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Progress in the Fight Against Multidrug-Resistant Bacteria? A Review of U.S. Food and Drug Administration–Approved Antibiotics, 2010–2015

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A weak antibiotic pipeline and the increase in drug-resistant pathogens have led to calls for more new antibiotics. Eight new antibiotics were approved by the U.S. Food and Drug Administration (FDA) between January 2010 and December 2015: ceftaroline, fidaxomicin, bedaquiline, dalbavancin, tedizolid, oritavancin, ceftolozane–tazobactam, and ceftazidime–avibactam. This study evaluates the development course and pivotal trials of these antibiotics for their innovativeness, development process, documented patient outcomes, and cost. Data sources were FDA approval packages and databases (January 2010 to December 2015); the *Red Book* (Truven Health Analytics); *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations* (FDA); and supplementary information from company filings, press releases, and media reports. Four antibiotics were approved for acute bacterial skin and skin-structure infection. Seven had similar mechanisms of action to those of previously approved drugs. Six were initially developed by small to midsized companies, and 7 are currently marketed by 1 of 3 large companies. The drugs spent a median of 6.2 years in clinical trials (interquartile range [IQR], 5.4 to 8.8 years) and 8 months in FDA review (IQR, 7.5 to 8 months). The median number of patients enrolled in the pivotal trials was 666 (IQR, 553 to 739 patients; full range, 44 to 1005 patients), and median trial duration was 18 months (IQR, 15 to 22 months). Seven drugs were approved on the basis of pivotal trials evaluating noninferiority. One drug demonstrated superiority on an exploratory secondary end point, 2 showed decreased efficacy in patients with renal insufficiency, and 1 showed increased mortality compared with older drugs. Seven of the drugs are substantially more expensive than their trial comparators. Limitations are that future research may show benefit to patients, new drugs from older classes may show superior effectiveness in specific patient populations, and initial U.S. prices for each new antibiotic were obtained from public sources. Recently marketed antibiotics are more expensive but have been approved without evidence of clinical superiority.

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Advances in the treatment and prevention of infectious diseases, in part due to antibiotic development, are one of the greatest gains in medicine of the past century (1–4). Many have identified the increase in drug-resistant pathogens as a serious threat in maintaining these gains (5–7). Despite the need for new antibiotics with improved effectiveness to address resistance, many stakeholders have observed that the antibiotic pipeline is weak (8–12), although these claims may be overstated (13). Screening of naturally occurring compounds and use of advanced platforms to identify targets have led to few returns in recent decades (14). In addition, numerous large, for-profit pharmaceutical companies have ceased active antibiotic development owing to concerns about returns on investment and the scientific challenges in antibiotic discovery (10, 15, 16).

These developments have led to calls for a variety of incentives to spur development of new antibiotics, particularly ones targeting multidrug-resistant, gram-negative bacteria (16–21). The Generating Antibiotic Incentives Now (GAIN) Act of 2012 awarded qualifying new products faster review times by the U.S. Food and Drug Administration (FDA), as well as 5 additional years of market exclusivity above the approximately 7 years already guaranteed to new small-molecule drugs (22). In 2015, the House of Representatives passed the 21st Century Cures Act, which would permit approval of antimicrobials on the basis of preclinical data and preliminary studies in small numbers of patients (23).

There are signs that the antibiotic pipeline may already be improving (13). In 2010, the Infectious Diseases Society of America set a goal for 10 novel antibiotics to reach the U.S. market by 2020 (20). Since then, the FDA has approved 8 new antibiotics. Regulators and advocates have celebrated the development and approval of these antibiotics (24). Does this increase in approvals represent important progress for patients? To answer this question, we evaluated the discovery, development course, pivotal trial results, and costs associated with these new drugs.

METHODS

Data Sources and Searches

For all new antibiotics from January 2010 through December 2015, we extracted key characteristics from their approval packages by using the Drugs@FDA database (25–30). We then determined the origins of the drugs and their development, including their corporate sponsorship history from company press releases and other public information.

We next reviewed the major steps in preclinical and clinical investigational development by collecting details associated with the FDA-designated "pivotal trials" used to demonstrate efficacy. Details were collected from FDA reviews and reports on Clinical Trials.gov.

We identified whether the FDA imposed any postapproval study requirements. We extracted postmarket

commitments or requirements from the FDA's online database (31) and assessed the status of each as of December 2015. We extracted postapproval incentives from the FDA's *Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations* (32) and company press releases.

Finally, to determine the cost of each drug for a recommended duration of course of treatment, we obtained the average wholesale U.S. price for each new antibiotic and its clinical trial comparator from the *Red Book* (33).

Study Selection

We studied all new molecular entity antibiotics approved by the FDA between January 2010 and December 2015.

Data Synthesis and Analysis

For each drug, we assessed the mechanism of action, larger drug class, year of discovery, and approved indications. We also identified in vitro activity against ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* species) (34, 35) and Centers for Disease Control and Prevention urgent-threat pathogens (*Clostridium difficile*, carbapenem-resistant *Enterobacteriaceae*, and drug-resistant *Neisseria gonorrhoeae* [cephalosporin resistance]) (6), on the basis of information included in the FDA approval packages. In vitro activity does not necessarily reflect benefits on actual patient clinical outcomes, as exemplified by such drugs as tigecycline and doripenem (36, 37).

To determine the corporate sponsorship history of the antibiotics, we examined the size of the company, given the different incentives that may be needed for different-sized companies. We classified "large companies" as those with more than 10 000 employees and small to midsized companies as those with 10 000 or fewer employees.

In assessing pivotal clinical trials for each antibiotic, we extracted indications, comparator drugs, end points, trial sizes, trial durations, and trial hypotheses (noninferiority versus superiority). We tracked primary end points of the trials, as well as FDA-recommended secondary end points (for example, a new recommended end point from the guidance document). Because the ceftolozane–tazobactam trials relied on pooled data, the time for each trial was averaged with its pooling counterpart.

We determined the length of time each antibiotic spent in clinical development as the time from investigational new drug (IND) status (the application to begin human trials) to new drug application (NDA) status (the sponsor's full submission to FDA). Regulatory review time ran from the date of NDA submission to FDA approval. We assessed whether each antibiotic qualified for special regulatory pathways or designations, including qualified infectious disease product, fast track, priority review, accelerated approval, breakthrough therapy, and orphan drug designation (see the **Appendix**, available at www.annals.org, for definitions of the preceding 6 terms). We also assessed whether each drug was awarded any postapproval incentives.

To determine the cost of each antibiotic, we calculated a price range on the basis of the overall dose and duration of the treatment from the average unit price extracted from the *Red Book* (33).

RESULTS

The 8 new antibiotics were ceftaroline, fidaxomicin, bedaquiline, dalbavancin, tedizolid, oritavancin, ceftolozane–tazobactam, and ceftazidime–avibactam. Four were approved in 2014. Five are administered intravenously and 2 orally, and 1 was approved in both formulations (**Table 1**).

Mechanisms of Action and Indications

Four drugs were initially indicated for acute bacterial skin and skin-structure infections; 2 for complicated intra-abdominal infection (CIAI) and complicated urinary tract infection (CUTI); and 1 each for community-acquired pneumonia, *C difficile*–associated diarrhea, and multidrug-resistant tuberculosis (**Table 1**). Three of the 8 drugs showed in vitro activity against ESKAPE pathogens; 1 of the drugs, fidaxomicin, demonstrated in vitro activity against a Centers for Disease Control and Prevention urgent-threat pathogen, *C difficile*. Only bedaquiline was specifically indicated for a disease due to a multidrug-resistant pathogen, although most demonstrated in vitro activity against gram-positive drug-resistant pathogens (38, 39). For example, although ceftaroline was found to have in vitro activity against methicillin-resistant *S aureus* (MRSA), the trials used to support FDA approval for pneumonia did not specifically study efficacy in disease due to MRSA. Still, the drug received an indication for skin infections due to MRSA (13, 40).

Seven antibiotics fell within established drug classes, the most common being β-lactams (ceftaroline, ceftolozane–tazobactam, and ceftazidime–avibactam). The one drug involving a new mechanism of action was bedaquiline, a diarylquinoline targeting adenosine triphosphate synthase to inhibit the growth of drug-resistant tuberculosis (39).

Drug Development

Six antibiotics were initially developed by small to midsized companies, and 7 were sponsored by small to midsized companies at the time of approval (**Figure**). Larger manufacturers then became involved after approval: 7 are currently marketed by 1 of 3 large companies. For example, Actavis (~17 000 employees) acquired dalbavancin and ceftazidime–avibactam after smaller companies had guided these products through FDA approval. In the case of dalbavancin, Pfizer (~78 000 employees) acquired Vicuron Pharmaceuticals in 2005, but voluntarily withdrew the NDA for dalbavancin. In 2009, Pfizer divested Vicuron Pharmaceuticals, with Durata Therapeutics (<100 employees) subsequently moving the drug through approval. In 2014, Durata Therapeutics was acquired by Actavis, which then merged with Allergan.

