

# The Intersection of Antimicrobial Stewardship, the Pharmaceutical Industry, and the Federal Legislature

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To mitigate the dangers of inappropriate antimicrobial use leading to increased multidrug-resistant organisms and mortality, antimicrobial stewardship programs have become a mainstay in many health systems. Unfortunately, some pharmaceutical manufacturers simultaneously have ended antimicrobial research and development efforts altogether due to suboptimal return on investments. An optimal and sustainable antimicrobial armamentarium requires a broad alliance between antimicrobial stewardship programs, the pharmaceutical industry, the legislature, and federal and state agencies. Public-private relationships such as the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) and legislative policies creating push and pull incentives, including the Generating Antibiotic Incentives Now (GAIN), Developing an Innovative Strategy for Antimicrobial-Resistant Microorganisms (DISARM), and Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Acts, are each a step in the right direction, but more work remains. Understanding these legislative actions is imperative for all clinicians, as is teamwork from those involved in the antimicrobial field to develop and maintain the life cycle of each drug that harbors societal value.

**Keywords.** antimicrobial stewardship; legislature; pharmaceutical industry.

The advent of antimicrobials changed the healthcare landscape by transforming previously considered deadly infections into mere inconveniences, but their use is not without risk of resistance developing. As of 2019, antimicrobial resistance (AMR) was attributed to 1.27 million deaths globally, which is expected to increase to 10 million by 2050 if no action is taken [1–3]. Today, more than half of all patients admitted to a hospital in the United States (US) receive at least 1 dose of an antibiotic, but even a 1-time administration of a broad-spectrum antibiotic puts patients at risk of either severe adverse drug reactions such as *Clostridioides difficile* infections or the development of AMR [4–7].

As such, the concept of antimicrobial stewardship (AS) emerged over the past 45 years, with antibiotic restriction to prevent the development of AMR being reported in the literature as early as 1975 [8]. Cost-containment was also an early

AS objective, and over time the focus morphed into the facilitation of optimized patient care through practices such as preauthorization and prospective audit and feedback, days of therapy reporting, and more all supported by regulatory and accreditation bodies, including the Centers for Disease Control and Prevention (CDC), the Joint Commission, and the Centers for Medicare and Medicaid Services (CMS) [9–13].

New drug uptake is often slow, resulting in the avoidance of the most appropriate antimicrobials when truly needed. For example, the median time to first administration of qualified infectious diseases products (QIDPs), which are specific antibiotic or antifungal agents used for serious or life-threatening infections caused by qualifying pathogens, was 398 days from the date of US Food and Drug Administration (FDA) approval in a nationwide survey of 132 hospitals [14, 15]. The decreased utilization may also be associated with an insufficient return on investment (ROI) for the pharmaceutical industry, prompting several major manufacturers to leave the antimicrobial space altogether [16]. Numerous contributing factors are certainly at play, but the vicious cycle discouraging the pursuit of expanding and maintaining the antimicrobial lifecycle results in a lack of innovative therapies, leaving clinicians without apparent means of providing life-saving antibiotics for resistant infections [17, 18]. This is ironic: AS programs desperately need new antimicrobial approvals but may also be asked to focus on process and fiscal metrics of the pharmacy department as opposed to clinical outcomes [17, 18].

Already well-aware of the growing AMR crisis in 2010, the Infectious Diseases Society of America (IDSA) announced

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the 10 × '20 initiative that same year to encourage a global initiative of incentives, remove barriers, and introduce more novel antimicrobials by 2020 [19]. Increased collaboration on behalf of both clinicians and the industry to create a truly synergistic relationship has since occurred and resulted in the FDA approval of 17 new antibiotics and 1 biologic since the call to action in 2010 [20]. Additional partnership modalities have been previously suggested by industry stakeholders and are likely to benefit all involved [21, 22].

Overall, strides have been made since the 10 × '20 initiative regarding both antimicrobial development and organized support, but it has not been enough to ensure active antimicrobials are available for each and every patient [23]. A third party, the legislative branch of the federal government, has also taken action to aid the cause and incentivize the work to come. Evaluating the current and proposed legal states of antimicrobial costs and reimbursement in the US is therefore required for all infectious diseases clinicians to develop a more thorough understanding of the future antimicrobial pipeline.

### CURRENT ECONOMIC STATE OF ANTIMICROBIAL COSTS AND REIMBURSEMENT

To reduce the price required to bring a new antimicrobial to market while promoting their continued research and development (R&D), incentives have been put in place to spur pharmaceutical manufacturers (Table 1). Push incentives decrease the overall cost of R&D and offer grants or tax credits early in the process [24]. Examples include public-private relationships between the FDA, academia, and the pharmaceutical industry to study early-stage molecules and assist with investigational new drug submissions. The National Institute of Allergy and Infectious Diseases (NIAID), the Antibacterial Resistance

Leadership Group, the Biomedical Advanced Research and Development Authority (BARDA), and the Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X) are just a few examples of organizations that serve in this function.

Additional push incentives include expedited drug approval and manufacturer tax credits. The Generating Antibiotic Incentives Now (GAIN) Act, signed into law as part of the FDA Safety and Innovation Act in 2012, is an example [14, 24]. The act created the aforementioned special category of novel antimicrobials called QIDPs, which are eligible for fast-track designation. This means approval is possible with data from phase 2 trials and priority review to decrease the time to approval from 10 to 6 months [14]. QIDPs now available for commercial use include dalbavancin, ceftazidime-avibactam, ceftolozane-tazobactam, meropenem-vaborbactam, imipenem-relebactam, isavuconazole, and delafloxacin, to name a few. Qualifying pathogens are resistant gram-positive organisms such as methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus* spp, gram-negatives including *Acinetobacter* spp and *Pseudomonas aeruginosa*, and others like multidrug-resistant tuberculosis [14].

Pull incentives support novel antimicrobials in later-stage trials and post-FDA approval. These assist pharmaceutical manufacturers in achieving an adequate ROI by offering market-entry bonuses, advanced reimbursement models, and tax benefits upon approval [23]. The GAIN Act is not only a push example but also a pull incentive. With 5 additional years of market exclusivity on top of previously awarded time, the GAIN Act enables manufacturers to market their products without generic competition for a longer duration [14]. Depending on the drug, this could allow for a varied market exclusivity period, ranging anywhere from 8 years (ie, 3 years for a new indication for a previously approved drug plus 5 years for a QIDP designation) to 12 years (ie, 7 years for a rare-disease drug plus 5 years for a QIDP designation), and 6 months more if the manufacturer pursues a companion diagnostic test used to aid in the identification of a qualifying pathogen (Table 2) [14].

The additional time on the market without a generic version taking a portion of the market share is supposed to equate to a more significant ROI for the manufacturer. Unfortunately, the GAIN Act may not be as beneficial as initially assumed. The Act was pushed from the legislative to the executive branch rather quickly: it took <2 months for the bill to be introduced in the House of Representatives and then signed into law. Given the haste in which it was passed, a closer economic evaluation may have been beneficial. For example, Darrow et al argue that the additional 5-year exclusivity period given to all QIDP drugs discourages rather than inspires true innovation. Instead of a prolonged total exclusivity period of 10 or 12 years, the shortest one could be the most financially beneficial due to

**Table 1. Research and Development Incentives for Pharmaceutical Manufacturers**

<i>Push Incentives:</i> Used to decrease the overall cost of R&D and offer grants and tax credits early in the development process	<i>Pull Incentives:</i> Used to support novel antibiotics in later-stage trials and post-FDA approval
<ol style="list-style-type: none"> <li>Public-private relationships between the FDA, academia, and the pharmaceutical industry, such as the NIAID, ARLG, BARDA, CARB-X, and more</li> <li>Generating Antibiotic Incentives Now (GAIN) Act of 2012</li> </ol>	<ol style="list-style-type: none"> <li>Generating Antibiotic Incentives Now (GAIN) Act of 2012</li> <li>21st Century Cures Act of 2016</li> <li>New technology add-on payments</li> <li>Developing an Innovative Strategy for Antimicrobial-Resistant Microorganisms (DISARM) Act<sup>a</sup></li> <li>Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act<sup>a</sup></li> </ol>

Source: [14].

