

10 × '20 Progress—Development of New Drugs Active Against Gram-Negative Bacilli: An Update From the Infectious Diseases Society of America

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Infections caused by antibiotic-resistant bacteria, especially the “ESKAPE” pathogens, continue to increase in frequency and cause significant morbidity and mortality. New antimicrobial agents are greatly needed to treat infections caused by gram-negative bacilli (GNB) resistant to currently available agents. The Infectious Diseases Society of America (IDSA) continues to propose legislative, regulatory, and funding solutions to this continuing crisis. The current report updates the status of development and approval of systemic antibiotics in the United States as of early 2013. Only 2 new antibiotics have been approved since IDSA's 2009 pipeline status report, and the number of new antibiotics annually approved for marketing in the United States continues to decline. We identified 7 drugs in clinical development for treatment of infections caused by resistant GNB. None of these agents was included in our 2009 list of antibacterial compounds in phase 2 or later development, but unfortunately none addresses the entire spectrum of clinically relevant GNB resistance. Our survey demonstrates some progress in development of new antibacterial drugs that target infections caused by resistant GNB, but progress remains alarmingly elusive. IDSA stresses our conviction that the antibiotic pipeline problem can be solved by the collaboration of global leaders to develop creative incentives that will stimulate new antibacterial research and development. Our aim is the creation of a sustainable global antibacterial drug research and development enterprise with the power in the short term to develop 10 new, safe, and efficacious systemically administered antibiotics by 2020 as called for in IDSA's “10 × '20 Initiative.”

Keywords. antibacterial agents; antimicrobials; gram-negative bacilli; drug development; clinical trials; antibiotic pipeline.

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^aThe Infectious Diseases Society of America (IDSA) is a national medical society representing infectious diseases physicians, scientists, and other healthcare professionals dedicated to promoting health through excellence in infectious diseases research, education, prevention, and patient care. The Society, which has >10 000 members, was founded in 1963 and is based in Arlington, Virginia. For more information, visit www.idsociety.org.

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Infections caused by antibiotic-resistant bacteria, especially the “ESKAPE” pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Enterobacter* species), cause significant morbidity and mortality [1, 2].

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These and other drug-resistant gram-negative bacilli (GNB) infections impact not only hospitalized patients undergoing surgical and other procedures, but also otherwise healthy nonhospitalized patients in the United States and worldwide [3–7].

Since 2002, the Infectious Diseases Society of America (IDSA) has voiced concern with the absence of progress in developing novel therapeutics to treat multidrug-resistant (MDR) infections, including those caused by GNB. In our 2009 report, no antibacterial agent in development with a purely gram-negative spectrum had reached phase 2 of clinical study [2].

The need for new agents to treat infections caused by GNB resistant to currently available agents is even more urgent than at the time of our 2009 report [2]. Furthermore, the withdrawal of several large pharmaceutical companies from antibacterial research and development (R&D) has compromised the infrastructure for discovering and developing new antimicrobials, especially in the United States.

In its July 2004 policy report “Bad Bugs, No Drugs: As Antibiotic R&D Stagnates, a Public Health Crisis Brews,” IDSA proposed legislative, regulatory, and funding solutions to address this increasing public health problem [8]. Recognizing the need for new, creative approaches to address the problem of the dwindling antibiotic pipeline, IDSA launched the “10×’20 Initiative” in 2010 [9]. This campaign calls for development and regulatory approval of 10 novel, efficacious, and safe systemically administered antibiotics by 2020 [9]. On World Health Day 2011, IDSA issued a policy statement titled “Combating Antimicrobial Resistance: Policy Recommendations to Save Lives,” which provides clear suggestions for addressing the “synergistic crises” of increasing antimicrobial resistance and decreasing availability of new antimicrobial therapies [10]. IDSA continues to work with Congress, the US Food and Drug Administration (FDA), US National Institutes of Health (NIH), Centers for Disease Control and Prevention (CDC), and other stakeholder groups to ensure that the focus on the problem will not waver.