Table 1. Antibiotic Drug Details, Development Milestones, and ESKAPE Status

Drug	IND Filed	NDA Filed	Approval Date	Current Manufacturer	Drug Class (Year of Discovery)	Method of Administration	Novel Mechanism of Action	Indications	In Vitro Activity Against ESKAPE Pathogens?
Ceftaroline	December 2004	December 2009	29 October 2010	Actavis	Cephalosporin (1928)	Intravenous	No	ABSSSI; CABP	Yes
Fidaxomicin	August 2003	November 2010	27 May 2011	Cubist Pharmaceuticals (subsidiary of Merck)	Macrolide (1948)	Oral	No	CDAD and prevention of recurrences	No*
Bedaquiline	November 2006	June 2012	28 December 2012	Janssen Research and Development (Johnson & Johnson)	Diarylquinoline (1997)	Oral	Yes	Pulmonary tuberculosis caused by multidrug-resistant tuberculosis	No†
Dalbavancin	July 2000	September 2013	23 May 2014	Actavis	Lipoglycopeptide (1953)	Intravenous	No	ABSSSI	No
Tedizolid	November 2007; August 2009	October 2013	20 June 2014	Cubist Pharmaceuticals (subsidiary of Merck)	Oxazolidinone (1955)	Oral; intravenous	No	ABSSSI	No
Oritavancin	August 1996	December 2013	6 August 2014	The Medicines Company	Glycopeptide (1953)	Intravenous	No	ABSSSI	No
Ceftolozane–tazobactam	July 2009	April 2014	19 December 2014	Cubist Pharmaceuticals (subsidiary of Merck)	Cephalosporin (1928) + β-lactamase inhibitor	Intravenous	No	CIAI; CUTI	Yes
Ceftazidime–avibactam	January 2008	June 2014	25 February 2015	AstraZeneca/ Actavis	Cephalosporin (1928) + β-lactamase inhibitor	Intravenous	No	CIAI; CUTI	Yes

ABSSSI = acute bacterial skin and skin-structure infection; CABP = community-acquired bacterial pneumonia; CDAD = *Clostridium difficile*–associated diarrhea; CIAI = complicated intra-abdominal infection; CUTI = complicated urinary tract infection; ESKAPE = *Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumonia, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter* species; IND = investigational new drug; NDA = new drug application.
* *Clostridium difficile* is a Centers for Disease Control and Prevention urgent-threat pathogen.
† Multidrug-resistant tuberculosis is a global health priority.

Development Times

The antibiotics in our cohort spent a median of 6.2 years between IND and NDA status (interquartile range [IQR], 5.4 to 8.8 years) and a median of 8 months between NDA status and FDA approval (IQR, 7.5 to 8 months) (Table 1). Ceftolozane–tazobactam spent the shortest time between IND and NDA status (4.8 years). Oritavancin had the longest development period (17.3 years), which was suspended for multiple years after initial trial results showed an increased rate of injection-site inflammation and the drug failed to demonstrate noninferiority in pivotal trials using daily dosing. Later, Targanta Therapeutics Corporation acquired rights to the drug and demonstrated that the inflammation was associated with high infusion rates and high drug concentrations, leading to approval for the drug on the basis of demonstration of noninferiority with weekly rather than daily dosing. Excluding oritavancin, the median time from IND to NDA status was 5.9 years (IQR, 5.3 to 6.8 years).

Characteristics of Trials Used to Support Approval

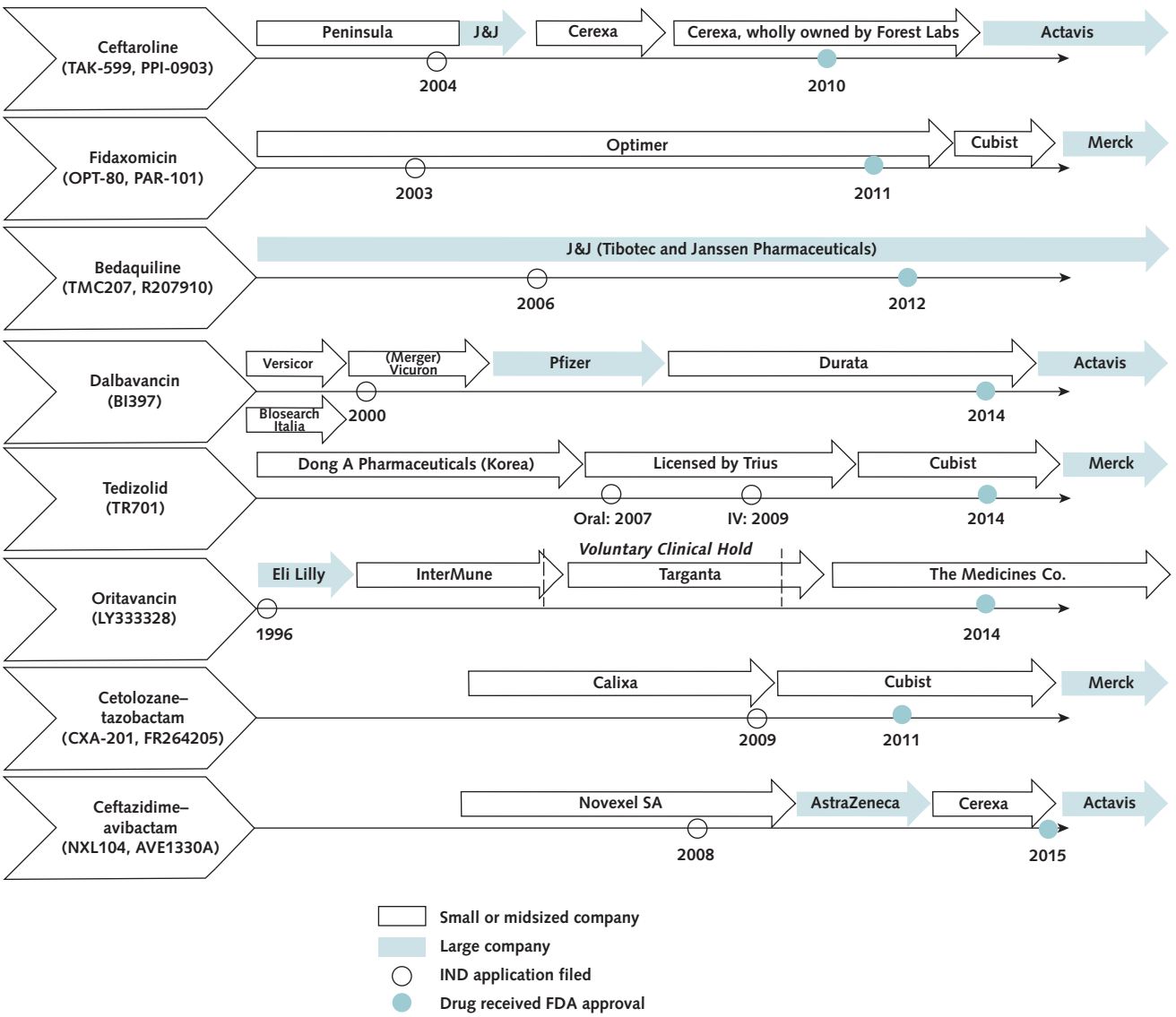
The median number of patients enrolled in the pivotal trials was 666 (IQR, 553 to 739; full range, 44 to 1005). The pivotal trials lasted a median of 18 months (IQR, 15 to 22 months). As shown in Table 2, the strength of evidence differed across the drugs. For example, approval of ceftolozane–tazobactam was based on 1 trial per indication, because data were pooled from 2 identical trials each for CUTI and CIAI. Assessment of the efficacy of ceftazidime–avibactam was based on 2 early-phase exploratory trials without prespecified hypotheses (rather than confirmatory phase 3 trials), along with previous findings of efficacy and published literature for ceftazidime alone and nonclinical studies and descriptive data for avibactam. Bedaquiline was approved on the basis of a phase 2 trial with 2 stages, and an uncontrolled case series (41).

Seven drugs were approved on the basis of pivotal trials designed with noninferiority hypotheses. All drugs except for ceftazidime–avibactam had a 10% noninferiority margin. The 2 early-phase trials for ceftazidime–avibactam did not have prespecified hypotheses with stated noninferiority margins or inferential statistical testing but were interpreted as demonstrating noninferiority, allowing large margins of inferiority exceeding 15% to 20%.

Tedizolid was tested based on a noninferiority hypothesis because it was hypothesized, on the basis of preclinical data, to have fewer adverse effects than linezolid. However, no hypotheses examined patient benefits other than improved effectiveness for any of the other noninferiority studies, despite benefits other than improved effectiveness being the primary justification for noninferior efficacy evaluations (42).

The pivotal trials of fidaxomicin showed noninferiority and superiority for effectiveness. Fidaxomicin met the primary hypothesis of noninferiority to the standard of care of vancomycin on the primary end point of clinical cure (decreased diarrhea episodes and clinician

Figure. Company sponsorship of antibiotics that were approved by the FDA from 2010 through 2015.