Abbreviations: ARLG, Antibacterial Resistance Leadership Group; BARDA, Biomedical Advanced Research and Development Authority; CARB-X, Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator; NIAID, National Institute of Allergy and Infectious Diseases; R&D, research and development.

<sup>a</sup>Not yet signed into law.

**Table 2. Market Exclusivity Awarded by the Generating Antibiotic Incentives Now (GAIN) Act**

Characteristic	Previously Awarded Exclusivity Period (Years)	New Exclusivity Period With the GAIN Act
Previously approved drug with a new indication	3	8 y
New active ingredient	4–5	9–10 y
Rare-disease (orphan) drug	7	12 y
Companion diagnostic test	Not applicable	6 additional months <sup>a</sup>

Abbreviation: GAIN, Generating Antibiotic Incentives Now.

<sup>a</sup>Companion diagnostic tests are those that aid in the diagnosis of a qualifying pathogen and act hand in hand with the qualified infectious disease product to give 6 additional months beyond the new exclusivity period.

the reduced net present value of expected revenue streams over time [25]. Manufacturers may be more incentivized as a result to take a more manageable and cheaper route to pursue a new indication for a previously approved drug instead of developing an entirely new molecule for a rare disease. Other concerns related to the current iteration of the GAIN Act include very few drugs approved with a novel mechanism of action; the use of noninferiority studies, leading to the belief that less costly and existing antimicrobials are just as effective if not overall better than QIDPs; and the lack of inclusion in the QIDP definition of antivirals, vaccines, and antiparasitics, among other antimicrobial-related drugs [25].

The 21st Century Cures Act of 2016 established the limited population pathway for antibiotic and antifungal drugs (LPAD), allowed for smaller antimicrobial clinical trials, and prompted CMS to create a new technology add-on payment (NTAP) program to provide increased reimbursement for the latest drugs and technology used [26, 27]. Drugs approved using the LPAD pathway are antibiotics or antifungals that treat a serious or life-threatening infection in a specific population with unmet needs [28]. The basis of these approvals is that the drug has only been shown to be safe and effective in a limited population, and as such, the drug labeling defines the particular patient group [28]. LPADs thus far approved are amikacin liposome inhalation suspension for *Mycobacterium avium* complex infection and pretomanid for pulmonary tuberculosis, 2 deadly and difficult-to-treat infections. NTAPs incentivize the utilization of QIDPs in hospitals and enable a higher severity level for diagnosis-related groups (DRGs) to be used with documented antibiotic resistance [27]. The goal is to encourage AS programs to use more innovative and typically expensive antimicrobials (ie, QIDPs) because reimbursement will be increased for hospitals caring for these patients.

Critics of the law could state that antibiotics may become commercially available with comparatively lower quality and potentially smaller powered studies. While this might

be true, there are many pros and cons to this risk-to-benefit argument. Some include the access to an antibiotic as quickly as possible for a life-threatening infection or waiting until it has been extensively studied in slow-enrolling and difficult-to-blind phase 3 studies. A large concern related to NTAPs is the laborious administrative effort required to request the associated payments. When reimbursement is received, a credit may not be attributed to the pharmacy budget, further disincentivizing the needed time and effort [29, 30]. The limitation related to the paperwork may not be worth the reimbursement return for antimicrobials, whereas it could be for much more expensive oncology therapeutics or diagnostic tools.