In this current communication, we report on the state of clinical development and regulatory approval of new, systemically administered antibacterials in the United States as of early 2013.

METHODS

As in our earlier report, we performed a literature review as well as an investigation of the clinical trials registry (www.clinicaltrials.gov). The following sources were utilized to identify antibiotic drug candidates in the development pipeline in the same manner as in our earlier report:

1. Abstracts from the 2010, 2011, and 2012 Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) were searched for investigational antimicrobials.

2. The website www.clinicaltrials.gov was accessed and searched by condition with a disease heading of “bacterial infections.” Compounds identified were confirmed by accessing the website of the innovator company. Given the high failure rate of compounds that have not successfully navigated phase 1 studies, only those compounds in phases 2 or 3 of development are discussed.

3. The PubMed database was searched for relevant English-language literature published between September 2009 and July 2012 by using the search terms *antimicrobial drug development*, *investigational antimicrobials*, and *novel antimicrobials*.

4. Interviews were conducted by the drafters of this report with leaders of the few remaining pharmaceutical and biotechnology companies identified in our earlier survey [2]; the websites of these companies were also accessed and data on drugs in development were reviewed.

We focus on new orally or intravenously administered antibiotics that have progressed to phase 2 or 3 studies, as these agents are more likely to reach the clinic and are associated with substantial investment by pharmaceutical sponsors. This update focuses on agents active against GNB as effective therapy, as these pathogens represent the most pressing medical needs. The focus is not to detract from the need for new orally active agents for treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) infection and vancomycin-resistant enterococci, as well as agents for treatment of increasingly resistant gonococci. Non-absorbable agents administered via the gastrointestinal tract (eg, rifaximin, fidaxomicin) were excluded. We do not include new indications of approved drugs or new indications for different formulations of approved drugs.

Recent discovery and development efforts aimed at MDR GNB have focused largely on important mechanisms of resistance including β -lactamases and carbapenemases, as these are responsible for a large burden of drug-resistant infections reported globally. While a number of definitions exist, a proposed International Standard defines MDR as nonsusceptibility to at least 1 agent in 3 or more antimicrobial classes [11]. Enterobacteriaceae, *P. aeruginosa*, and *A. baumannii* that produce extended-spectrum β -lactamases (ESBLs) and/or carbapenemases have been increasingly reported. The β -lactamases act via enzymatic hydrolysis to break open the β -lactam ring and inactivate β -lactam antibiotics. The ESBLs confer resistance to most β -lactam antibiotics, including penicillins, cephalosporins, and the monobactam aztreonam, whereas carbapenemases confer additional resistance to carbapenem antibiotics (as well as some other β -lactam antibiotics) [12]. The β -lactamases are classified according to the Ambler classification (A–D) based on amino acid sequence structure or according to the Bush-Jacoby-Medeiros scheme [13]. Hydrolytic mechanisms in class A, C, and D β -lactamases all require an active-site serine at position 70; these are often called serine β -lactamases. Class B

Table 1. Systemic Antibacterial Drug Approvals Since 1998^a

Antibacterial	Year Approved	Novel Mechanism?
Rifapentine ^b	1998	No
Quinupristin/dalfopristin ^c	1999	No
Moxifloxacin	1999	No
Gatifloxacin ^d	1999	No
Linezolid	2000	Yes
Cefditoren pivoxil	2001	No
Ertapenem	2001	No
Gemifloxacin ^d	2003	No
Daptomycin	2003	Yes
Telithromycin ^d	2004	No
Tigecycline ^e	2005	Yes
Doripenem	2007	No
Telavancin	2009	Yes
Ceftaroline fosamil	2010	No

^a Rifaxamin (Food and Drug Administration [FDA] approved in 2004) and fidaxomicin (FDA approved in 2011) are not systemically absorbed, and so are not included on this list.

^b Antituberculous agent.

^c Infrequently used due to adverse event profile.

^d Withdrawn from market due to adverse event profile.

^e Label warning regarding possible excess mortality.