Company sponsorship timelines and key milestones related to FDA approval are shown. The information in parentheses below each antibiotic is the name of the drug while under development. FDA = U.S. Food and Drug Administration; IND = investigational new drug; IV = intravenous; J&J = Johnson & Johnson.

judgment of no need for further antibiotic therapy) at the end of treatment, on the basis of a 10% margin. It also demonstrated superiority to the active comparator in 2 studies for the secondary exploratory end point of global cure rate—the number of participants in each treatment group who were considered cured and did not have a recurrence of diarrhea within 21 days after the last dose. However, for patients with *C difficile*–associated diarrhea due to the epidemic BI/NAP1/027 strain, fidaxomicin did not demonstrate superiority in global cure.

The single trial of ceftolozane–tazobactam in CUTI was designed with a noninferiority hypothesis but showed superiority compared with the control drug levofloxacin on the composite outcome of clinical and microbiological success. Superiority was driven by the surrogate end point of negative urine cultures in the subgroups of patients with levofloxacin-resistant organisms. There were no significant differences between ceftolozane–tazobactam and levofloxacin in the direct patient outcomes of symptoms of urinary tract infection, adverse effects, or deaths, even in the subgroup with levofloxacin resistance (43). Both ceftolozane–tazobactam and ceftazidime–avibactam demonstrated decreased efficacy compared with older control agents in patients with baseline renal insufficiency.

Bedaquiline was the only approved antibiotic in our study that was tested solely via a superiority hypothesis. A surrogate end point of sputum clearance was used in the single pivotal trial (41), and bedaquiline

Table 2. Characteristics of Pivotal Trials Used to Support FDA Approval of Antibiotics, 2010–2015

Drug and Trial Name	Indication	Comparator Drug	End Point	Analysis Population			Hypothesis
				Absolute Risk Reduction (95% CI)	Patients Who Received Drug, *n*	Patients in Comparator Group, *n*	
Ceftaroline							
P903-08	CABP	Ceftriaxone	Clinical cure at test-of-cure*	MITTE: 6.2% (–0.2% to 12.5%) CE: 8.4% (1.4% to 15.4%)	MITTE: 291 CE: 224	MITTE: 300 CE: 234	Noninferiority (–10%)
P903-09	CABP	Ceftriaxone	Clinical cure at test-of-cure*	MITTE: 5.9% (–1.0% to 12.8%) CE: 5.2% (–2.2% to 12.8%)	MITTE: 284 CE: 232	MITTE: 269 CE: 214	Noninferiority (–10%)
P903-06	ABSSSI	Vancomycin + aztreonam	Clinical cure at test-of-cure†	MITT: 1.0% (–4.2% to 6.2%) CE: –2.2% (–6.6% to 2.1%)	MITT: 351 CE: 316	MITT: 347 CE: 347	Noninferiority (–10%)
P903-07	ABSSSI	Vancomycin + aztreonam	Clinical cure at test-of-cure†	MITT: 0.1% (–4.4% to 4.5%) CE: –0.4% (–5.8% to 5.0%)	MITT: 342‡ CE: 294‡	MITT: 338‡ CE: 292‡	Noninferiority (–10%)
Fidaxomicin							
101.1.C.003	CDAD	Vancomycin	Clinical cure at end-of-treatment§ Global cure (cure response with no recurrence through poststudy visit)	MITT: 4.2% (–1.4% to 9.7%) MITT: 10.2% (2.8% to 17.5)	MITT: 289	MITT: 307	Noninferiority (–10%) Superiority (0%)
101.1.C.004	CDAD	Vancomycin	Clinical cure at end-of-treatment§ Global cure (cure response with no recurrence through post-study visit)	MITT: 0.2% (–5.9% to 6.4%) MITT: 13.4% (5.4 to 21.1)	MITT: 253	MITT: 256	Noninferiority (–10%) Superiority (0%)
Bedaquiline							
C208 stage 1	Pulmonary TB caused by MDR-TB	Placebo with background regimen	Time to sputum culture conversion (2 consecutive negative cultures from sputa collected at least 25 d apart)	Culture conversion rates to MITT: Week 8: 38.9% (12.3% to 63.1%) Week 24: 14.8% (–11.9% to 41.9%) Final treatment success: 4.6% (–25.5% to 34.1%)	MITT: 21	MITT: 23	Exploratory
C208 stage 2	Pulmonary TB caused by MDR-TB	Placebo with background regimen	Time to sputum culture conversion (2 consecutive negative cultures from sputa collected at least 25 d apart)	MITT: median: 83 d (56 to 97 d) Placebo: median, 125 d (98 to 168 d)	MITT: 79	MITT: 81	Superiority based on surrogate end point
Dalbavancin							
DUR001-301	ABSSSI	Vancomycin or linezolid	Early response at 48–72 h (spread cessation, absence of fever) Reduction in lesion area from baseline at 48–72 h	ITT: 1.5% (–4.6% to 7.9%) ITT: –1% (–5.7% to 4.0%)	ITT: 288	ITT: 285	Noninferiority (–10%)
DUR001-302	ABSSSI	Vancomycin or linezolid	Early response at 48–72 h (spread cessation, absence of fever) Reduction in lesion area from baseline at 48–72 h	ITT: –1.5% (–7.4% to 4.6%) ITT: 1.7% (–3.2% to 6.7%)	ITT: 371	ITT: 368	Noninferiority (–10%)
Tedizolid							
TR701-112	ABSSSI	Linezolid	Early clinical response (spread cessation) at 48–72 h ≥20% reduction in primary lesion with no fever	ITT: 0.1% (–6.1% to 6.2%) ITT: 1.9% (–4.5% to 8.3%)	ITT: 332	ITT: 335	Noninferiority (–10%)
TR701-113	ABSSSI	Linezolid	Early clinical response (≥20% reduction in primary lesion) at 48–72 h	ITT: 2.6% (–3.0% to 8.2%)	ITT: 332	ITT: 334	Noninferiority (–10%)
Oritavancin							
SOLO1	ABSSSI	Vancomycin	Clinical response (spread cessation, no fever, no rescue antibiotic) ≥20% reduction in lesion	MITT: 3.7% (–1.4% to 8.7%) MITT: 3.94% (–0.59% to 8.47%)	MITT: 473	MITT: 481	Noninferiority (–10%)
SOLO2	ABSSSI	Vancomycin	Clinical response (spread cessation, no fever, no rescue antibiotic) ≥20% reduction in lesion	MITT: –2.8% (–7.5% to 2.0%) MITT: 0.6% (–3.7% to 5.0%)	MITT: 503	MITT: 502	Noninferiority (–10%)

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Table 2–Continued

Drug and Trial Name	Indication	Comparator Drug	End Point	Analysis Population			Hypothesis
				Absolute Risk Reduction (95% CI)	Patients Who Received Drug, *n*	Patients in Comparator Group, *n*	
Ceftolozane-tazobactam							
CXA-CUTI-10-04 and 10-05	CUTI	Levofloxacin	Composite clinical and microbiological cure at test-of-cure (investigator judgment that symptoms had resolved and microbiological eradication of the causative pathogen)	Microbiological MITT: 8.5% (2.31% to 14.57%)	Microbiological MITT: 398	Microbiological MITT: 402	Noninferiority (–10%)
CXA-CIAI-10-08 and 10-09	CIAI	Meropenem	Clinical response at test-of-cure†	Microbiological ITT: –4.6% (–9.4% to 0.1%)	Microbiological ITT: 389	Microbiological ITT: 417	Noninferiority (–10%)
Ceftazidime-avibactam							
NXL104/2001	CUTI when limited or no treatment options are available	Imipenem-cilastatin	Microbiological response (reduction of the baseline uropathogen at entry from $>10^5$ CFU/mL to $<10^4$ CFU/mL)	ME: –1.1% (–27.2% to 25.0%)	ME: 27	ME: 35	No prespecified hypotheses, but results interpreted at noninferiority
			Clinical and microbiological response (cure + eradication)	Microbiological MITT: 12% (–9.1% to 31.7%)	Microbiological MITT: 46	Microbiological MITT: 49	
NXL104/2002	CIAI, in combination with metronidazole when limited or no treatment options are available	Meropenem	Clinical response (clinical cure: complete resolution or significant improvement in symptoms of index infection with no further therapy needed; eradication presumed with favorable clinical response)	ME: –2.2% (–20.4% to 12.2%) Microbiological MITT: –6.4% (–18.0% to 5.2%)	ME: 68 Microbiological MITT: 85	ME: 76 Microbiological MITT: 89	No prespecified hypotheses, but results interpreted as noninferiority

ABSSSI = acute bacterial skin and skin-structure infection; CABP = community-acquired bacterial pneumonia; CDAD = *Clostridium difficile*–associated diarrhea; CE = clinically evaluable; CFU = colony-forming units; CIAI = complicated intra-abdominal infection; CUTI = complicated urinary tract infection; FDA = U.S. Food and Drug Administration; ITT = intention to treat; MDR-TB = multidrug-resistant tuberculosis; ME = microbiologically evaluable; MITT = modified intention to treat; MITTE = modified intention to treat efficacy; TB = tuberculosis.
* Total resolution of symptoms, or improvement with absence of fever such that no additional antibiotics necessary.
† Total resolution of all signs and symptoms, or improvement such that no additional antibiotics necessary.
‡ Data from reference 40.
§ No further therapy 2 d after completion; 3 or fewer unformed stools for 2 consecutive d and remained well before discontinuation; or marked reduction in number of unformed stools, with residual abdominal discomfort deemed as recovering bowel, provided no further therapy required.

showed 79% clearance versus 58% at 24 weeks in the standard-of-care group, although the difference was not significant at later time points. However, incidence of death, generally from tuberculosis, increased 5-fold among patients randomly assigned to the experimental group compared with those assigned to receive standard treatment (45).

