Antibiotics Currently in Clinical Development

As of March 2015, an estimated 36 new antibiotics[1] that have the potential to treat serious bacterial infections are in clinical development for the U.S. market. The success rate for drug development is low; at best, only 1 in 5 candidates that enter human testing will be approved for patients.* This snapshot of the antibiotic pipeline will be updated periodically, based on publicly available information and informed by an external expert, as products advance or are known to drop out of development. Please contact abxpipeline@pewtrusts.org with additions or updates.

Drug name	Development phase[2]	Company	Drug class	Expected activity against resistant Gram-negative ESKAPE pathogens?[3]	Expected activity against a CDC urgent threat pathogen?[4]	Potential indication(s)?[5]
Tedizolid (Sivextro)	Approved June 20, 2014	Cubist Pharmaceuticals (wholly owned subsidiary of Merck & Co.)	Oxazolidinone	No	No	*Approved for:* **acute bacterial skin and skin structure infections;** *other potential indications:* **hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia**
Dalbavancin (Dalvance)	Approved May 23, 2014	Actavis (formerly Durata Therapeutics)	Lipoglycopeptide	No	No	*Approved for:* **acute bacterial skin and skin structure infections;** *other potential indications:* community-acquired bacterial pneumonia
Oritavancin (Orbactiv)	Approved Aug. 6, 2014	The Medicines Co.	Glycopeptide	No	No	*Approved for:* **acute bacterial skin and skin structure infections caused by Gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA)**
Ceftolozane+Tazobactam (Zerbaxa)	Approved Dec. 19, 2014	Cubist Pharmaceuticals (wholly owned subsidiary of Merck & Co.)	Novel cephalosporin+beta-lactamase inhibitor	Yes	No	*Approved for:* **complicated urinary tract infections, complicated intra-abdominal infections,** acute pyelonephritis (kidney infection); *other potential indications:* **hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia**
Ceftazidime+Avibactam (Avycaz)	Approved Feb. 25, 2015[13]	AstraZeneca/Actavis (formerly Forest Laboratories)	Cephalosporin + novel beta-lactamase inhibitor	Yes	Yes	*Approved for:* **complicated urinary tract infections, complicated intra-abdominal infections,** acute pyelonephritis (kidney infection); *other potential indications:* **hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia,** bacteremia
OP0595 (RG 6080)	Phase 1[10]	Meiji Seika Pharma Co. Ltd./Fedora Pharmaceuticals Inc. (Roche licensee)	Beta-lactamase inhibitor	Possibly	Possibly	Bacterial infections

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Aztreonam+Avibactam[7] (ATM-AVI)	Phase 1[10]	AstraZeneca/Actavis (formerly Forest Laboratories)	Monobactam + novel beta-lactamase inhibitor	Yes	Yes	Bacterial infections
BAL30072	Phase 1	Basilea Pharmaceutica	Monosulfactam	Yes	Yes	Multidrug-resistant Gram-negative bacterial infections[6]
CRS3123	Phase 1	Crestone	Methionyl tRNA synthetase (MetRS) inhibitor	No	Yes	*Clostridium difficile* infection
LCB01-0371	Phase 1[10]	LegoChem Biosciences (South Korea)	Oxazolidanone	No	No	Bacterial infections
TD-1607	Phase 1	Theravance Biopharma	Glycopeptide-cephalosporin heterodimer	No	No	**Acute bacterial skin and skin structure infections,[6] hospital-acquired pneumonia/ ventilator-associated pneumonia,[6] bacteremia[6]**
WCK 2349	Phase 1	Wockhardt	Fluoroquinolone (WCK 771 pro-drug)	No	No	Bacterial infections
WCK 771	Phase 1	Wockhardt	Fluoroquinolone	No	No	Bacterial infections
MRX-I	Phase 2	MicuRx Pharmaceuticals	Oxazolidinone	No	No	Acute bacterial skin and skin structure infections
Debio 1450	Phase 2[14]	Debiopharm Group	FabI inhibitor (Debio 1452 pro-drug)	No	No	**Acute bacterial skin and skin structure infections (staphylococcal-specific)**
EXT0914	Phase 2	Entasis Therapeutics[15]	DNA gyrase and Topoisomerase IV inhibitor	No	Yes	**Uncomplicated gonorrhea**
S-649266	Phase 2	Shionogi	Cephalosporin	Yes	Yes	Complicated urinary tract infections
POL7080 (RG 7929)	Phase 2[10]	Polyphor (Roche licensee)	Macrocycle (protein epitope mimetic) LptD inhibitor	Yes (*Pseudomonas*)	No	**Ventilator-associated bacterial pneumonia (caused by *Pseudomonas aeruginosa*),** lower respiratory tract infection, bronchiectasis
Debio 1452	Phase 2	Debiopharm Group	FabI inhibitor	No	No	**Acute bacterial skin and skin structure infections (staphylococcal-specific)**
Avarofloxacin	Phase 2	Actavis (formerly Furiex Pharmaceuticals)	Fluoroquinolone	No	No	**Community-acquired bacterial pneumonia, acute bacterial skin and skin structure infections**
Brilacidin	Phase 2	Cellceutix	Defensin-mimetic	No	No	**Acute bacterial skin and skin structure infections**
Ceftaroline+Avibactam	Phase 2	AstraZeneca/Actavis (formerly Forest Laboratories)	Cephalosporin + novel beta-lactamase inhibitor	Yes	Yes	Bacterial infections[6]