### PROPOSED ECONOMIC STATE OF ANTIMICROBIAL COSTS AND REIMBURSEMENT

Additional push and pull incentives will be necessary to guarantee a synergistic relationship between AS programs and the pharmaceutical industry [21, 22]. One such program is the Developing an Innovative Strategy for Antimicrobial-Resistant Microorganisms (DISARM) Act, first introduced in the US House of Representatives in 2019 [31]. While not yet signed into law, the Act calls for higher non-DRG reimbursement payments for QIDP drugs approved on or after 1 December 2014 if indicated for infections with high morbidity and mortality rates [24]. To qualify for the payments, which are supposed to plug gaps in the NTAP program, hospitals must meet specific criteria, including establishing an AS program that reports data to the CDC National Healthcare Safety Network (NHSN) Antimicrobial Use and Resistance (AUR) module or a similar surveillance system [31]. The FDA, National Institutes of Health, and CDC would perform specific functions under the DISARM Act. To further break down barriers related to antimicrobial R&D, these agencies will be asked to study and provide recommendations to other stakeholders [24, 31]. Finally, a study assessing the utilization and consequent resistance development would be performed by the CDC and reported out for future optimization [24]. Critics of the Act may, however, state that AS programs must be prepared to ensure that blatant overuse of the QIDPs does not occur to increase hospital reimbursement.

In addition to the DISARM Act, there is momentum for a model that delinks antimicrobial reimbursement from sales volumes. By finding ways to disconnect sales with ROI, pharmaceutical companies may discourage the use of products for unnecessary indications, AS programs might restrict the drugs less forcefully, and private and public organizations could partner more effectively to ensure global patient access to the drugs. Rex et al suggested that a pull incentive like this could allow companies to be paid for their antimicrobials based on societal value and a milestone progression, such as a new drug application (NDA) submission, FDA approval, and the

**Table 3. Similarities and Differences of the Possible Manufacturer Requirements Related to Transitional Subscription and Subscription Contracts Through the Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act**

Requirement	Transitional Subscription Contract	Subscription Contract
Drug access	No related requirement	Produce the drug at a reasonable volume determined with the Secretary of Health to ensure patient access to the drug
	No related requirement	Price the drug so it is not lower than a comparable generic drug
	Ensure commercial and federal availability in the US of the antimicrobial drug within 30 d of receiving first payment under the contract	Ensure commercial and federal availability in the US of the antimicrobial drug within 30 d of receiving first payment under the contract, and sufficient supply for susceptibility device manufacturers
	Ensure a reliable drug supply chain, where any interruptions to the supply chain will not last for more than 60 d in the US	
	Submit a plan for registering the antimicrobial drug in additional countries where an unmet medical need exists	
Antimicrobial drug resistance data	Identify, track, and publicly report drug resistance data and trends using available data related to the antimicrobial drug	
Widespread education	Develop and implement education and communications strategies, including communications for individuals with limited English proficiency and individuals with disabilities, for healthcare professionals and patients about appropriate use of the antimicrobial drug	
Postmarketing studies and utilization	Make meaningful progress toward completion of the FDA-required postmarketing studies, including such studies that are evidence based	Complete any postmarketing studies required by the FDA in a timely manner
	No related requirement	Submit an appropriate use assessment to the Secretary of Health, expert committee, FDA, and CDC every 2 years regarding use of the antimicrobial drug, including how the drug is being marketed
Manufacturing practices	No related requirement	Abide by the manufacturing and environmental best practices in the supply chain to ensure that there is no discharge into, or contamination of, the environment by antimicrobial agents or products as a result of the manufacturing process

Source: [34].

Abbreviations: CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration; US, United States.

number of years post-FDA approval [32]. Of course, determining the societal value of an antimicrobial is a daunting task. Some characteristics driving increased value may include incremental improvements in health outcomes [33]. Others could include pharmacology-specific novelties like an original mechanism of action, first-in-class drug target, an indication against multidrug-resistant organisms, or perhaps significant cost-savings opportunities like a previously unavailable oral antibiotic option or an intravenous formulation that is administered once weekly rather than daily [33]. Manufacturers of me-too drugs, or copycats of previously approved drugs, would be paid slightly less comparatively [32]. Regardless, this proposed system must be careful not to provide the same reimbursement rate for all antibiotics. Otherwise, innovation could stall.

The Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (PASTEUR) Act of 2020 attempts to address this very problem. As stated in one of the opening lines of the bill, the goal is “to establish a program to develop antimicrobial innovations targeting the most challenging pathogens and most threatening infections” [34]. An expert committee with specific charges would be formed, consisting of representatives from the NIAID, CDC, BARDA, FDA, CMS, the Veterans Health Administration, and the Department of Defense [34]. To encourage R&D, the committee would be tasked with defining the aforementioned societal worth of antimicrobials and making a prioritized infection list based on pathogens and infections where an unmet need is present. A required update to the prioritized infection list would occur every 3 years to ensure informed decision-making [34].