Most of the primary and key secondary end points examined in the trials were clinical "cures" and "responses" based on subjective clinician judgments of unclearly defined composites of signs, symptoms, and laboratory values or radiologic results. For example, in the case of fidaxomicin, a component of the end point of interest was clinician judgments on need for additional antibiotics for *C difficile* (46). Exceptions included the bedaquiline trials (sputum clearance surrogate); CUTI studies that used a composite of "clinical" and microbiological outcomes of urine cultures; and acute bacterial skin and skin-structure infection trials for dalbavancin, tedizolid, and oritavancin (the well-defined clinician-reported outcome of ≥20% reduction in lesion size in addition to clinical cure or response). None used patient mortality or direct measures of patient disability as primary end points.

Regulatory Review Characteristics

Each of the 8 antibiotics received at least 1 expedited drug development or FDA review designation. All 8 were fast-tracked, and 7 received priority review. For the most recent 5 antibiotics, the fast-track status and priority review were conferred on the basis of the drugs receiving the qualified infectious disease product designation. Bedaquiline also received accelerated approval. Four of the drugs—dalbavancin, tedizolid, oritavancin, and ceftolozane/tazobactam—were awarded additional market exclusivity through the GAIN Act. One drug, bedaquiline, was awarded orphan drug status and earned its manufacturer a priority review voucher—an incentive created to reward sponsors for developing drugs to treat neglected diseases.

Postmarket Commitments and Requirements

Among the associated postmarket commitments and requirements (**Appendix Table 1**, available at www.annals.org), the development of bacterial resistance over 5 years after introduction of the drug to the market (using in vitro data alone without a requirement for cor-

relation with patient outcomes) had to be assessed for all 8 drugs, and tests in pediatric populations were required for all drugs except bedaquiline. Three drugs had additional postmarket requirements intended to clarify safety and efficacy questions: worse outcomes noted for ceftazidime–avibactam compared with the standard of care among patients with baseline renal impairment; the pharmacokinetics of oritavancin in patients with severe hepatic or renal impairment, particularly during coadministration of narrow therapeutic index drugs (such as warfarin); and assessment of long-term outcomes of failure or relapse or death for bedaquiline. Johnson & Johnson was also required to conduct a follow-up trial confirming the efficacy of bedaquiline because of its accelerated approval based on a surrogate end point, but was given until 2022 to complete it. A trial to answer the question of whether the surrogate end point of sputum culture conversion leads to direct patient benefits, such as improved survival, had not been initiated as of April 2016, according to ClinicalTrials.gov.

Duration of Treatment and Drug Prices

The duration of treatment ranged from a single dose, in the case of oritavancin, to 24 weeks, in the case of bedaquiline. Prices (Table 3 and Appendix Table 2, available at www.annals.org) ranged from $1195 to $4183 (4 to 14 days of ceftolozane–tazobactam for CIAI) to $36 000 (24 weeks of bedaquiline). With the exception of tedizolid, these prices are much higher than those of the comparator drugs—usually generics—used in the pivotal trials (33).

DISCUSSION

We found that most new antibiotics were additions to existing drug classes, and half were for the same indication. Recently added incentives for antibiotic de-

Table 3. Dose, Duration, and Cost of Antibiotic Drugs and Trial Comparators

New Antibiotic			Comparator			Cost Ratio
Drug	**Dose and Duration**	**Cost Range, $***	**Drug**	**Dose and Duration**	**Cost Range, $***	
Ceftaroline	CABP: 600 mg every 12 h for 5–7 d	CABP: 1666.30–2332.82	CABP: ceftriaxone	CABP: 1 g of ceftriaxone once daily for 5–7 d	CABP: 9.00–329.35	CABP: 185:1 to 7:1
	ABSSSI: 600 mg every 12 h for 5–14 d	ABSSSI: 1666.30–4665.64	ABSSSI: vancomycin + aztreonam	ABSSSI: 1 g of vancomycin twice daily and 1 g of aztreonam twice daily for 5–14 d	ABSSSI: 470.10–1681.68	ABSSSI: 4:1 to 3:1
Fidaxomicin	200 mg twice daily for 10 d	3969.20	Vancomycin†	125-mg capsule 4 times daily for 10 d	1252.00–1392.00	3:1
Bedaquiline	400 mg daily for 2 wk, then 200 mg 3 times/wk for 22 wk	36 000.12	Placebo (both groups received a background multidrug anti–TB treatment regimen)	–‡	–‡	–‡
Dalbavancin	1 dose of 1000 mg, then 500 mg 8 d later	5364.00	Vancomycin or linezolid	1 g of vancomycin twice daily for 3–14 d, with optional switch to 600 mg of linezolid twice daily for 8 d	Vancomycin: 44.82–574.56 Linezolid: 2938.72	Vancomycin: 120:1 to 9:1 Linezolid: 2:1
Tedizolid	200 mg once daily for 6 d	Oral: 2124 IV: 1692	Linezolid	600 mg twice a day for 10 d	3673.40	Oral: 0.5:1 IV: 0.5:1
Oritavancin	1200 mg dose administered by IV once	3480.00	Vancomycin	1 g every 12 h for 7–10 d	104.58–410.40	33:1 to 9:1
Ceftolozane–tazobactam	CUTI: 1.5 g every 8 h for 7 d	CUTI: 2091.60	CUTI: levofloxacin	CUTI: 750 mg levofloxacin daily for 7 d	CUTI: 0.35–0.70	CUTI: 5976:1 to 2988:1
	CIAI:1.5 g every 8 h for 4–14 d	CIAI: 1195.20–4183.20	CIAI: meropenem	CIAI: 1 g of meropenem every 8 h for 4–10 d	CIAI: 154.20–2111.10	CIAI: 8:1 to 2:1
Ceftazidime–avibactam	CUTI: 2.5 g every 8 h for 7–14 d	CUTI: 7182–14 364	CUTI: imipenem–cilastatin	CUTI: 500 mg imipenem–cilastatin every 6 h for 7–14 d (optional switch to ciprofloxacin after 4 d)	CUTI: 352.80–1680.00	CUTI: 20:1 to 9:1
	CIAI: 2.5 g every 8 h for 5–14 d + MTZ	CIAI: 5130–14 364	CIAI: meropenem	CIAI: 1 g of meropenem every 8 h for 5–14 d	CIAI: 192.75–2955.54	CIAI: 27:1 to 5:1

ABSSSI = acute bacterial skin and skin-structure infection; CABP = community-acquired bacterial pneumonia; CIAI = complicated intra-abdominal infection; CUTI = complicated urinary tract infection; IV = intravenous; MTZ = metronidazole; TB = tuberculosis.
* Based on reference 33.
† Although the fidaxomicin trials used oral vancomycin (cost shown here), some providers may compound generic IV into oral administration, greatly reducing the cost.
‡ Background multidrug anti-TB regimen varied by individual. Possible drugs included ethionamide, kanamycin, ofloxacin, pyrazinamide, and terizidine (all off-patent).

velopment have not yet led to new products with improved outcomes in patients with disease due to critical resistant pathogens at the time of approval, such as ESKAPE pathogens (35). Although the Infectious Diseases Society of America's goal of 10 new antibiotics approved by 2020 is likely to be met (20, 35, 38), recently approved antibiotics have generally been lacking in biological innovation or public health importance (47).

One major exception was bedaquiline, which was developed to treat a pressing global public health priority in multidrug-resistant tuberculosis. Yet, even for bedaquiline, the clinical trials results show increased mortality and its initial impact has been limited owing to its lack of availability and lack of data on its use (48). Postmarket commitments for this product remain in progress, a finding consistent with current limitations in our ability to conduct timely postmarket oversight of drugs approved via expedited pathways (49).

We also found important deficiencies in the clinical trials leading to approval of these new antibiotic products. First, because most pivotal trial designs were primarily noninferiority trials, the antibiotics were not studied to evaluate whether they have substantial benefits in efficacy over what is currently available. None of the drugs demonstrated superior outcomes on patient survival or disability in their pivotal trials despite promising in vitro, animal, and pharmacokinetic data. For example, the apparent superiority of ceftolozane–tazobactam was based on a surrogate end point of negative urine cultures, and bedaquiline worsened survival despite positive results on a surrogate end point.

Second, none of the trials evaluated direct patient outcomes as primary end points. Clinical cure and response end points examined in these trials were based on clinician judgments of a composite of signs, symptoms, or laboratory tests, sometimes with no clear definition of what was measured or how clinicians were to gauge success. In the trials of dalbavancin, oritavancin, and tedizolid, the primary end point of clinical response was cessation of spread of the baseline lesion, absence of fever, and no rescue antibiotic medication, none of which are direct measures of patient survival or disability (50–52).