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CG-400549	Phase 2	CrystalGenomics	FabI inhibitor	No	No	Acute bacterial skin and skin structure infections, osteomyelitis[6]
Finafloxacin[11]	Phase 2[12]	MerLion Pharmaceuticals	Fluoroquinolone	Yes[16]	Possibly[17]	**Complicated urinary tract infections, acute pyelonephritis (kidney infection), complicated intra-abdominal infections, acute bacterial skin and skin structure infections**
GSK2140944	Phase 2	GlaxoSmithKline	Type 2 topoisomerase inhibitor	No	Yes	Respiratory tract infections, acute bacterial skin and skin structure infections, uncomplicated urogenital gonorrhea
Lefamulin (BC-3781)	Phase 2	Nabriva Therapeutics	Pleuromutilin	No	No	**Acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia,** hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia[6]
Imipenem/ cilastatin+relebactam (MK-7655)	Phase 2	Merck	Carbapenem + novel beta-lactamase inhibitor	Yes	Yes	**Complicated urinary tract infections,** acute pyelonephritis, **complicated intra-abdominal infections, hospital-acquired bacterial pneumonia/ventilator-associated bacterial pneumonia**
Nemonoxacin[8]	Phase 2	TaiGen Biotechnology	Quinolone	No	No	**Community-acquired bacterial pneumonia,** diabetic foot infection, **acute bacterial skin and skin structure infections**
Omadacycline	Phase 2	Paratek Pharmaceuticals	Tetracycline	Yes	Possibly[17]	**Community-acquired bacterial pneumonia, acute bacterial skin and skin structure infections, complicated urinary tract infections**
Radezolid	Phase 2	Melinta Therapeutics	Oxazolidinone	No	No	**Acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia**
Ramoplanin	Phase 2	Nanotherapeutics	Lipoglycopeptide	No	Yes	*C. difficile*-associated diarrhea,[6] *C. difficile* relapse prevention[6]
Zabofloxacin	Phase 2	Dong Wha Pharmaceutical	Fluoroquinolone	No	No	Community-acquired bacterial pneumonia
SMT 19969	Phase 2	Summit		No	Yes	***C. difficile*-associated diarrhea**
Cadazolid	Phase 3	Actelion Pharmaceuticals	Quinolonyl-oxazolidinone	No	Yes	***C. difficile*-associated diarrhea**
Taksta (Fusidic acid)[9]	Phase 3	Cempra Inc.	Fusidane	No	No	Prosthetic joint infections, acute bacterial skin and skin structure infections

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Carbavance (RPX709+meropenem)	Phase 3	Rempex Pharmaceuticals (wholly owned subsidiary of the Medicines Co.)	Meropenem + novel boronic beta-lactamase inhibitor	Yes	Yes	**Complicated urinary tract infections, complicated intra-abdominal infections, hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia, febrile neutropenia,** bacteremia, acute pyelonephritis (some indications specifically target infections caused by carbapenem-resistant Enterobacteriaceae)
Delafloxacin	Phase 3	Melinta Therapeutics	Fluoroquinolone	Possibly	Possibly	**Acute bacterial skin and skin structure infections,** hospital-acquired bacterial pneumonia,[6] complicated urinary tract infections,[6] complicated intra-abdominal infections[6]
Eravacycline	Phase 3	Tetraphase Pharmaceuticals	Tetracycline	Yes	Yes	**Complicated intra-abdominal infections, complicated urinary tract infections,** hospital-acquired bacterial pneumonia[6]
Plazomicin	Phase 3	Achaogen	Aminoglycoside	Yes	Yes	**Complicated urinary tract infections, catheter-related bloodstream infections, hospital-acquired bacterial pneumonia/ ventilator-associated bacterial pneumonia, complicated intra-abdominal infections** (some indications specifically target infections caused by carbapenem-resistant Enterobacteriaceae)
Solithromycin	Phase 3	Cempra Inc.	Macrolide (fluroketolide)	No	Yes	**Community-acquired bacterial pneumonia, uncomplicated urogenital gonorrhea,** urethritis[6]
Surotomycin	Phase 3	Cubist Pharmaceuticals (wholly owned subsidiary of Merck & Co.)	Lipopeptide	No	Yes	***C. difficile*-associated diarrhea**

Note: The following drugs have been removed from the pipeline. They will be included in future updates if development resumes.

March 2015 review: No changes.

December 2014 review: EDP-788 (Enanta Pharmaceuticals) and TD-1792 (Theravance Biopharma) were removed during the December 2014 review. These drugs were either no longer included in the research and development pipelines on the company website, or there was direct communication from the company regarding the status of the drugs. Additionally, GSK-2696266, which had been removed during the September review, is included in this pipeline again as S-649266, which is being developed by Shionogi.

September 2014 review: GSK-2696266 and GSK-1322322 (GlaxoSmithKline), ACHN-975 (Achaogen), and LFF571 (Novartis) were removed during the September 2014 review. These drugs were either no longer included in the research and development pipelines on the company website, or there was direct communication from the company regarding the status of the drugs.

June 2014 review: Ceftobiprole, an antibiotic developed by Basilea Pharmaceutica, had been included in our analysis; however, the company announced in June 2014 that it is not pursuing further development in the United States until a partner has been acquired.

* Michael Hay et al., "Clinical Development Success Rates for Investigational Drugs," *Nature Biotechnology* 32, no. 1 (2014): 40–51, doi:10.1038/nbt.2786. See more at http://www.pewtrusts.org/en/multimedia/data-visualizations/2014/antibiotics-currently-in-clinical-development#sthash.XLzMLQta.dpuf.

Endnotes

1. Antibiotics listed here include products containing at least one component not approved in the United States previously. All analyses were strictly limited to systemic antibiotics (drugs that work throughout the body) and drugs to treat *Clostridium difficile*-associated disease. The Centers for Disease Control and Prevention cited *C. difficile* as an urgent public health threat in a 2013 report (*Antibiotic Resistance Threats in the United States*, 2013, Sept. 16, 2013, http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf). We also limited this pipeline to drugs with the potential to treat serious or life-threatening infections. Specifically excluded were drugs to treat mycobacterial infections, such as tuberculosis and *Mycobacterium avium* complex, *H. Pylori*, and biothreat pathogens. Additionally, we excluded biological products, vaccines, and locally acting drugs such as topical, ophthalmic, and inhaled products. Avibactam, a novel beta-lactamase inhibitor, is being studied in combination with three approved antibiotics, and all three were counted for this report, because each combination targets a distinct set of pathogens.
2. Based on the most advanced development phase for any indication according to trials registered in clinicaltrials.gov, unless direct communication from the company indicated differently. If no trials were included in clinicaltrials.gov, then the phase listed on the company website or provided directly by the company is noted. Antibiotics that have been approved will remain listed for one year following approval of the initial indication.
3. A 'yes' in this column indicates that a drug has *in-vitro* data showing both activity against one or more Gram-negative species that are considered ESKAPE pathogens (*Enterobacter species, Klebsiella pneumoniae, Acinetobacter baumanii,* or *Pseudomonas aeruginosa*) and the potential for clinically significant improved coverage of resistant isolates of these species relative to currently available antibiotics. Excluded are drugs that may have shown *in-vitro* activity but currently have no relevant indications listed in this pipeline. This does not apply to Phase 1 drugs, where indications are often unknown. Two drugs are listed as 'possibly' according to these criteria. It is suspected that OP0595 will meet the criteria for this column, but is listed as 'possibly' pending public release of data and identification of the beta-lactam antibiotic with which it will be combined. Delafloxacin is also listed as 'possibly'. Although current data show the potential for improved coverage compared with currently available fluoroquinolones in acidic environments, it is not clear how this *in-vitro* benefit will translate into clinical efficacy. This column focuses on only one area of unmet medical need. However, stakeholders often highlight resistant Gram-negative ESKAPE pathogens as an area in which innovation is urgently needed and drug discovery and development are particularly challenging. This column is based on information available in the literature, but we welcome any additional information a company may be able to provide. The column definition was revised in March 2015. In previous versions of this chart, the column included all drugs with Gram-negative activity (including drugs active against *Neisseria gonorrhoeae* or *Haemophilus influenzae*).
4. A 'yes' in this column indicates that a drug has the potential to address one of the pathogens identified by the Centers for Disease Control and Prevention as an 'urgent threat' to public health. These include *Clostridium difficile*, carbapenem-resistant Enterobacteriaceae, and drug-resistant *Neisseria gonorrhoeae*. Excluded are drugs that may have shown in-vitro activity but currently have no relevant indications listed in this pipeline. This does not apply to Phase 1 drugs, where indications are often unknown. Delafloxacin and OP0595 are listed as 'possibly' in this column, for the reasons explicated in Note 3. Finafloxacin and omadacycline are also listed as 'possibly' (see Note 17).
5. Based on clinical trials currently registered in clinicaltrials.gov and/or reported qualified infectious disease product (QIDP) designations unless otherwise noted. Boldface indications are reported QIDP designations. QIDP designations are given by the Food and Drug Administration to antibiotics intended to treat serious or life-threatening infections. QIDPs are eligible to receive benefits under the Generating Antibiotic Incentives Now Act (signed into law as part of the Food and Drug Administration Safety and Innovation Act), including expedited FDA review and extended exclusivity for approved products.
6. Not currently registered on clinicaltrials.gov. Information obtained from the company via a corporate website, news release, and/or direct communication.
7. Avibactam is a new beta-lactamase inhibitor being tested in conjunction with three individual antibiotics. We list all three combinations here.
8. Nemonoxacin has been approved for community-acquired bacterial pneumonia in Taiwan; a new drug application was submitted in China.
9. Taksta was granted an orphan drug designation for the indication of prosthetic joint infections.
10. Registered in clinicaltrials.gov, but with no current study sites within the United States.
11. In February 2015, FDA approved an otic suspension formulation of finafloxacin to treat acute otitis externa. Because a systemic formulation of finafloxacin has not received approval in the U.S., this drug remains in our pipeline.
12. Phase 2 trials for finafloxacin do not currently include any U.S. study sites; however, the company indicated in a December 2012 news release that the trial was based on updated guidance from FDA.
13. Avycaz was approved based on Phase 2 data.
14. The Phase 2 study for Debio 1450 was registered in clinicaltrials.gov after the March review, but before this update was published. This trial was scheduled to start in May 2015.
15. Entasis Therapeutics was created by AstraZeneca as a stand-alone subsidiary company after the March review but before publication of this update.
16. Finafloxacin has shown the potential for improved activity under certain conditions, namely acidic environments. Additionally, a company news release noted that Phase 2 complicated urinary tract infection study results (unpublished) have shown improved clinical outcomes in patients treated with finafloxacin compared with patients treated with the current standard of care.
17. Both finafloxacin and omadacycline have in-vitro activity against Enterobacteriaceae; however, published studies have not specifically referenced whether these drugs were tested against carbapenem-resistant strains.

Citations

i. Citeline, "Pharmaprojects," (2012), http://www.citeline.com/products/pharmaprojects.

ii. BioCentury, "Antibiotics NCE Pipeline," accessed Oct. 28, 2013, http://www.biocentury.com/antibioticsncepipeline.htm.

iii. U.S. National Institutes of Health, "Search for Studies," http://www.clinicaltrials.gov.

iv. Helen W. Boucher et al., "10 x '20 Progress—Development of New Drugs Active Against Gram-Negative Bacilli: An Update From the Infectious Diseases Society of America," *Clinical Infectious Diseases* 56 (2013): 1685–94, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3707426.

v. Michael J. Pucci and Karen Bush, "Investigational Antimicrobial Agents of 2013," *Clinical Microbiology Reviews* 26 (2013): 792–821, http://cmr.asm.org/content/26/4/792.

vi. Centers for Disease Control and Prevention, *Antibiotic Resistance Threats in the United States*, 2013 (Sept. 16, 2013), http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf.

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