman says

Pipeline for antibiotics with gram-negative potential

Drug name	Company S	tatus (as of Dec. 2016)	Potential indications*
Cefepime + Zidebactam (WCK 5222)	Wockhardt Ltd.	Phase 1	Complicated urinary tract infections, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia
Finafloxacin	MerLion Pharmaceuticals Pte Ltd.	Phase 2	Complicated urinary tract infections, acute kidney infection, complicated intra-abdominal infections, acute bacterial skin and skin structure infections
POL7080	Polyphor Ltd.	Phase 2	Ventilator-associated bacterial pneumonia caused by <i>Pseudomonas aeruginosa</i>
Ceftaroline + Avibactam	Pfizer Inc./ Allergan PLC	Phase 2	Multi-drug resistant gram-positive and common enteric gram-negative infections
Aztreonam + Avibactam ^{7,10} (ATM-AVI)	Pfizer Inc./ Allergan PLC	Phase 2	Complicated intra-abdominal infections, multi-drug resistant gram-negative infections
Carbavance (meropenem + vaborbactam)	Rempex Pharmaceuticals Inc. (subsidiary of The Medicines Co.)	Phase 3	Complicated urinary tract infections, complicated intra-abdominal infections, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia, febrile neutropenia
Omadacycline	Paratek Pharmaceuticals Inc.	Phase 3	Community-acquired bacterial pneumonia, acute bacterial skin and skin structure infections, complicated urinary tract infections
Plazomicin	Achaogen Inc.	Phase 3	Complicated urinary tract infections, catheter-related bloodstream infections, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia, complicated intra-abdominal infections
Cefiderocol (S-649266)	Shionogi & Co. Ltd.	Phase 3	Complicated urinary tract infections, Carbapenem-resistant gram-negative bacterial infections
EravacyclineT	etraphase Pharmaceuticals Inc.	Phase 3	Complicated intra-abdominal infections, complicated urinary tract infections
Imipenem/cilastatin + relebactam (MK-7655)	Merck & Co. Inc.	Phase 3	Complicated urinary tract infections, complicated intra-abdominal infections, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia

* This column does not reflect all the indications of each drug.
Sources: Pew Charitable Trusts Antibiotic Resistance Project and corporate websites
Credit: Augusto Raymund Justiniano Jr.

can fight any bacteria and its mutation. Antibiotics have their roots in natural sources such as mold, though an increasing number are at least partially synthetic. Recce said its wholly synthetic variation translates to quicker and more economic manufacturing.

However, it is the potential to fight mutations that could potentially remove Recce from the precious drug paradox, in which super-effective treatments are kept under lock and key.

“Our product is not susceptible to resistance brought about by the germ mutating,” Graham Melrose, Recce’s founder and executive chairman, told S&P Global Market Intelligence. Unlike “lock and key” antibiotics, or those that only work by targeting specific bacteria, Recce’s antibiotic focuses on attacking the proteins around any bacteria, he said.

Executive Director James Graham said the company has tested against six out of the 12 bacteria listed by WHO, and its antibiotic killed all six bacteria, resistant or not.

While the drug is still in very early stages — the company is aiming to apply to the FDA for investigative new drug status in the second half of 2017 and begin phase 1 trials next year — Melrose said the nature of Recce’s product could reduce pricing pressures.

“Our pricing, as far as antibiotics go, will definitely be economic and available,” he said.

In the meantime, big pharma has not entirely abandoned the space. After acquiring AstraZeneca PLC's anti-infective business in 2016, Pfizer Inc. launched combination therapy Zavicefta in the U.K. and Germany on March 14, with expected non-U.S. global rollout throughout 2017-2018. Allergan PLC has the U.S. rights to the drug and markets it as Avycaz.

Pfizer said Zavicefta has proven effective against two of the WHO's critical priority pathogens, *Pseudomonas aeruginosa* and Enterobacteriaceae, as well as several other infections that have not formed resistance. According to Pew's pipeline data, Pfizer and Allergan have two similar combination therapies in phase 2 trials for the U.S.