Finally, some drugs did not have confirmatory evidence from a second independent trial or did not have any confirmatory trials (as was the case for ceftazidime–avibactam). The FDA has traditionally preferred 2 trials per indication because the results of any single trial "may be subject to unanticipated, undetected systematic biases" or occur by chance alone (53), although approval on the basis of a single pivotal trial occurred about one third of the time in a recent review. Continued monitoring and evidence generation are still needed for these antibiotics to ensure demonstration of their efficacy in relevant populations and resistance profiles related to patient outcomes moving forward (49).

Despite unclear evidence of additional benefit, most of these drugs have been priced at a premium. Yet, none of these antibiotics have attained substantial sales since their approval. Ceftaroline, for example, recorded $13.1 million in sales in 2013 (54). One reason could be the poor clinical evidence supporting their use; private payers have sometimes resisted reimbursing high-priced new drugs without solid underlying evidence of additional benefits over available lower-priced therapies (even if the FDA does not require such evidence for approval). For example, the Centers for Medicare & Medicaid Services refused to grant additional reimbursement to dalbavancin under the new technology add-on payment program, which is designed to support timely access to important but potentially costly new therapies, owing to the absence of evidence demonstrating superiority or that improved convenience affected patient-centered outcomes (16).

Our data show that the FDA is efficiently approving new antibiotics. The FDA review time was shorter than for small-molecule anti-infective drugs approved in previous years (55). Antibiotic clinical trials are also speedy. The length of the pivotal clinical trials—which are supposed to be the longest and most detailed evaluation of a drug—was consistent with or was even shorter than that for other drugs (56). Finally, the number of patients enrolled in antibiotic pivotal trials historically has been smaller compared with other therapeutic areas (56). These data undermine the claim that clinical development of antibiotics is unreasonably burdensome (57, 58).

Despite the ease of testing and approving new antibiotics, research and development is still largely being driven outside of the major pharmaceutical manufacturers. Financial incentives tailored to small or midsized companies may therefore be most effective in leading to new innovation. Some examples that have been offered include transferrable tax credits, generous patent buyouts, and prizes (59). Such financial incentives could also be tailored to ensure that they apply only to novel therapies directed at infections of particular public health importance. The upfront investment needed in the field of antibiotics also may not be as high as expected; indeed, a recent model of antibiotic drug development assumed longer review times and longer clinical development times than we report here (59).

Our study has limitations. First, future research may show that these new antibiotics could offer substantial benefits to patients—for example, in terms of dosing convenience facilitating earlier discharge from hospitals—even though such data were lacking at the time of approval. Second, new drugs from older classes may show superior effectiveness over older drugs in the same class in specific patient populations. Finally, we obtained the initial U.S. price for each new antibiotic from public sources, as opposed to the manufacturers of the drugs. This does not allow us to adequately account for differences in negotiated rates associated with public and private payers.

In conclusion, we found that recent antibiotic development activity has been impressive in terms the quantity of antibiotics developed and approved for marketing, but does not constitute a substantial im-

provement in terms of quality in clinical practice on patient outcomes. A range of regulatory and other incentives have targeted antibiotic development, and the FDA has demonstrated efficiency in approving antibiotics. However, many of the drugs in our cohort were approved for the same indication, only 1 was first in class, and numerous deficiencies were identified in the clinical trial evidence collected at the time of approval. Only 1 drug was studied in patients with multidrug-resistant disease. As antibiotic innovation continues to move forward, greater attention needs to be paid to incentives for developing high-quality new products with demonstrated superiority to existing products on outcomes in patients with multidrug-resistant disease, replacing the current focus on quantity and presumed future benefits.

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References

1. **U.S. Department of Commerce and Labor.** Mortality Statistics, 1900 to 1904. Washington, DC: US Gov Pr Office; 1906.
2. **Centers for Disease Control and Prevention (CDC).** Control of infectious diseases. MMWR Morb Mortal Wkly Rep. 1999;48:621-9. [PMID: 10458535]
3. **Laxminarayan R, Matsoso P, Pant S, Brower C, Røttingen JA, Klugman K, et al.** Access to effective antimicrobials: a worldwide challenge. Lancet. 2016;387:168-75. [PMID: 26603918] doi:10.1016/S0140-6736(15)00474-2
4. **Armstrong GL, Conn LA, Pinner RW.** Trends in infectious disease mortality in the United States during the 20th century. JAMA. 1999;281:61-6. [PMID: 9892452]
5. **Roberts RR, Hota B, Ahmad I, Scott RD 2nd, Foster SD, Abbasi F, et al.** Hospital and societal costs of antimicrobial-resistant infections in a Chicago teaching hospital: implications for antibiotic stewardship. Clin Infect Dis. 2009;49:1175-84. [PMID: 19739972] doi:10.1086/605630
6. **Centers for Disease Control and Prevention.** Antibiotic Resistance Threats in the United States, 2013. Atlanta, GA: Centers for Disease Control and Prevention; 2013.
7. **World Health Organization.** Antimicrobial Resistance: Global Report on Surveillance. Geneva: World Health Organization; 2014.
8. **Morel CM, Mossialos E.** Stoking the antibiotic pipeline. BMJ. 2010;340:c2115. [PMID: 20483950] doi:10.1136/bmj.c2115
9. **Spellberg B, Powers JH, Brass EP, Miller LG, Edwards JE Jr.** Trends in antimicrobial drug development: implications for the future. Clin Infect Dis. 2004;38:1279-86. [PMID: 15127341]
10. **Projan SJ.** Why is Big Pharma getting out of antibacterial drug discovery? Curr Opin Microbiol. 2003;6:427-30. [PMID: 14572532]
11. **Coates A, Hu Y, Bax R, Page C.** The future challenges facing the development of new antimicrobial drugs. Nat Rev Drug Discov. 2002;1:895-910. [PMID: 12415249]
12. **Norrby SR, Nord CE, Finch R; European Society of Clinical Microbiology and Infectious Diseases.** Lack of development of new antimicrobial drugs: a potential serious threat to public health. Lancet Infect Dis. 2005;5:115-9. [PMID: 15680781]
13. **Outterson K, Powers JH, Seoane-Vazquez E, Rodriguez-Monguio R, Kesselheim AS.** Approval and withdrawal of new antibiotics and other antiinfectives in the U.S., 1980-2009. J Law Med Ethics. 2013;41:688-96. [PMID: 24088160] doi:10.1111/jlme.12079
14. **Lewis K.** Platforms for antibiotic discovery. Nat Rev Drug Discov. 2013;12:371-87. [PMID: 23629505] doi:10.1038/nrd3975
15. **So AD, Gupta N, Brahmachari SK, Chopra I, Munos B, Nathan C, et al.** Towards new business models for R&D for novel antibiotics. Drug Resist Updat. 2011;14:88-94. [PMID: 21439891] doi:10.1016/j.drup.2011.01.006
16. **Outterson K, Powers JH, Daniel GW, McClellan MB.** Repairing the broken market for antibiotic innovation. Health Aff (Millwood). 2015;34:277-85. [PMID: 25646108] doi:10.1377/hlthaff.2014.1003
17. **The White House.** National Strategy for Combating Antibiotic-Resistant Bacteria. Washington, DC: US Gov Pr Office; 2014.
18. **Centers for Disease Control and Prevention.** Antibiotic resistance solutions initiative 2015. 2015. Accessed at www.cdc.gov/drugresistance/solutions-initiative/index.html on 13 October 2015.
19. **World Health Organization.** WHO Global Strategy for Containment of Antimicrobial Resistance. Geneva: World Health Organization; 2001.
20. **Infectious Diseases Society of America.** The 10 x '20 Initiative: pursuing a global commitment to develop 10 new antibacterial drugs by 2020. Clin Infect Dis. 2010;50:1081-3. [PMID: 20214473] doi:10.1086/652237
21. **Clift C, Gopinathan U, Morel C, Outterson K, Røttingen J, So A, eds; Chatham House Working Group on New Antibiotic Business Models.** Towards a New Global Business Model for Antibiotics: Delinking Revenues from Sales. London: The Royal Institute of International Affairs; 2015.
22. Food and Drug Administration Safety and Innovation Act of 2013 § 3187 (2013).
23. 21st Century Cures Act, H.R. 6 (2015).
24. **Woodcock J.** Three encouraging steps towards new antibiotics. FDA Voice Blog. 23 September 2014. Accessed at http://blogs.fda.gov/fdavoice/index.php/2014/09/three-encouraging-steps-towards-new-antibiotics on 26 April 2016.
25. **U.S. Food and Drug Administration.** CDER new molecular entity (NME) & new BLA calendar year approvals as of December 31, 2010.