β -lactamases require zinc for activity and hence are also called metallo- β -lactamases; important examples include VIM, IMP, and NDM. The metallo- β -lactamases are inactivated by chelators, such as ethylenediaminetetraacetic acid, but not by β -lactamase inhibitors (eg, tazobactam) [12–14]. This report will classify what is known about activity of the drugs in development versus these important enzymes [15].

RESULTS

Despite ongoing efforts, only 2 new antibiotics—telavancin and ceftaroline fosamil—have been approved since our 2009 report (Table 1). We consider ceftaroline fosamil one of the hoped-for “10 × ’20” drugs. The number of new antibiotics annually approved for marketing in the United States has continued to decline (Figure 1). Importantly, the number of large multinational pharmaceutical companies (ie, “Big Pharma”) actively developing antimicrobial drugs also continues to decline (Table 2).

We identified 7 parenteral drugs in clinical development for treatment of infections caused by MDR GNB (Table 3), and one whose phase 2 development program was recently halted [16–22]. As indicated in Table 3, complicated urinary tract infection (cUTI), complicated intraabdominal infection (cIAI), and acute bacterial skin and skin structure infection (ABSSSI) are the initially targeted regulatory indications. Of the 7 agents, 4 are β -lactam plus β -lactamase inhibitor combination drugs; 2

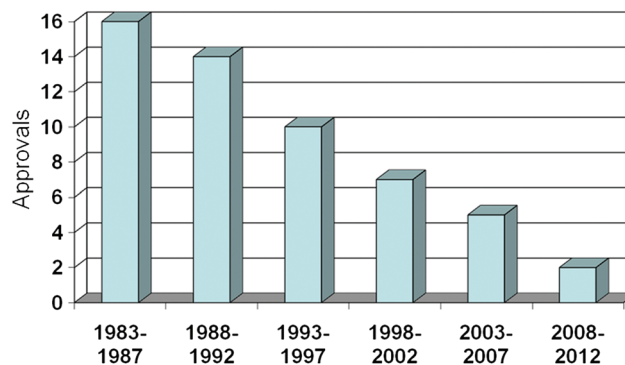


Figure 1. New systemic antibacterial agents approved by the US Food and Drug Administration per 5-year period, through 2012. Modified from Spellberg 2004 [23].

are protein synthesis inhibitors (one with a novel mechanism of action and one aminoglycoside); and one is a peptide mimetic. The antibiotic whose development was halted is a transfer RNA (tRNA) synthetase inhibitor. In addition, some promising compounds are in phase 1 development. The number of drugs in phase 1 development provide another, potentially useful metric of the pool of new drugs in development. However, in addition to the high phase 1 failure rates, the absence of publicly available data led to our decision to exclude phase 1 candidate compounds.

Ceftolozane/tazobactam, ceftazidime/avibactam, ceftaroline/avibactam, and MK-7655/imipenem are β -lactam/ β -lactamase inhibitor combination products that act by inhibiting the β -lactamases (tazobactam, avibactam, MK-7655 are the inhibitors) so that the partner antibiotic (ceftolozane, ceftazidime, ceftaroline, and imipenem) can interfere with cell wall synthesis. Each of these drug combinations offers the potential to enhance β -lactam therapeutic options [16, 24].

Table 2. Antibacterial Pipeline (Anti-Gram Positive and Anti-Gram Negative), Big Pharma

Company	Since 1998	Phase 2/3
Abbott Laboratories	0	0
AstraZeneca	0	2
Bayer	0	0
GlaxoSmithKline	0	1
Lilly	0	0
Merck/Schering-Plough	1	1
Novartis	0	0
Ortho McNeil/Johnson & Johnson	1	0
Pfizer/Wyeth	2	0
Roche	0	0
Sanofi	0	0

Table 3. Intravenous Antimicrobials Active Against Gram-Negative Bacilli in Advanced (Phase 2 or 3) Clinical Development^a