Most notably, the bill would create a pay-up-front subscription model to access novel antimicrobials with 2 different contract methods available (see comparison in Table 3). The first would be known as a transitional subscription contract. Using this method, a contract lasting up to 3 years would be available starting 30 days after the bill is signed into law, and it would end once the next contract is finalized, known as a subscription contract. The transitional subscription contract payments intend to fund manufacturing, postmarketing clinical studies, and other preclinical or clinical efforts. Eligible drugs may include QIDPs or novel biological or immunomodulators and they must be appropriate for the treatment of infections listed in the CDC’s Antibiotic Resistance Threats in the United States report, most recently published in 2019 [34, 35].

The second contract opportunity, known as a subscription contract, applies to drugs given the “critical need antimicrobial” designation. Manufacturers can apply for this designation once an investigational new drug exemption is handed down or until 5 years post-FDA approval have passed. The designation is valid for 10 years, whether or not the infection treated by the critical need antimicrobial is taken off the CDC’s Antibiotic Resistance Threats in the United States report [34].

While the designation period is not negotiable, the subscription contract may last anywhere from 5 to 10 years or for any remaining patent protection or exclusivity period [34]. In terms of monetary value, lifetime payments determined in consultation with the expert committee range from 750 million to 3 billion US dollars (USD) and are to be adjusted for inflation [34]. To support the initiative, 11 billion USD is expected to be appropriated in the first year of its approval alone. Although valued at lower rates, subscription contracts are expected to be available for generic and biosimilar versions of critical need antimicrobials [34]. Contract values could be reevaluated every other year and extensions may be provided in very specific situations assuming new data are published, suggesting that changes are warranted. If desired by the manufacturer, up to 50% of the last contract year's reimbursement could be paid in the first contract year to help offset manufacturing costs. However, in the event a manufacturer receives both a transitional subscription contract and a subscription contract for the same critical need antimicrobial, the amount of the transitional subscription contract is to be subtracted from the subscription contract [34]. In the end, these funds are to be used to meet specific requirements of the Act, such as guaranteeing a sustainable supply chain, registration in other countries, and completing FDA-required postmarketing studies [34].

Although high cost, the PASTEUR Act heavily promotes a prosperous and healthy antibiotic industry. To avoid antibiotic overuse, safeguards are incorporated into the bill. These include diagnostic plans, regularly updated clinical guidelines or guidance documents, and biannual marketing and usage reports submitted to the expert committee, FDA, and CDC [34]. Of note, the recently published IDSA Guidance on the Treatment of Antimicrobial-Resistant Gram-Negative Infections versions 1.0 and 2.0 are present-day examples of documents that could meet the qualifications of regularly updated clinical guidelines [36, 37]. Establishment of AS programs with assistance from academic medical centers and participation in the NHSN AUR module are to be 2 key efforts performed by hospitals [34]. AUR data would become publicly available as a result as well. Grant funding of 500 million USD would even be available to support AS programs at critical access hospitals, tribal facilities, and safety-net hospitals [34].

The numerous legislative advances and aspirations undoubtedly have either improved or have the potential to improve the economic state of antimicrobial costs and reimbursement. However, there is still work to be done. Supporting a positive, synergistic relationship between AS programs, drug manufacturers, governmental authorities, and the public is critical. The most likely avenues to success combine push and pull incentives, creating win/win/win scenarios for all parties involved with the GAIN, DISARM, and PASTEUR acts. However, in evaluating the current and proposed future states of antimicrobial costs and reimbursement, no one stakeholder can stop the

spread of AMR. Instead, both infectious diseases and antimicrobial stewardship clinicians and those in the pharmaceutical industry are encouraged to stay knowledgeable of the legislative climate in which they practice because global collaboration is required to support all stakeholders while maintaining the antimicrobial armamentarium.

## Note

**Potential conflicts of interest.** The authors: No reported conflicts of interest.

Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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