2010. Accessed at www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/DrugandBiologicApprovalReports/UCM242677.pdf on 26 April 2016.
26. **U.S. Food and Drug Administration.** Novel new drugs summary 2012. 2013. Accessed at www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM337830.pdf on 26 April 2016.
27. **U.S. Food and Drug Administration.** Novel new drugs 2011. 2012. Accessed at www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm293663.pdf on 26 April 2016.
28. **U.S. Food and Drug Administration.** Novel new drugs 2014 summary. 2015. Accessed at www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM430299.pdf on 26 April 2016.
29. **U.S. Food and Drug Administration.** Novel new drugs 2013 summary. 2014. Accessed at www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DrugInnovation/UCM381803.pdf on 26 April 2016.
30. **U.S. Food and Drug Administration.** New Molecular Entity and New Therapeutic Biological Product Approvals for 2015. Silver Spring, MD: U.S. Food and Drug Administration; 2015. Accessed at www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm430302.htm on 26 April 2016.
31. **U.S. Food and Drug Administration.** Postmarket requirements and commitments. 2013. Accessed at www.accessdata.fda.gov/scripts/cder/pmc on 26 April 2016.
32. **U.S. Food and Drug Administration.** Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. 2013. Accessed at www.accessdata.fda.gov/scripts/cder/ob/default.cfm on 4 April 2016.
33. Red Book Online [online database]. Greenwood Village, CO: Truven Health Analytics. Accessed at http://sites.truvenhealth.com/redbook/index.html on 26 April 2016.
34. **Rice LB.** Federal funding for the study of antimicrobial resistance in nosocomial pathogens: no ESKAPE [Editorial]. J Infect Dis. 2008; 197:1079-81. [PMID: 18419525] doi:10.1086/533452
35. **Boucher HW, Talbot GH, Bradley JS, Edwards JE, Gilbert D, Rice LB, et al.** Bad bugs, no drugs: no ESKAPE! An update from the Infectious Diseases Society of America. Clin Infect Dis. 2009;48:1-12. [PMID: 19035777] doi:10.1086/595011
36. **Prasad P, Sun J, Danner RL, Natanson C.** Excess deaths associated with tigecycline after approval based on noninferiority trials. Clin Infect Dis. 2012;54:1699-709. [PMID: 22467668] doi:10.1093/cid/cis270
37. **U.S. Food and Drug Administration.** Doribax (doripenem): drug safety communication–risk when used to treat pneumonia on ventilated patients. 2014. Accessed at www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm388328.htm on 4 April 2016.
38. **Bassetti M, Merelli M, Temperoni C, Astilean A.** New antibiotics for bad bugs: where are we? Ann Clin Microbiol Antimicrob. 2013; 12:22. [PMID: 23984642] doi:10.1186/1476-0711-12-22
39. **Kotz J.** Targeting tuberculosis. Nat Chem Biol. 2005. Accessed at www.nature.com/nchembio/journal/vaop/nprelaunch/full/nchembio002.html on 26 April 2016.
40. **Wilcox MH, Corey GR, Talbot GH, Thye D, Friedland D, Baculik T; CANVAS 2 investigators.** CANVAS 2: the second phase III, randomized, double-blind study evaluating ceftaroline fosamil for the treatment of patients with complicated skin and skin structure infections. J Antimicrob Chemother. 2010;65 Suppl 4:iv53-iv65. [PMID: 21115455] doi:10.1093/jac/dkq255
41. **Diacon AH, Pym A, Grobusch MP, de los Rios JM, Gotuzzo E, Vasilyeva I, et al; TMC207-C208 Study Group.** Multidrug-resistant tuberculosis and culture conversion with bedaquiline. N Engl J Med. 2014;371:723-32. [PMID: 25140958] doi:10.1056/NEJMoa1313865
42. **International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.** ICH harmonised tripartite guideline: choice of control group and related issues in clinical trials E10. 2000. Accessed at www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E10/Step4/E10_Guideline.pdf on 26 April 2016.
43. **U.S. Food and Drug Administration.** Statistical Review, Ceftolozane/Tazobactam (Zerbaxa). Silver Spring, MD: U.S. Food and Drug Administration; 2014.
44. 21 C.F.R. 314.500 (2015).
45. **Cox E, Laessig K.** FDA approval of bedaquiline–the benefit-risk balance for drug-resistant tuberculosis. N Engl J Med. 2014;371:689-91. [PMID: 25140952] doi:10.1056/NEJMp1314385
46. **U.S. Food and Drug Administration.** Medical Review: Dificid (Fidaxomicin). Silver Spring, MD: U.S. Food and Drug Administration; 2011.
47. **Doshi P.** Speeding new antibiotics to market: a fake fix? BMJ. 2015;350:h1453. [PMID: 25814536] doi:10.1136/bmj.h1453
48. **Brigden G, Hewison C, Varaine F.** New developments in the treatment of drug-resistant tuberculosis: clinical utility of bedaquiline and delamanid. Infect Drug Resist. 2015;8:367-78. [PMID: 26586956] doi:10.2147/IDR.S68351
49. **U.S. Government Accountability Office.** Drug Safety: FDA Expedites Many Applications, but Data for Postapproval Oversight Need Improvement. Washington, DC: U.S. Government Accountability Office; 2015.
50. **Prokocimer P, De Anda C, Fang E, Mehra P, Das A.** Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: the ESTABLISH-1 randomized trial. JAMA. 2013; 309:559-69. [PMID: 23403680] doi:10.1001/jama.2013.241
51. **Corey GR, Good S, Jiang H, Moeck G, Wikler M, Green S, et al; SOLO II Investigators.** Single-dose oritavancin versus 7-10 days of vancomycin in the treatment of gram-positive acute bacterial skin and skin structure infections: the SOLO II noninferiority study. Clin Infect Dis. 2015;60:254-62. [PMID: 25294250] doi:10.1093/cid/ciu778
52. **Boucher HW, Wilcox M, Talbot GH, Puttagunta S, Das AF, Dunne MW.** Once-weekly dalbavancin versus daily conventional therapy for skin infection. N Engl J Med. 2014;370:2169-79. [PMID: 24897082] doi:10.1056/NEJMoa1310480
53. **U.S. Food and Drug Administration.** Guidance on Providing Clinical Evidence of Effectiveness for Human Drugs and Biologics. Silver Spring, MD: U.S. Food and Drug Administration; 1998:4-5.
54. **Actavis + Forest Laboratories.** Forest Laboratories, Inc. reports fiscal year fourth quarter 2013 earnings per share of $0.17 including $0.08 per share of acquisition amortization [press release]. 23 April 2013. Accessed at http://investor.frx.com/press-release/corporate-news/forest-laboratories-inc-reports-fiscal-year-fourth-quarter-2013-earning on 13 October 2015.
55. **Reichert JM.** Trends in development and approval times for new therapeutics in the United States. Nat Rev Drug Discov. 2003;2:695-702. [PMID: 12951576]
56. **DiMasi JA, Hansen RW, Grabowski HG.** The price of innovation: new estimates of drug development costs. J Health Econ. 2003;22:151-85. [PMID: 12606142]
57. **Rex JH, Goldberger M, Eisenstein BI, Harney C.** The evolution of the regulatory framework for antibacterial agents. Ann N Y Acad Sci. 2014;1323:11-21. [PMID: 24797794] doi:10.1111/nyas.12441
58. **Alemayehu D, Quinn J, Cook J, Kunkel M, Knirsch CA.** A paradigm shift in drug development for treatment of rare multidrug-resistant gram-negative pathogens. Clin Infect Dis. 2012;55:562-7. [PMID: 22610933] doi:10.1093/cid/cis503
59. **Sertkaya A, Eyraud J, Birkenbach A, Franz C, Ackerley N, Overton V, et al.** Analytical Framework for Examining the Value of Antibacterial Products. Washington, DC: U.S. Department of Health and Human Services; 2014.
60. **U.S. Food and Drug Administration.** Guidance for Industry: Expedited Programs for Serious Conditions–Drugs and Biologics. Silver Spring, MD: U.S. Food and Drug Administration; 2014.
61. The Orphan Drug Act of 1983 (1983).

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Appendix: Definitions of FDA-Expedited Development or Review Programs

Accelerated approval allows approval to be based on a surrogate end point or an intermediate clinical end point that is reasonably likely to predict a drug's clinical benefit on how patients feel, function, or survive (60).

Breakthrough therapy offers increased resources and cross-disciplinary attention within the FDA that are intended to speed development (60).

Fast track affords the sponsor frequent interactions with the FDA review team and the promise of more efficient review, if the FDA determines that the product for life-threatening disease may be effective and may have added benefits over available therapies after preliminary evaluation of the clinical data (60).

Orphan drug status provides a sponsor with tax breaks, access to special grant funding, waiver of regulatory fees, and 7 years of market exclusivity after approval (61).

Priority review guarantees initial FDA review within 6 months instead of the standard 10-month deadline (60).

Qualified infectious disease product designation, available since 2012, is made before any clinical data are available. It provides incentives that include the prospect of a shorter preapproval development period, automatic priority review, and a 5-year extension of exclusivity after approval. Unlike the standard fast track, the new drug does not need to have promise of added benefits (22).