	Product	Class (Mechanism of Action)	Novel Mechanism of Action?	Status	Activity Targets							
					Enterobacteriaceae			<i>Pseudomonas aeruginosa</i>			<i>Acinetobacter</i> spp	
					ESBL	sCBP	mCBP	WT	MDR	mCBP	WT	MDR
1	Ceftolozane/taxobactam (CXA-201; CXA-101/tazobactam)	Antipseudomonal cephalosporin/BLI combination (cell wall synthesis inhibitor)	No	Phase 3 (cUTI, cIAI)	Yes	No	No	Yes	IE	No	No	No
2	Ceftazidime-avibactam (ceftazidime/NXL104)	Antipseudomonal cephalosporin/BLI combination (cell wall synthesis inhibitor)	No	Phase 3 (cIAI)	Yes	Yes	No	Yes	IE	No	No	No
3	Ceftaroline-avibactam (CPT-avibactam; ceftaroline/NXL104)	Anti-MRSA cephalosporin/BLI combination (cell wall synthesis inhibitor)	No	Phase 2 (cUTI, cIAI)	Yes	Yes	No	No	No	No	No	No
4	Imipenem/MK-7655	Carbapenem/BLI combination (cell wall synthesis inhibitor)	No	Phase 2 (cUTI, cIAI)	Yes	Yes	No	Yes	IE	No	IE	No
5	Plazomicin (ACHN-490)	Aminoglycoside (protein synthesis inhibitor)	No	Phase 2 (cUTI)	Yes ^b	Yes ^b	IE	No	No	No	No	No
6	Eravacycline (TP-434)	Fluorocycline (protein synthesis inhibitor targeting the ribosome)	No	Phase 2 (cIAI)	Yes ^b	Yes	IE	No	No	No	IE	IE
7	Brilacidin (PMX-30063)	Peptide defense protein mimetic (cell membrane disruption)	Yes?	Phase 2 (ABSSSI)	Yes	IE	IE	IE	IE	IE	No	No

Activity based on available information.

Abbreviations: ABSSSI, acute bacterial skin and skin structure infection; BLI, β -lactamase inhibitor; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; ESBL, extended-spectrum β -lactamase producers; IE, insufficient evidence available; mCBP, metallo-carbapenamase producers (eg, NDM, VIM, IMP); MDR, multidrug-resistant pattern including co-resistances to aminoglycosides (amikacin, gentamicin, tobramycin), fluoroquinolones, tetracyclines, and broad-spectrum β -lactams by various mechanisms carried on common genetic elements; MRSA, methicillin-resistant *Staphylococcus aureus*; sCBP, serine carbapenamase producers such as KPC; WT, wild-type pattern for species.

^a Intravenous antimicrobials not listed in IDSA's 2009 drug status report [2].

^b Incomplete coverage of some species (*Proteus mirabilis* and indole-positive *Proteus* species).

Ceftolozane (CXA-101, Cubist) demonstrates enhanced affinity for *P. aeruginosa* penicillin-binding proteins, thus providing excellent intrinsic activity for *P. aeruginosa*. The combination with tazobactam as ceftolozane/tazobactam is being studied in clinical trials. Tazobactam is a “tried and true” β -lactamase inhibitor, whose spectrum extends to class A and some class C β -lactamases (eg, plasmid-borne cephalosporinase). Although not as broad a β -lactamase inhibitor as some new non- β -lactam β -lactamase inhibitors mentioned below, tazobactam provides activity against the important and increasingly common CTX-M-15 β -lactamase as well as other ESBLs. Ceftolozane alone or as the combination has limited activity against *A. baumannii*.

Ceftolozane/tazobactam is currently in phase 3 studies of cUTI and cIAI; this combination drug could become available in the next few years. In cUTI, including pyelonephritis, intravenous ceftolozane/tazobactam is being compared to parenteral levofloxacin [25]. In cIAI, the comparator agent is intravenous meropenem [26]. The sponsor recently announced plans to study ventilator-associated bacterial pneumonia (VABP) in a global trial. They plan an approximately 950-patient noninferiority study comparing a higher dose of ceftolozane/tazobactam, 3 g every 8 hours, to imipenem-cilastatin. This study will use a 28-day mortality endpoint [27].

