Building the antibiotic pipeline

The big picture is mostly unchanged. As of March, a total of 42 small molecule drugs were in development to treat serious bacterial infections, a global public health problem. Of this number, 39 are in Phase 1-3 clinical trials and three are applying for a regulatory approval in the US or Japan. These figures come from the PEW Charitable Trusts, a charity which publishes and regularly updates the status of global antibiotic drug development. The list is a measure of what the pharma industry is doing to replenish the antibiotic pipeline. It is also a reminder of what still needs to be done. PEW estimates that only one in five of the candidate antibiotics on its tables and entering human trials today will eventually reach patients.

"The bottom line is that we need more antibiotics and it's not just to combat bugs today, but we need to think about what is coming down in terms of resistance five to 10 years from now. If we are not planning for those and doing the clinical studies for those, in five to 10 years we will be left empty-handed," Wes Kim, a senior officer of the Trust, said in an interview.

There is no ideal number. What is more important is to ensure that the portfolio is diverse and includes novel molecules, he added.

Since 2014, the charity's list of antibiotics in the clinic has fluctuated between a low of 36 and a high of 48 as new compounds come into development and others leave, either because they have been approved by a regulator or worse – have been abandoned by their developers.

PEW has specific inclusion and exclusion criteria for its tables in order to be sure that they capture the most important molecules in development and align with priorities set by public bodies such as the World Health Organization. The antibiotics must be systemic and represent new chemical entities. Reformulations of existing drugs are excluded. Also excluded are drugs being developed against fungal infections and tuberculosis. Compounds that are included target bacteria which are the cause of complicated urinary tract infections, hospital-acquired bacterial pneumonia and *C. difficile* infections, to name just a few. Just under half of the pipeline consists of drugs targeting Gram-negative bacteria. (Please see page 6 for this list).

Since 2014, the US Food and Drug Administration has approved 10 new antibiotics appearing on the PEW lists including Sivextro for serious bacterial skin infections, Nuzyra for community-acquired bacterial pneumonia and Zerbaxa and Zemdri for complicated urinary tract infections.

However, the approval of Zemdri, in June 2018, was followed 10 months later by the bankruptcy of the developer Achaogen Inc. Achaogen filed a petition under Chapter 11 of the US bankruptcy code on 15 April because the company's management could not make ends meet. Zemdri had been approved for the treatment of urinary tract infections caused by *Enterobacteriaceae*, a large family of Gram-negative bacteria. At the time of the bankruptcy, Achaogen had secured a place for the antibiotic on 156 US hospital formularies and contracts were in place for over 200 physician-owned outpatient infusion centres. But this was not enough to keep the company afloat.

Dr Kim said the bankruptcy has focused minds on the antibiotic business model. "We need to constantly replenish the pipeline. Part of the challenge is not only the science behind clinical development; what's particularly difficult for antibiotics is the economics as well," he commented.

Antibiotic specialists describe the economic models as consisting of 'push' incentives to help companies get started in development, and 'pull' to get new antibiotics onto the market. The models all involve incentives that wouldn't normally be available to pharma. The reasoning is that antibiotics need to be developed and used sparingly. Consequently they won't generate large sales.

One of the push incentives is the FDA's 'qualified infectious disease product designation' for antibacterial or antifungal drugs that are designed to treat life-threatening infections. If approved, products with this status get a longer period of market exclusivity. Companies in the US can also get development assistance from the National Institute of Allergy and Infectious Diseases and the Biomedical Advanced Research and Development Authority. Globally, the WHO and the Drugs for Neglected Disease Initiative have launched the Global Antibiotic Research and Development Partnership (GARDP) to support antibacterial research and development. Early research is also supported by funds from the non-profit partnership Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X). In addition, private companies like Novo Holdings A/S have jumped into the field with incentives for antibiotic development. In 2018 Novo launched the REPAIR Impact Fund to invest $20 to $40 million per year over three to five years in about 20 antibiotic projects in the US and Europe. The goal is to get at least one new antibiotic medicine from these projects onto the market.

By comparison there are far fewer pull incentives. Ideas under discussion include changes to national reimbursement systems to reward antibiotics and market entry rewards that would be paid out over a period of years to companies with drugs that meet a defined public health need. Another idea is a voucher scheme that would allow antibiotic developers to get an additional exclusivity period for other, non-antibiotic drugs in their portfolios.

"You probably can't afford to pay these market entry rewards in perpetuity but [they might] at least stabilise the market…At the end of the day someone has to pay for it whether it's the hospitals or the taxpayers. Hopefully we can spread the cost so it's not too onerous," Dr Kim said.

While discussing these ideas with others PEW has launched a virtual platform with data for researchers that are investigating new antibiotics. On 10 May, it announced that Novartis had agreed to contribute two datasets to the platform from a discontinued antibiotic discovery programme. The contribution includes more than 10,000 data points that will be combined with the platform's existing data.

This article is based on an interview and research by the *MedNous* editor. Thanks are extended to the PEW Charitable Trusts for sharing their data for publication.

