Longitudinal Analysis of the Antibiotics Clinical Pipeline

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Background

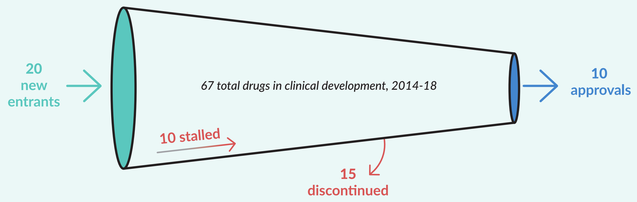
As resistant bacteria continue to emerge and existing antibiotics become less effective, finding new ways to combat these dangerous pathogens is essential. Yet many large pharmaceutical companies have abandoned investments in antibiotic innovation, and the remaining smaller companies have fewer resources to tackle this public health threat. In 2014, The Pew Charitable Trusts' antibiotic resistance project began tracking the pipeline of small molecule antibiotics in clinical development to inform public policies aimed at spurring innovation of new antibiotics. Each pipeline update characterizes the number of drugs that have potential activity against globally recognized priority pathogens, and this analysis compares those data across years.

This analysis examines the antibiotics pipeline from 2014 to 2018, utilizing data collected from Pew's small molecule pipeline analyses and the Food and Drug Administration's (FDA's) drug approval database. The goal of this research is to enhance our understanding of trends in antibiotic discovery and development activities, and to compare the state of the global antibiotic pipeline with drugs for other therapeutic areas. Further, this analysis characterizes the proportion of large pharmaceutical companies and smaller pre-revenue companies developing antibiotics from 2014 to 2018. These longitudinal analyses underscore the long-standing concerns of scientists, doctors, public health officials, and other stakeholders regarding the dangerously low number of antibiotics in development to address current and future patient needs.

Methods

Citeline Inc.'s Pharmaprojects pipeline drug intelligence service provided an initial list of each antibiotic candidate and approved drug from 2014 to 2018, and it was supplemented through the collection of publicly available clinical trial and FDA drug approval registries, company websites and press releases, peer-reviewed literature, and conference presentations.[1] The following information was collected for each candidate: clinical development phase, organization(s) developing the candidate, drug class and target, and expected activity against Gram-negative ESKAPE pathogens, those labeled urgent by the U.S. Centers for Disease Control and Prevention or a critical threat by the World Health Organization (WHO).[2] Approved drugs classified as a new molecular entity were also identified based on FDA review category and by therapeutic area as reported by the agency's website.[3] Company characterizations were based on their respective portfolios as shown on their websites. Pre-revenue companies are defined as those that had not developed and launched a new molecular entity drug.

What Does the 5-Year Analysis Show?

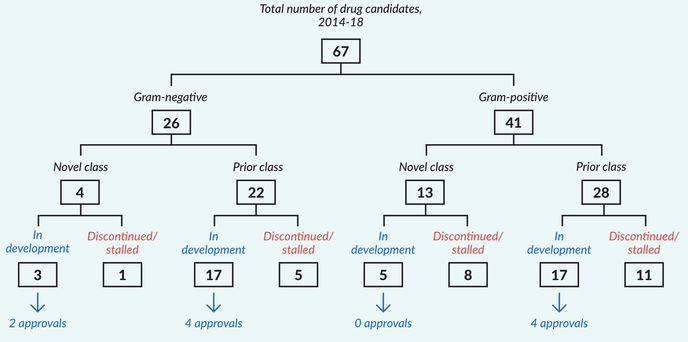


Notes: The 67 drugs include candidates in development, new entrants, stalled and discontinued candidates, and approvals. Forty-two drugs remained in active development as of December 2018.

- Year-over-year number of candidates ranged between 37 and 46.
- Nearly 60 percent of drugs targeted Gram-positive pathogens.
- Of 17 drugs representing novel chemical classes, almost half either stalled or were discontinued.
- Of 50 remaining drugs based on previous discoveries, less than a third were discontinued over the same period.
- 18 drugs had potential to address at least one WHO critical threat pathogen: carbapenem-resistant Enterobacteriaceae (CRE), *Acinetobacter baumannii* (CRAB), or *Pseudomonas aeruginosa* (CRPA).
  - 13 had activity against most CRE.
  - 4 drugs were active against CRAB.
  - 3 drugs were active against CRPA.

Overview of findings

Majority of antibiotic drugs in development utilize previous discoveries



Do FDA Antibiotic Approvals Compare With Those of Other Therapeutic Drugs?

10 antibiotics approved from 2014-18

Drug	Company	Approved	Novel	Activity against Gram-negative ESKAPE?	Indicated for WHO critical pathogen?
Dalvance (dalbavancin)	Durata Therapeutics Inc.	2014	x	x	x
Orbactiv (oritavancin)	The Medicines Company	2014	x	x	x
Sivextro (tedizolid)	Cubist Pharmaceuticals Inc.	2014	x	x	x
Zerbaxa (ceftolozane + tazobactam)	Cubist Pharmaceuticals Inc.	2014	x	✓	x
Avycaz (ceftazidime + avibactam*)	AstraZeneca plc/ Actavis plc	2015	✓	✓	x
Baxdela (delafloxacin)	Melinta Therapeutics, Inc.	2017	x	x	x
Vabomere (meropenem + vaborbactam*)	The Medicines Company	2017	✓	✓	x
Zemdri (plazomicin)	Achaogen Inc.	2018	x	✓	x
Nuzyra (omadacycline)	Paratek Pharmaceuticals Inc.	2018	x	✓	x
Xerava (eravacycline)	Tetraphase Pharmaceuticals Inc.	2018	x	✓	x

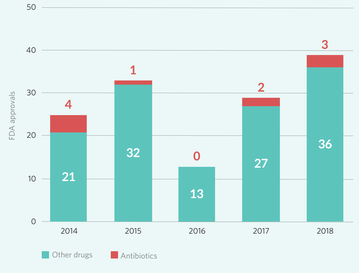
Note: Indications based on labels of FDA approvals.
* The novel components are beta-lactamase inhibitors avibactam and vaborbactam.