Ceftazidime/avibactam (CAZ/avibactam; AstraZeneca/Forest Laboratories) demonstrates in vitro activity against most strains of *P. aeruginosa*, MDR Enterobacteriaceae (ESBL producers), and *Klebsiella pneumoniae*-producing serine carbapenemases (KPCs), but not metallo- β -lactamase producers (eg, VIM, NDM) [28–34]. Avibactam (previously NXL 104) is a potent, reversible, non- β -lactam β -lactamase inhibitor, the spectrum of which includes primarily class A and class C β -lactamases. As is true for ceftolozane, the antimicrobial component of CAZ/avibactam has only very modest activity against *Acinetobacter* species. Currently in phase 3 development, trials are recruiting patients for a study of CAZ/avibactam plus metronidazole versus meropenem for cIAI, and one comparing ceftazidime/avibactam with doripenem in cUTI [35, 36]. In addition, AstraZeneca/Forest plans an open-label study of CAZ/avibactam in addition to the best available therapy (“standard of care”) for treatment of CAZ-resistant GNB infections (eg, caused by ESBL-producing organisms) [37].

Ceftaroline/avibactam (CPT/avibactam, ceftaroline fosamil [CPT] plus NXL 104) shows in vitro potency versus MRSA and Enterobacteriaceae (including those producing ESBLs and KPCs) but not *P. aeruginosa* or *A. baumannii*. This combination, also in development by AstraZeneca/Forest, is in phase 2 studies of cUTI and cIAI [33, 38, 39].

Imipenem/MK-7655 (Merck) is a combination of the carbapenem imipenem-cilastatin and a β -lactamase inhibitor similar in chemical structure to NXL104 (a class A and class C β -lactamase inhibitor). The combination demonstrates in vitro activity against

P. aeruginosa and many ESBL producers, including carbapenem-resistant strains, but not against metallo-carbapenemases [40]. Activity against *A. baumannii* is limited. Two separate phase 2 studies of 2 doses (125 or 250 mg) of MK-7655 plus imipenem-cilastatin versus imipenem-cilastatin alone for treatment of cUTI or cIAI were initiated by Merck in early 2012 [41, 42].

Plazomicin (ACHN-490), a next-generation “neoglycoside” from Achaogen, demonstrates in vitro potency and in vivo activity against ESBL-producing pathogens, fluoroquinolone-resistant and aminoglycoside-resistant GNB, and GNB-expressing Amp C cephalosporinases, carbapenemases, and metallo- β -lactamases, but not *Proteus* species or strains with aminoglycoside-resistant methylase genes (eg, ArmA, RmtC) [16]. Activity against *P. aeruginosa* and *A. baumannii* remains limited. Data from a phase 2 study of intravenous plazomicin versus levofloxacin for treatment of cUTI were reported in September 2012 [43, 44].

Eravacycline (TP-434, Tetrphase) is a broad-spectrum fluoroquinolone antibiotic that—like other tetracycline agents—binds to bacterial ribosomes, thereby inhibiting protein synthesis [45]. In addition, TP-434 demonstrates stability to common tetracycline-resistance mechanisms, that is, tetracycline-specific efflux and ribosomal protection. This molecule demonstrates in vitro inhibitory activity against MRSA, vancomycin-resistant enterococci, and KPC-producing GNB, but not against *Pseudomonas* species or *Acinetobacter* species. Tetrphase is proceeding with development of the intravenous formulation; an oral formulation is also being investigated. Phase 1 studies of the latter are under way. Data from a phase 2, randomized, double-blind, double-dummy, multicenter, prospective study of 2-dose regimens of intravenous TP-434 compared with ertapenem in the treatment of adult community-acquired cIAI were recently reported [46, 47].

Brilacidin (PMX-30063, Polymedix), a peptide mimetic, disrupts bacterial membranes. In vitro studies of this molecule support activity against enteric GNB but uncertain activity against *P. aeruginosa* and no activity versus *A. baumannii*. In a phase 2 study of PMX-30063 versus daptomycin for treatment of ABSSSI due to methicillin-susceptible *S. aureus*, safety findings included sensory nerve symptoms and hypertensive episodes of unclear significance [48–50].

BAL30072, a siderophore sulfactam being developed by Basilea Pharmaceutica, has activity against *Acinetobacter* species, *P. aeruginosa*, *Burkholderia cepacia*, and some MDR Enterobacteriaceae but lower potency versus selected ESBL-producing Enterobacteriaceae [51–54]. However, this agent, which resembles aztreonam, is still in phase 1 study, and will likely be combined with meropenem in clinical development studies. BAL30072 targets >1 penicillin-binding protein and has stability against metallo- β -lactamase-producing GNBs. Another β -lactam/ β -lactamase inhibitor combination, carbavance (biapenem/RPX7009), is being developed by Rempex Pharmaceuticals

and is in late phase 1 study [55, 56]. Carbavance combines the activity of a well-studied carbapenem, biapenem, with a β -lactamase inhibitor potent against serine carbapenemases (class A). Enterobacteriaceae-producing ESBLs and KPC enzymes are inhibited as are *P. aeruginosa* and *A. baumannii* at minimum inhibitory concentration values similar to those of other carbapenems tested alone. Metallo- β -lactamase-producing isolates remain resistant to this combination. Clinical indications and study designs are pending.

GSK 052 (GlaxoSmithKline, previously AN3365 from Anacor) is a novel boron-based tRNA synthesis inhibitor that specifically targets the bacterial enzyme leucyl-tRNA synthetase, which is required for protein synthesis. This molecule is active in vitro against *E. coli*, *K. pneumoniae*, *Citrobacter* species, *Serratia marcescens*, *Proteus vulgaris*, *Providencia* species, *P. aeruginosa*, and *Enterobacter* species, although not against *Acinetobacter* species and some *Pseudomonas* species. Unfortunately, phase 2 studies in cIAI and cUTI were halted in February 2012, after discovery of an undefined “microbiologic finding” among cUTI patients [57]. GlaxoSmithKline announced discontinuation of clinical development of GSK 052 on 5 October 2012 [58].

None of the 7 drugs in full clinical development (phase 2 or 3) were included in our 2009 list of late-stage antibacterial compounds [2]. Unfortunately, none demonstrates activity against the entire spectrum of clinically relevant GNB resistance. Table 3 illustrates the glaring absence of β -lactam drugs able to withstand enzymatic attack by metallo-carbapenemases and the absence of drugs with predictable activity against *A. baumannii*. In addition, we were unable to identify any phase 2 or 3 clinical trials designed to address the important conditions of community-acquired bacterial pneumonia (CABP), hospital-acquired bacterial pneumonia (HABP), or bloodstream infection.

DISCUSSION

The number of antibacterial compounds in phase 2 or 3 development remains alarmingly low. The pace of R&D must accelerate to reach the goal of 10 new systemic drugs to treat infections caused by resistant bacteria by the year 2020 [9].

Of greatest concern is the near absence of drug candidates potentially active against GNB that produce metallo- β -lactamases, for example, IMP or VIM or NDM in Enterobacteriaceae, *P. aeruginosa*, and *A. baumannii*. In addition, the latter organism often possesses concomitant resistant mechanisms that result in resistance to virtually all other antimicrobial classes except the polymyxins, glycolcyclines (eg, tigecycline), and fosfomicin.

The number of novel compounds in development admittedly does not tell the whole story. Although truly novel compounds with a new mechanism of action provide substantive advances in treatment of infections compared with already available

antibiotics, incremental improvements in existing classes can be very valuable and should not be dismissed [59].

In 2013, antibacterial drug development largely lies in the hands of small pharmaceutical or biotechnology companies, as well as some larger companies in Japan [60]. Our investigation found only 4 large multinational pharmaceutical companies engaged in antibacterial discovery. The “brain drain” that accompanies the loss of large pharmaceutical research organizations will surely be felt for years to come.