Drugs in development that target Gram-negative bacteria Source: The PEW Charitable Trusts						
Drug name	**Phase**	**Company**	**Drug class**	**Target**	**Potential indication(s)**	**Expected activity against ESKAPE pathogens**
AIC499	Phase 1	AiCuris	β-lactam	PBP	Complicated intra-abdominal infections and complicated urinary tract infections	Possibly
Cefepime + VNRX-5133	Phase 1	VenatoRx Pharmaceuticals Inc	β-lactam (cephalosporin) + β-lactamase inhibitor (cyclic boronate)	PBP, β-lactamase	Complicated intra-abdominal infections and complicated urinary tract infections	Yes
Cefepime + zidebactam (WCK 5222)	Phase 1	Wockhardt Ltd	β-lactam (cephalosporin) + β-lactamase inhibitor (diazabicyclooctane)	PBP, β-lactamase	Complicated urinary tract infections and hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia	Yes
ETX0282CPDP	Phase 1	Entasis Therapeutics Inc	β-lactam (cephalosporin) + β-lactamase inhibitor (diazabicyclooctane)	PBP, β-lactamase	Urinary tract infections	Yes
KBP-7072	Phase 1	KBP BioSciences Pharmaceutical Technical Co. Ltd	Tetracycline	30S subunit of bacterial ribosome	Community-acquired bacterial pneumonia	Possibly
Meropenem + nacubactam (OP0595/RG6080)	Phase 1	Meiji Seika Pharma Co. Ltd./Fedora Pharmaceuticals Inc (Roche licensee)	β-lactam (carbapenem) + β-lactamase inhibitor (diazabicyclooctane)	PBP, β-lactamase, PBP2	Bacterial infections	Yes
SPR206	Phase 1	Spero Therapeutics	Polymyxin	cell membrane	Complicated urinary tract infections and hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia	Yes
SPR741	Phase 1	Spero Therapeutics	Polymyxin	cell membrane	Bacterial infections	Possibly
TP-271	Phase 1	Tetraphase Pharmaceuticals Inc	Tetracycline	30S subunit of bacterial ribosome	Community-acquired bacterial pneumonia	Possibly
TP-6076	Phase 1	Tetraphase Pharmaceuticals Inc	Tetracycline	30S subunit of bacterial ribosome	Bacterial infections	Yes
ETX2514SUL	Phase 2	Entasis Therapeutics Inc	β-lactam (sulbactam) + β-lactamase inhibitor (diazabicyclooctane)	PBP, β-lactamase	Complicated urinary tract infection including acute pyelonephritis, and hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia	Yes
Finafloxacin	Phase 2	MerLion Pharmaceuticals Pte Ltd	Fluoroquinolone	Bacterial type II topoisomerase	Acute bacterial skin and skin structure infections, complicated intra-abdominal infections, and complicated urinary tract infections including pyelonephritis	Yes
BOS-228 (LYS228)	Phase 2	Boston Pharmaceuticals (Licensed from Novartis AG)	β-lactam (monobactam)	PBP	Complicated urinary tract infections and complicated intra-abdominal infections	Yes
Cefepime + AAI101	Phase 3	Allecra	β-lactam (cephalosporin) + β-lactamase inhibitor (β-lactam)	PBP, β-lactamase	Complicated urinary tract infections including pyelonephritis, complicated intra-abdominal infections, and hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia	Yes
Cefiderocol (S-649266)	Phase 3	Shionogi & Co. Ltd	Siderophore-β-lactam (cephalosporin)	PBP	Complicated urinary tract infections, hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia, bloodstream infections, and sepsis	Yes
Ceftobiprole	Phase 3	Basilea Pharmaceutica Ltd	β-lactam (cephalosporin)	PBP	Acute bacterial skin and skin structure infections, bacteremia, community-acquired bacterial pneumonia, and hospital-acquired bacterial pneumonia	Yes
Imipenem/ cilastatin + relebactam (MK-7655A)	Phase 3	Merck & Co. Inc	β-lactam (carbapenem) + β-lactamase inhibitor (diazabicyclooctane)	PBP, β-lactamase	Complicated urinary tract infections including pyelonephritis, complicated intra-abdominal infections, and hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia	Yes
Murepavadin (POL7080)	Phase 3	Polyphor AG	Antimicrobial peptide mimetic	LptD	Hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia (caused by *Pseudomonas aeruginosa*)	Yes (Pseudomonas)
SPR994	Phase 3	Spero Therapeutics	β-lactam (carbapenem)	PBP	Community-acquired bacterial pneumonia, complicated urinary tract infections, diabetic foot infection, and acute pyelonephritis	Yes
Sulopenem	Phase 3	Iterum Therapeutics	utics β-lactam (carbapenem)	PBP	Complicated urinary tract infections, uncomplicated urinary tract infections, and complicated intra-abdominal infections	Yes

Note: The ESKAPE pathogens are *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter* species.