Appendix Table 1. Postmarket Commitments and Requirements as of December 2015*

Drug	PMR/Commitment (Status†)
Ceftaroline fosamil	1. Perform a trial in pediatric patients being treated concomitantly with antibacterial agent(s) to evaluate single-dose pharmacokinetic parameters and assess safety of Teflaro (ceftaroline fosamil) in all pediatric age groups. Required under PREA (fulfilled) 2. Perform a randomized comparison of Teflaro (ceftaroline fosamil) and comparator in pediatric patients with CABP utilizing an enrichment strategy for enrollment of patients with MRSA. Pediatric patients aged <17 y with CABP must be enrolled, with a minimum of 150 patients receiving Teflaro (ceftaroline fosamil). Required under PREA (submitted) 3. Perform a randomized comparison of Teflaro (ceftaroline fosamil) and comparator in pediatric population with ABSSSI, including patients with infection suspected or demonstrated to be caused by MRSA. Pediatric patients aged <17 y with ABSSSI must be enrolled, with a minimum of 150 patients receiving Teflaro (ceftaroline fosamil). Required under PREA (submitted) 4. Perform a trial assessing the CSF concentration profile of Teflaro (ceftaroline fosamil) in infants aged <2 mo. A minimum of 12 infants aged <2 mo receiving antibacterials for treatment of late-onset neonatal sepsis must be studied. Required under PREA (pending) 5. Perform a randomized comparison of Teflaro (ceftaroline fosamil) and comparator in infants aged <2 mo with ABSSSI and CABP, including patients with infections suspected or demonstrated to be caused by MRSA. Required under PREA (pending) 6. Conduct a prospective study over a 5-y period after introduction of Teflaro (ceftaroline fosamil) to the market to determine whether decreased susceptibility to Teflaro (ceftaroline fosamil) is occurring in the target bacteria included in the Indications section of the approved Teflaro (ceftaroline fosamil) package insert. Provide a detailed protocol describing the study to the FDA for review and comment before commencing the study. Required under FDAAA (ongoing)
Fidaxomicin	1. Conduct a prospective clinical trial of 10 d of Dificid (fidaxomicin) in at least 32 pediatric patients (aged 6 mo to <18 y) with *Clostridium difficile*–associated diarrhea to evaluate the safety and pharmacokinetics (including serum and fecal concentrations) of Dificid (fidaxomicin). Required under PREA (fulfilled) 2. Conduct a prospective, randomized clinical trial to demonstrate safety and effectiveness of Dificid (fidaxomicin) compared with vancomycin in pediatric patients (aged 6 mo to <18 y) with *C difficile*–associated diarrhea. Required under PREA (pending) 3. Conduct a prospective study over a 5-y period after introduction of Dificid (fidaxomicin) to the market to determine whether decreased susceptibility to Dificid (fidaxomicin) is occurring in *C difficile*. Provide a detailed protocol describing the study to the FDA for review and comment before commencing the study. Required under FDAAA (ongoing) 4. Conduct a prospective, randomized, comparative trial to demonstrate the efficacy of Dificid (fidaxomicin) in the treatment of patients with multiple recurrences of *C difficile* associated diarrhea (pending)
Bedaquiline	1. Conduct a confirmatory randomized, double-blind, placebo-controlled, multicenter, phase 3 trial in persons with sputum smear–positive pulmonary MDR-TB. This trial should assess long-term outcomes of failure or relapse or death ≥6 mo after all MDR-TB treatment is completed. Required under accelerated approval (ongoing) [Note: Described as "ongoing" in the FDA database, but not listed as under way on ClinicalTrials.gov] 2. Develop a patient registry for bedaquiline-treated patients to assess incidence rates of serious adverse events, including death. Required under FDAAA (pending) 3. To inform PMR 5, conduct a study to define the quality control ranges of bedaquiline for MDR-TB isolates using standard proportion methods. Required under FDAAA (fulfilled) 4. To inform PMR 5, conduct a study to define the quality control ranges of bedaquiline for MDR-TB isolates using MIC methods. Required under FDAAA (fulfilled) 5. Conduct a prospective in vitro study over a 5-y period after introduction of Sirturo (bedaquiline) to the market to determine MICs of MDR-TB isolates to bedaquiline for the first 5 y from marketing. Report interpretation of these MICs once additional quality control testing methods are developed as noted in the required postmarketing studies for PMRs 3 and 4. Provide a detailed protocol describing the study to the FDA for review and comment before commencing the study. Required under FDAAA (pending) 6. Conduct an in vitro study to characterize the potential of bedaquiline and M2 as a substrate, inhibitor or inducer of the OATP1B1 and OATP1B3 drug transporters. Required under FDAAA (fulfilled) 8. Submit final study report and electronic data for Study C208 Stage II (fulfilled) 9. Submit final study report and electronic data for Study C209 (fulfilled)
Dalbavancin	1. Conduct a single-dose pharmacokinetic study in children aged 3 mo to <12 y. Required under PREA (ongoing) 2. Conduct a single-dose pharmacokinetics study in neonates/infants aged 0 to <3 mo. Required under PREA (pending) 3. Conduct a phase 3, randomized, comparator-controlled study of dalbavancin in children aged 3 mo to 17 y with ABSSSI. Required under PREA (pending) 4. Conduct a phase 3, randomized, comparator-controlled study of dalbavancin in neonates/infants from birth to age <3 mo with ABSSSI. Required under PREA (pending) 5. Conduct U.S. surveillance studies for 5 y from the date of marketing Dalvance to determine whether resistance to dalbavancin has developed in those organisms specific to the indication in the label for ABSSSI. Required under FDAAA (pending) 6. Conduct studies to define the mechanism(s) of resistance for isolates identified as being resistant to dalbavancin during the surveillance period (5 y from the date of marketing). Required under FDAAA (pending) 9. Conduct an in vitro study evaluating interactions between dalbavancin hydrochloride and coagulation tests. Required under FDAAA (pending)
Tedizolid	1. Conduct a randomized, single-blind, multicenter safety and efficacy study of intravenous to oral Sivextro (tedizolid phosphate) and intravenous to oral comparator for the treatment of acute bacterial skin and skin structure infections in pediatric patients aged 12 to <18 y. Required under PREA (pending) 2. Conduct a randomized, single-blind, multicenter safety and efficacy study of intravenous to oral Sivextro (tedizolid phosphate) and intravenous to oral comparator for the treatment of acute bacterial skin and skin structure infections in pediatric patients aged >3 mo to <12 y. Required under PREA (pending) 3. Conduct an open-label, multicenter study of 10-14 d of IV Sivextro (tedizolid phosphate) for hospital-acquired late-onset sepsis in full-term and preterm neonates and infants aged 5 d to <3 mo. Required under PREA (pending)

Continued on following page

Appendix Table 1–Continued

Drug	PMR/Commitment (Status†)
	4. Conduct a phase 1 single-dose safety and pharmacokinetic study of oral and IV Sivextro (tedizolid phosphate) in patients aged 2 y to <12 y. Required under PREA (pending) 5. Conduct a phase 1 single-dose safety and pharmacokinetic study of oral and intravenous Sivextro (tedizolid phosphate) in inpatients aged <2 y. Required under PREA (pending) 6. Conduct U.S. surveillance studies for 5 y from the date of marketing Sivextro to determine whether resistance to tedizolid has developed in those organisms specific to the indication in the label for ABSSSI. Required under FDAAA (pending)
Oritavancin	1. Conduct an open-label, dose-finding, pharmacokinetics, safety, and tolerability study of Orbactiv (oritavancin diphosphate) single-dose infusion in pediatric patients aged <18 y with suspected or confirmed bacterial infections. Required under PREA (pending) 2. Conduct a multicenter, evaluator-blinded, randomized study to evaluate the safety and tolerability of single-dose IV Orbactiv (oritavancin diphosphate) versus vancomycin for the treatment of pediatric patients aged <18 y with ABSSSI. Required under PREA (pending) 3. Conduct a U.S. surveillance study over a 5-y period from the date of marketing Orbactiv (oritavancin diphosphate) to determine whether resistance to oritavancin has developed in those organisms specific to the indication in the label for ABSSSI. Required under FDAAA (pending) 4. Conduct an open-label trial evaluating the safety of a single 1200 mg IV dose of Orbactiv (oritavancin diphosphate) in patients on concomitant chronic warfarin therapy who are being treated for ABSSSI. Required under FDAAA (pending) 5. Conduct an open-label trial to assess the clinical significance of the drug–drug interaction between a single 1200-mg IV dose of Orbactiv (oritavancin diphosphate) and warfarin in healthy volunteers. Required under FDAAA (pending) 6. Conduct a single-center, open-label trial to evaluate the effects of a single 1200-mg IV dose of Orbactiv (oritavancin diphosphate) on the results of multiple coagulation tests in healthy volunteers. Required under FDAAA (pending) 7. Conduct a study to evaluate the effects of oritavancin on phospholipid- and non–phospholipid-based coagulation tests in vitro. Required under FDAAA (pending)
Ceftolozane–tazobactam	1. Conduct a randomized, double-blind, multicenter, comparative study to establish the safety and tolerability profile of ceftolozane–tazobactam compared with that of meropenem in hospitalized children from birth to age <18 y with CUTI. The dose for this study will be determined upon review of the data to be submitted by December 2016 from a single-dose, multicenter, noncomparative study assessing the pharmacokinetics of ceftolozane–tazobactam in pediatric patients ages 0 to <18 y that was initiated in June 2014. Required under PREA (pending) 2. A randomized, double-blind, multicenter, comparative study to establish the safety and tolerability profile of ceftolozane–tazobactam compared with that of meropenem in hospitalized children from birth to age <18 y with CIAI. The dose for this study will be determined upon review of the data to be submitted by December 2016 from the single-dose, multicenter, noncomparative study assessing the pharmacokinetics of ceftolozane–tazobactam in pediatric patients aged 0 to <18 y that was initiated in June 2014. Required under PREA (pending) 3. Conduct a prospective study over a 5-y period after the introduction of Zerbaxa (ceftolozane–tazobactam) to the market to determine whether decreased susceptibility to Zerbaxa (ceftolozane–tazobactam) is occurring in the target population of bacteria that are in the approved Zerbaxa (ceftolozane–tazobactam) label. Required under FDAAA (pending)
Ceftazidime–avibactam	1. Conduct a randomized, multicenter, active-controlled trial to evaluate the safety and tolerability of Avycaz (ceftazidime–avibactam) in children aged 3 mo to <18 y with CUTI. The dose for this study will be determined upon review of the data to be submitted by June 2015 from a single-dose, multicenter, noncomparative study assessing the pharmacokinetics of Avycaz (ceftazidime–avibactam) in pediatric patients aged 3 mo to <18 y. Required under PREA (pending) 2. Conduct a randomized, multicenter, active-controlled trial to evaluate the safety and tolerability of Avycaz (ceftazidime–avibactam) in children aged 3 mo to <18 y with CIAI. The dose for this study will be determined upon review of the data to be submitted by June 2015 from a single-dose, multicenter, noncomparative study assessing the pharmacokinetics of Avycaz (ceftazidime–avibactam) in pediatric patients aged 3 mo to <18 y. Required under PREA (pending) 3. Conduct a trial to evaluate the pharmacokinetics, safety, and tolerability of Avycaz (ceftazidime–avibactam) in children from birth to age <3 mo with late-onset sepsis. Required under PREA (pending) 4. Conduct a prospective study over a 5-y period after the introduction of Avycaz (ceftazidime–avibactam) to the market to determine whether decreased susceptibility to Avycaz (ceftazidime–avibactam) is occurring in the target population of bacteria that are in the approved Avycaz (ceftazidime–avibactam) label. Required under FDAAA (pending) 5. Conduct a trial or submit data from the phase 3 trial in CIAI to evaluate the pharmacokinetics, safety, and clinical outcomes in adult patients with baseline renal impairment (creatinine clearance ≤50 mL/min) receiving Avycaz (ceftazidime–avibactam) dosing regimens adjusted for renal function. Required under FDAAA (ongoing)

ABSSSI = acute bacterial skin and skin-structure infection; CABP = community-acquired bacterial pneumonia; CIAI = complicated intra-abdominal infection; CSF = cerebrospinal fluid; CUTI = complicated urinary tract infection; FDA = U.S. Food and Drug Administration; FDAAA = FDA Amendments Act; IV = intravenous; MDR-TB = multidrug-resistant tuberculosis; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *Staphylococcus aureus*; PREA = Pediatric Research Equity Act; PMR = postmarket requirement.

* Some numbers are not listed because they were not found in the FDA database.

† *Pending:* The study has not been initiated (i.e., no participants have been enrolled or animals dosed), but does not meet the criterion for delayed (i.e., the original projected date for initiation of patient accrual or initiation of animal dosing has not passed). *Ongoing:* The study is proceeding according to, or is ahead of, the original schedule. *Delayed:* The progression of the study is behind the original study schedule. *Terminated:* The applicant ended the study before completion, and has not yet submitted a final study report to the FDA. *Submitted:* The applicant has concluded or terminated the study and has submitted a final study report to the FDA, but FDA has not yet notified the applicant in writing that the study commitment has been fulfilled or that the commitment has been released. *Fulfilled:* The applicant has submitted the final study report for the commitment, and upon review of the final study report, FDA is satisfied that the applicant has met the terms of the commitment. *Released:* FDA has informed the applicant that it has been released from its obligation to conduct the postmarketing study because the study is either no longer feasible or would no longer provide useful information.

Appendix Table 2. Detailed Dose, Duration, and Cost of Antibiotic Drugs and Trial Comparators

New Antibiotic					Comparator					Cost Ratio
Drug	**Dose and Duration**	**AWP Unit Price, $***	**Unit**	**Cost Range, $**	**Drug**	**Dose and Duration**	**AWP Unit Price Range, $***	**Unit**	**Cost Range, $**	
Ceftaroline	CABP: 600 mg every 12 h for 5–7 d	166.63	600 mg	CABP: 1666.30–2332.82	CABP: Ceftriaxone	CABP: Ceftriaxone, 1 g once daily for 5–7 d	CABP: 1.80– 47.05	Ceftriaxone, 1 g	CABP: 9.00–329.35	CABP: 185:1 to 7:1
	ABSSSI: 600 mg every 12 h for 5–14 d			ABSSSI: 1666.30–4665.64	ABSSSI: Vancomycin + aztreonam	ABSSSI: Vancomycin, 1 g twice daily plus aztreonam, 1 g twice daily for 5–14 d	ABSSSI: vancomycin, 7.47–20.52; aztreonam, 39.54	Vancomycin, 1 g, plus aztreonam, 1 g	ABSSSI: 470.10–1681.68	ABSSSI: 4:1 to 3:1
Fidaxomicin	200 mg twice daily for 10 d	198.46	200 mg	3969.20	Vancomycin†	125-mg capsule 4 times daily for 10 d	31.30–34.80	125 mg	1252.00–1392.00	3:1
Bedaquiline	400 mg daily for 2 wk, then 200 mg 3 times/wk for 22 wk	191.49	100 mg	36 000.12	Placebo (both groups received a background multidrug anti–TB treatment regimen)	-‡	-‡	-‡	-‡	-‡
Dalbavancin	One dose of 1000 mg ,then 500 mg 8 d later	1788.00	500 mg	5364.00	Vancomycin or linezolid	Vancomycin, 1 g twice daily for 3–14 d, with optional switch to linezolid, 600 mg twice daily for 8 d	Vancomycin: 7.47–20.52 Linezolid: 183.67	Vancomycin, 1 g Linezolid, 600 mg	Vancomycin: 44.82–574.56 Linezolid: 2938.72	Vancomycin: 120:1 to 9:1 Linezolid: 2:1
Tedizolid	200 mg once daily for 6 d	Oral: 354.00 IV: 282.00	200 mg	Oral: 2124 IV: 1692	Linezolid	600 mg twice a day for 10 d	183.67	600 mg	3673.40	Oral 0.5:1 IV 0.5:1
Oritavancin	1200 mg dose administered by IV once	1160.00	400 mg	3480.00	Vancomycin	1 g every 12 h for 7–10 d	7.47–20.52	1 g	104.58–410.40	33:1 to 9:1
Ceftolozane–tazobactam	CUTI: 1.5 g every 8 h for 7 d	99.60	1.5 g	CUTI: 2091.60	CUTI: Levofloxacin	CUTI: Levofloxacin, 750 mg daily for 7 d	CUTI: 0.05–0.10	Levofloxacin, 750 mg	CUTI: 0.35–0.70	CUTI: 5976:1 to 2988:1
	CIAI:1.5 g every 8 h for 4–14 d			CIAI: 1195.20–4183.20	CIAI: Meropenem	CIAI: Meropenem, 1 g every 8 h for 4–10 d	CIAI: 12.85–70.37	Meropenem, 1 g	CIAI: 154.20–2111.10	CIAI: 8:1 to 2:1
Ceftazidime–avibactam	CUTI: 2.5 g every 8 h for 7–14 d	342.00	2.5 g	CUTI: 7182–14 364	CUTI: Imipenem–cilastatin	CUTI: Imipenem–cilastatin, 500 mg every 6 h for 7–14 d (optional switch to ciprofloxacin after 4 d)	CUTI: 12.60–30.00	Imipenem–cilastatin, 500 mg	CUTI: 352.80–1680.00	CUTI: 20:1 to 9:1
	CIAI: 2.5 g every 8 h for 5–14 d + MTZ			CIAI: 5130–14 364	CIAI: Meropenem	CIAI: Meropenem, 1 g every 8 h for 5–14 d	CIAI:12.85–70.37	Meropenem, 1 g	CIAI: 192.75–2955.54	CIAI: 27:1 to 5:1

ABSSSI = acute bacterial skin and skin-structure infection; AWP = average wholesale price; CABP = community-acquired bacterial pneumonia; CIAI = complicated intra-abdominal infection; CUTI = complicated urinary tract infection; IV = intravenous; MTZ = metronidazole; TB = tuberculosis.

† Although the fidaxomicin trials used oral vancomycin (cost shown here), some hospitals may compound generic IV into oral capsules, greatly reducing the cost.

‡ Background multidrug anti-TB regimen varied by individual. Possible drugs included ethionamide, kanamycin, ofloxacin, pyrazinamide, and terizidine (all off-patent).