SIGNS OF HOPE

Recent focus on the problem of antimicrobial resistance from the World Health Organization, the US Congress, and the US FDA, NIH, and CDC support the idea that leaders in government now recognize the urgency of the current situation [5]. FDA leadership has publicly acknowledged the crisis [61, 62]. The FDA has invested in antibiotic-focused collaborations with the Brookings Institution, the Clinical Trials Transformation Initiative, and the Biomarkers Consortium of the Foundation for the NIH, which is assessing novel endpoints for antibacterial registrational trials in 3 clinical indications [63]. In addition, the European Commission initiated a landmark public-private collaboration. The pharmaceutical industry’s Innovative Medicines Initiative has initial funding of €223.7 million and is aimed at the dual problem of antibiotic resistance and speeding the delivery of new antibiotics to patients [64]. Moreover, in June 2012, the US Congress enacted new incentives intended to advance antibiotic development.

IDSA’S ROLE

IDSA continues to support initiatives that create an R&D infrastructure that responds to current antimicrobial resistance and anticipates evolving resistance. Numerous professional and philanthropic societies have supported our efforts. Recent government actions are encouraging, and IDSA will continue to work with our partners to press for additional measures to ensure a sustainable antibacterial R&D infrastructure is in place [10].

Concomitantly, IDSA is committed to strengthened antibiotic public health and stewardship programs so as to preserve the current inventory of effective drugs. Optimizing use of currently available antibacterial drugs, via improved resistance data collection, surveillance, prevention, and control measures, including antimicrobial stewardship efforts, remains vital to combating bacterial resistance [9, 59, 65, 66].

REGULATORY GUIDANCE

IDSA will continue to support action on the regulatory front. The need for clear regulatory guidance remains greatest in studies

of drugs for life-threatening infections and those caused by resistant GNB. Although the FDA has made progress recently, more is needed, especially for CABP and HAPB/VABP [62, 66–71]. IDSA also supports the urgent approval of FDA guidance on pathogen-specific clinical trials, which will help development of new antimicrobial drugs that target infections caused by drug-resistant pathogens. Creation of a new FDA approval pathway for limited-population antibacterial drugs would permit antibiotic approvals based on smaller clinical trials of the most serious bacterial infections, where insufficient therapeutic options exist [72]. Harmonization of FDA guidance and European Medicines Agency guidance is another critical need [73].

APPROPRIATE FINANCIAL INCENTIVES

Securing a solution will require ongoing investment by pharmaceutical sponsors. Both Big Pharma and smaller biotechnology companies require mitigation of the current disincentives to antibacterial R&D, as well as new incentives to make developing antibiotics a viable financial option. Notably, Congress' recent passage of the FDA Safety and Innovation Act legislated an additional 5 years of exclusivity for antibacterial and antifungal drugs that treat serious and life-threatening infections.

IDSA also supports the adoption of “push” incentives that can facilitate investment in early-stage development, such as R&D tax credits and grants and contracts, as well as consideration of new reimbursement models [10, 72].

IDSA also enthusiastically favors increasing support for new and existing public–private partnerships that provide a supplemental means of support for antibacterial research and development [10]. Recent examples of successful partnerships include awards from the Biomedical Advanced Research and Development Authority at the Department of Health and Human Services for up to \$94 million in US government funding to support development of GSK 052 in 2011 and up to \$67 million for development of TP-434 [74, 75]. Advancing a sustainable solution also will require significantly increased commitments by the National Institute of Allergy and Infectious Diseases and the Department of Defense.

CONCLUSIONS

Our survey results demonstrate some tangible progress in the clinical development of new antibacterial drugs that target infections caused by drug-resistant GNB. However, progress remains alarmingly slow. The prognosis for sustainable R&D infrastructure depends upon clarification of FDA regulatory clinical trial guidance, and fair and appropriate economic incentives for small and large pharmaceutical companies.

In the meantime, the preservation of the miracle of antibacterials will not be possible without a determined focus on protecting our currently available antibacterial drugs via strong antibiotic stewardship and infection prevention.

Notes

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