Key findings:

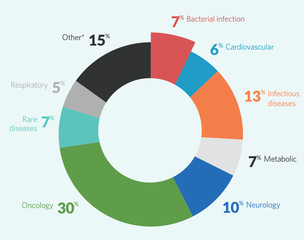
- 10 antibiotics were approved from 2014-18.
  - Two utilize novel beta-lactamase inhibitors paired with previously approved antibiotics.
  - On their FDA drug labels, none are indicated against WHO critical pathogens carbapenem-resistant Enterobacteriaceae (CRE), *A. baumannii* (CRAB), or *P. aeruginosa* (CRPA).

Antibiotics account for 7% of FDA-approved new molecular entities (NMEs), 2014-18, compared with drugs in other therapeutic areas

Comparison of Antibiotic Approvals to Those of Other Drugs, 2014-18



NME Drugs Approved, 2014-18



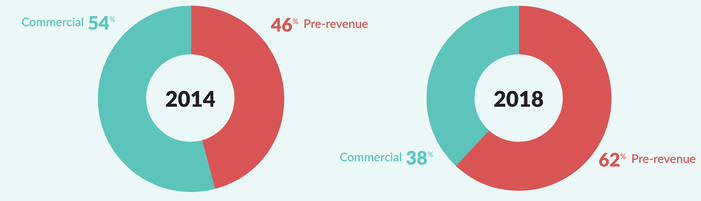
* "Other" approved drugs include those with ≥6 percent of the total in the following therapeutic areas: autoimmune, chronic high prevalence diseases, endocrine, gastroenterology, hematology, psychiatry, and urology.
Note: Antibiotics accounted for only 7 percent of all drug approvals from 2014 to 2018; in comparison, oncology drugs accounted for 30 percent (n = 41), other infectious diseases drugs (excluding bacterial infections) for 13 percent (n = 18), and rare diseases drugs for 7 percent (n = 10).

How Has the Antibiotics Market Landscape Evolved?

Key findings:

- The number of companies developing antibiotics has remained nearly steady: 39 in 2014, 37 in 2018.
  - However, 62 percent of the 2018 companies were pre-revenue versus only 46 percent in 2014.
  - 11 percent of the 2018 companies were ranked in the top 50 based on revenue,* compared with 15 percent in 2014.
- Small biotechs accounted for 9 of the 10 approved antibiotics.
  - In 2018, both Achaogen Inc. and Melinta Therapeutics Inc. announced plans to reduce their respective research and development programs.†
    - In 2018, The Medicines Company divested its antibiotics program to Melinta‡
    - In 2019, Achaogen announced that it was filing for Chapter 11 bankruptcy reorganization.§
  - In 2019, Tetraphase Pharmaceuticals Inc. also announced the elimination of its internal research function.‖
  - These 4 companies were responsible for 5 of the 10 FDA-approved antibiotics.

Companies developing antibiotics are now smaller, pre-revenue entities



Note: A pre-revenue company has not previously had a new drug approved that it subsequently commercialized and marketed, antibiotic or otherwise.

* Pharmaceutical Executive, "Pharm Exec's Top 50 Companies 2018" (2018), http://www.pharmexec.com/pharm-execs-top-50-companies-2018?pageID=2.

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Conclusions

The antibiotics pipeline has remained stagnant over the past five years and is insufficient to address the growing public health threat of antibiotic resistance. This longitudinal trend analysis highlights key gaps that exist in the pipeline today, in particular, that not enough novel drugs address multidrug-resistant Gram-negative ESKAPE pathogens. Antibiotics account for only 7 percent of FDA-approved drugs. Furthermore, the pipeline today consists primarily of pre-revenue companies, which generally do not have the resources and/or infrastructure to market and commercialize antibiotics.

Acknowledgments

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2 Centers for Disease Control and Prevention, "Antibiotic Resistance Threats in the United States, 2013" (2013), https://www.cdc.gov/drugresistance/pdf/ar-threats-2013-508.pdf; World Health Organization, "Global Priority List of Antibiotic-Resistant Bacteria to Guide Research, Discovery, and Development of New Antibiotics" (2017), https://www.who.int/medicines/publications/global-priority-list-antibiotic-resistant-bacteria/en; World Health Organization, "Antibacterial Agents in Clinical Development: An Analysis of the Antibacterial Clinical Development Pipeline, Including Tuberculosis" (2017), http://www.who.int/medicines/areas/rational_use/antibacterial_agents_clinical_development/en.

3 U.S. Food and Drug Administration, "Drugs@FDA: FDA Approved Drug Products," accessed May 31, 2019, https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm.