Statement of the Infectious Diseases Society of America (IDSA)

Promoting Anti-Infective Development and Antimicrobial Stewardship through the U.S. Food and Drug Administration Prescription Drug User Fee Act (PDUFA) Reauthorization

Before the House Committee on Energy and Commerce’s Subcommittee on Health

March 8, 2012
The Infectious Diseases Society of America (IDSA) appreciates this opportunity to submit testimony for the record in support of the House Energy and Commerce Committee Health Subcommittee’s efforts to enact strong incentives to spur new anti-infective research and development (R&D) and promote antimicrobial stewardship (i.e., the appropriate use of these critically important drugs) as part of the U.S. Food and Drug Administration (FDA) Prescription Drug User Fee Act (PDUFA) reauthorization legislation. This is an opportunity that we cannot afford to miss. IDSA thanks the Subcommittee Chairman and Ranking Member for including a focus on antibiotics in today’s hearing and for including IDSA’s statement in the hearing record. The Society also commends Representatives Gingrey and Green, and all of the bipartisan cosponsors of the Generating Antibiotic Incentives Now (GAIN) Act for their leadership in beginning to craft solutions to the complex and most urgent problems of antimicrobial resistance and the dry antibiotic R&D pipeline.

IDSA represents nearly 10,000 infectious diseases physicians and scientists devoted to patient care, prevention, public health, education, and research in the area of infectious diseases. Our members care for patients of all ages with serious infections. Of relevance to today’s hearing, our members also care for an increasing number of patients with serious and life-threatening antimicrobial-resistant infections—infected against which we have frighteningly few effective therapeutics available. To call attention to this growing public health crisis, IDSA issued a landmark report in 2004 to launch our Bad Bugs, No Drugs advocacy campaign. To broaden the scope of this critical effort to include other countries and to provide a measurable goal for progress and success, in 2010, IDSA launched “The 10 x ’20 Initiative,” which calls for a global commitment to develop 10 new systemic antibiotics by the year 2020. In January 2012, a group of 50 organizations representing patients, health care providers, health systems, veterans, women’s health, children’s health, seniors, and other key stakeholders wrote to House and Senate leaders in support of The 10 x ’20 Initiative and urged Congress to address the serious and growing problems of antimicrobial resistance and the dry antibiotic R&D pipeline as part of PDUFA. A copy of their letter is attached for the hearing record.

IDSA’s statement today will briefly summarize the synergistic crises of rising rates of antibiotic resistance and waning approvals of new antibiotics. IDSA’s goal is to represent the best interests of patients and health care professionals by recommending, within the context of the GAIN Act and PDUFA, public policy strategies to reverse antibiotics’ decline and save lives. To this end, in addition to focusing on ways to reduce the economic disincentives that have persisted leading to a market failure in antibiotic R&D, IDSA today also is raising for the Subcommittee’s consideration a new FDA approval mechanism, tentatively called “Special Population Limited Medical Use (SPLMU) Drugs” (see page 5) which we believe could be a potential game changer for the most urgently needed anti-infective products. After reviewing IDSA’s statement,
should you be interested in learning more about the problem of antimicrobial resistance as well as additional solutions, please review IDSA’s recent policy paper titled “Combating Antimicrobial Resistance: Policy Recommendations to Save Lives,” and other important resources, available on The 10 x ’20 Initiative website at: http://www.idsociety.org/10x20.


In 2000, Nobel Laureate Dr. Joshua Lederberg wrote in the journal Science that “the future of humanity and microbes will likely evolve as episodes … of our wits versus their genes.” In only 12 years since Dr. Lederberg wrote these prescient words, the world has witnessed an enormous expansion of infections resistant to antibacterial agents (“antibiotics”). For example, antibiotic-resistant Gram-negative bacteria (GNB) have spread widely through U.S. and global health care systems. Increasingly they have become resistant to all antibiotics available for treatment—i.e., pan-drug resistant (PDR). A wide array of patients are particularly vulnerable to GNB infections, including individuals recovering from surgery or trauma, cystic fibrosis patients, burn victims, cancer patients undergoing chemotherapy, and transplant recipients. These dangerous and often deadly bacteria can infect the skin, brain, bones, joints, and urinary tract and may cause abdominal infections, pneumonia, meningitis, and bacteremia. Examples of PDR GNB organisms include Acinetobacter baumannii (which is threatening soldiers returning from Afghanistan as well as patients throughout the U.S. and the world), carbapenemase-producing Klebsiella pneumoniae, and Pseudomonas aeruginosa. Such infections kill an astonishingly high percentage of infected patients (e.g., greater than 50%-60% of patients with infection in the blood, greater than 40%-50% of patients with lung infection, etc.) despite any available treatment. Furthermore, extended-spectrum beta lactamase (ESBL)-producing Enterobacteriaceae (e.g., Escherichia coli [E. coli] and Enterobacter spp.), which often are resistant to all orally administered antibiotics, have spread through health care systems and more recently into communities. Such infections make it impossible to treat common urinary tract or abdominal infections with antibiotic pills, requiring hospitalization for intravenous antibiotic therapy. Most recently, a new antibiotic resistance mechanism (New Delhi metallo-β-lactamase 1 or NDM-1) emerged in India and spread to communities in the United States, United Kingdom, and elsewhere. NDM-1, E. coli, and several other GNB strains are resistant to all antibiotics except perhaps tigecycline or colistin, and increasingly to these drugs as well.

In October 2011, 562 infectious diseases physicians who are members of IDSA’s Emerging Infections Network (EIN) responded to a survey about antibacterial-resistant infections. More than half (63%) of respondents reported caring for a patient with an infection resistant to all available antibacterial drugs in the prior year. 64% of respondents reported using colistin during the past year to treat a patient suffering from these infections. Colistin is an antibiotic that was discovered in the 1940s, but was found to be highly toxic having great potential to cause kidney and other organ damage. For this reason, colistin’s use was all but abandoned in the 1950s—until, in the wake of the growing tide of antimicrobial resistance over the last decade, it has become the drug of last resort despite the fact that it has well-known toxicity, its effectiveness has been questioned, and resistance to the drug has increased. With so few therapeutic options, physicians are grasping at straws.
Collectively, highly problematic antibiotic-resistant organisms are summarized by the ESKAPE mnemonic: *Enterococcus, Staphylococcus, Klebsiella, Acinetobacter, Pseudomonas*, and *ESBL (Enterobacter and E. coli)*. ESKAPE indicates that these bacteria have developed defenses that permit them to escape the actions of available, effective therapies. The ESKAPE pathogens are currently the most important causes of the antibiotic resistance crisis in the U.S. and other developed countries. Such pathogens also are spreading through developing countries, which already are experiencing significant public health problems from extreme drug-resistant (XDR) or PDR *Mycobacterium tuberculosis* (TB). Collectively, disease caused by the ESKAPE pathogens, TB, and other highly problematic antibiotic-resistant bacterial pathogens, including hypervirulent and fluoroquinolone-resistant *Clostridium difficile*, and multi-drug resistant (MDR) *Streptococcus pneumoniae* and *Neisseria gonorrhoeae*, result in enormous morbidity, mortality, and health care expense in the U.S. and throughout the world.

According to the U.S. Centers for Disease Control and Prevention (CDC), in 2006, just one organism alone, methicillin-resistant *Staphylococcus aureus* (MRSA), killed more Americans (~19,000) than emphysema, HIV/AIDS, Parkinson’s disease, and homicide combined. Almost 2 million Americans per year develop hospital-acquired infections (HAIs), resulting in 99,000 deaths, the vast majority of which are due to antibiotic-resistant pathogens. Indeed, two common HAIs alone (sepsis and pneumonia) killed nearly 50,000 Americans and cost the U.S. health care system more than $8 billion in 2006. In a recent survey, approximately half of patients in more than 1,000 intensive care units in 75 countries suffered from an infection, and these infected patients had twice the risk of dying in the hospital as uninfected patients. Based on studies of the costs of infections caused by antibiotic-resistant pathogens versus antibiotic-susceptible pathogens, the annual costs to the U.S. health care system and society of antibiotic-resistant infections is $21 billion and $34 billion, respectively, and more than 8 million additional hospital days. Antimicrobial resistance was recently recognized as one of the greatest threats to human health on the planet. For that reason, the World Health Organization (WHO) proclaimed antimicrobial resistance the focus of World Health Day (April 7) 2011.

*Clostridium difficile* (C. diff), the top cause of infectious diarrhea in hospitals, is a bacterium that has become increasingly common in health care facilities across the U.S. Though C. diff is frighteningly common in hospitals, 75% of C. diff infections now start in places such as nursing homes or doctor’s offices. C. diff is increasingly resistant to antibiotics, and an epidemic strain is highly resistant to a very common class of antibiotics known as fluoroquinolones. Inappropriate antibiotic use is significantly contributing to this growing problem. A recent study found that C. diff will lengthen a hospital stay by an average of 6 days for infected patients. Not only is this drug-resistant infection placing a serious burden on our health care system, it also is costing patients their lives. C. diff infections kill 14,000 Americans each year, and deaths caused by this pathogen increased 400% between 2000 and 2007.

Finally, the problem of antimicrobial resistance is not specific to bacteria—medically important fungi (e.g., *Candida spp.*), viruses (e.g., HIV, influenza), and parasites (e.g., malaria) also develop antimicrobial resistance.
II. The Dry Antibiotic Pipeline

Ironically, as the number of patients succumbing to antibiotic-resistant infections rises, the number of new antibiotics in development is plummeting. Since IDSA’s 2009 report on the status of the antibacterial R&D pipeline\(^1\), only two new antibiotics have been approved in the U.S. and the number of new antibiotics approved annually continues to decline. A 2011 study found nine intravenous compounds active against resistant GNB in clinical development (phase II or phase III studies). Only two of these compounds demonstrated a novel mechanism of action, and none of the candidate drugs was active against all pan-resistant GNB. These findings continue to underscore the need for antibiotic incentives and a feasible approval pathway to advance desperately needed new antibiotics. Moreover, in 1990, there were nearly 20 pharmaceutical companies with large antibiotic R&D programs. Today, few remain. Not only does the tumbling private investment in antibiotics R&D jeopardize the development and availability of sorely needed new antibiotics in the United States, it also drains indispensable jobs and intellectual capital as companies seek to do business in countries with more favorable economic and regulatory climates.

Antibiotic R&D poses unique scientific, regulatory, and economic challenges, which often makes antibiotic R&D riskier than R&D for other types of drugs. One company reports that over a 10-year period, it took 72 lead candidate antibiotic compounds in the early discovery phase to yield one FDA-approved product; other drug types only took 15 leads to yield an FDA approval. Antibiotics also provide less financial reward for companies as they are used for a short duration (i.e., often 7 to 14 days), typically are priced low, and are encouraged to be held in reserve to protect against the development of drug resistance, rather than used widely as most other drugs are once approved.

Antibiotics play a unique role in medicine and are extremely valuable to society. The appropriate use of these drugs, when they are available, helps stop the spread of serious and often deadly bacterial infections from one person to another. If the antibiotic crisis is not addressed soon, we face a future that resembles the days before these miracle drugs were developed, one in which people died of common infections, and where many medical interventions that we take for granted—including care for premature infants, surgery, chemotherapy, organ transplantation, and even dentistry for some patients (like those with hip replacements, etc.)—become impossible.

Strengthened investment in new antimicrobial agents also is essential for U.S. national security. An October 2011 Bio-Response Report Card issued by the Bipartisan WMD Terrorism Research Center—chaired by former Senators Bob Graham and Jim Talent—concluded that a terrorist armed with an antibiotic-resistant pathogen could produce a large-scale event with “catastrophic consequences,” resulting in a “potentially uncontrollable number of illnesses and/or deaths,” “civil and political unrest in the affected region,” and a “global economic impact.”

If Congress fails to incentivize antibiotic R&D, this crisis will deepen, more lives will be lost, and more health care dollars will be needlessly spent.

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III. New Antimicrobials: Providing Regulatory Pathways to Approval

During a recent policy meeting, representatives from the few pharmaceutical companies still investing in antibiotic R&D said they plan to focus their future efforts on European, Asian, and Latin American markets and not on the United States. The primary reason for this shift: the regulatory environment. For more than a decade, FDA’s antibacterial human drug review process has been fraught with uncertainty that has shaken the foundation of the nation’s antibacterial pharmaceutical industry. FDA has failed to fully appreciate, prioritize, and address the unique challenges facing antibiotic development, and the lack of a clear antibiotic approval pathway, coupled with economic disincentives, has brought antibiotic development to its knees. Companies need consistency, feasibility, predictability, and timeliness in order to make investment decisions. FDA has made it difficult, if not impossible, for companies to plan new investments in the antibiotics area first by throwing out existing rules without having new guidelines available to replace them and more recently by proposing new requirements that have been deemed infeasible both by industry and by independent infectious diseases physician experts. While FDA must periodically update the rules for approving new drugs to keep pace with the advancing science, they also must provide an approval pathway that works.

FDA has an essential role to play in ensuring that Americans have access to safe and effective drugs. But, in so doing, the agency must ensure that the risks associated with approving new products are appropriately balanced against the products’ benefits to patients and to society. To date, when it comes to antibiotics, and particularly antibiotics needed to treat the most serious bacterial infections, FDA’s risk benefit equation has been out of balance. The urgent need for new anti-infective therapies to treat patients with serious or life-threatening infections who lack satisfactory therapeutic options, usually because of resistance to available therapies, requires new thinking and action.

**Special Population Limited Medical Use Approval Mechanism**

To begin to address the most urgent needs in anti-infective R&D, IDSA is proposing, for the Subcommittee’s consideration and as a critical addition to the GAIN Act, a new FDA approval mechanism, tentatively called “Special Population Limited Medical Use (SPLMU) Drugs.” The mechanism would provide an important new approval pathway option for companies interested in and able to develop drugs to treat patients with the most serious infections where few or no therapeutic options exist. Using the mechanism, a drug sponsor would seek a designation for and the FDA would approve the designation of eligible SPLMU drugs. The drug’s safety and effectiveness would be studied in substantially smaller, more rapid, and less expensive clinical trials than traditionally required. In return, the drug would be narrowly indicated for use in a small, specific population of patients for whom the benefits of the drug have been shown to outweigh the risks. The designation, a description of the population in which the drug is indicated, the rationale for limiting use to that population, and a logo signifying the designation would appear in the drug’s label and labeling. The SPLMU mechanism would effectively limit marketing of the anti-infective to the population in which a positive benefit-risk ratio has been established and, importantly, it would foster prudent use of anti-infective drugs to slow the rate at which resistance to the drugs develops.
The fundamental purpose of the SPLMU drug development program is to enable drug development targeting serious infections that lack available, satisfactory therapeutic options—very much like the Orphan Drug Program, under which these products do not fit, according to FDA officials. IDSA believes this new mechanism could bring critically needed innovation to the anti-infective pipelines and help focus development on areas of particular unmet medical need. Furthermore, the concept likely will have potential benefits for other serious diseases and conditions as well (e.g., obesity). IDSA is aware of at least seven companies with urgently needed antibiotics in their portfolios; establishment of this new drug pathway could immediately help these companies bring new antibiotics to the ever-increasing number of patients who desperately need them. **IDSA has discussed the SPLMU Drug mechanism with leaders at FDA and in industry, and there seems to be strong interest in exploring the concept’s merits.** In fact, one company has indicated to IDSA a strong interest in pursuing the SPLMU mechanism for their urgently needed antibiotic, if the pathway can be established quickly enough to accommodate their development cycle. **We encourage Subcommittee members and staff to explore the concept with Dr. Janet Woodcock, director of FDA’s Center for Drug Evaluation and Research, and individual companies for their assessment, during and following today’s Subcommittee hearing.**

What is the problem the SPLMU mechanism is intended to address and how will it work? Many diseases, such as those caused by bacterial, viral, and fungal infections, have a broad spectrum of severity. The SPLMU mechanism is intended to address the needs of a special population of patients with serious manifestations of such diseases who lack satisfactory treatments. In caring for such severely ill patients with limited treatment options, health care providers, regulators, and society can tolerate a greater degree of uncertainty about overall risk associated with a drug than can be tolerated in patients with milder manifestations of the disease, or those who have more satisfactory therapeutic options. Using the SPLMU mechanism, FDA will have an important role to play in ensuring that the appropriate conditions of use are described in a drug’s labeling, but will not have a role in authorizing or prohibiting use of approved products within the practice of medicine. Instead, through the use of this new high profile designation, logo, and labeling, FDA will be providing notice to the health care community, including health care facilities, practitioners, and payors, as well as to patients, that these products carry less precise estimates of risk because of smaller pivotal clinical trials and, hence their use must be limited to the indicated population.

To further help assure the drugs are used appropriately and encourage use according to the labeled indication, the drug’s sponsor would submit a general post-market surveillance plan to FDA prior to the drug’s approval outlining how the sponsor plans to monitor drug utilization. The company also would submit all promotional materials related to the product during the preapproval period and, following approval, to FDA at least 30 days (or another timeframe determined by FDA to be appropriate) before dissemination of these materials.

We anticipate that a SPLMU designation that targets an extremely small segment of the population, will, like an Orphan Drug Act designation, markedly decrease costs of development and simultaneously increase the price of these critically-needed new drugs, making investment in their R&D more attractive to pharmaceutical companies. The same assumption of increased pricing will mean payors too will play a more active role ensuring the drugs are used as indicated
and that confirmatory follow-up tests (i.e., culturing specimens) are being conducted to validate a drug’s appropriate use. As a result, the development of drug resistance to the SPLMU antibiotic should occur more slowly.

**How will the SPRMU make it easier for companies to achieve approval for the critically needed new drugs addressing specific unmet medical need?**

Traditionally the FDA has required conduct of two, large, phase III non-inferiority clinical trials (in addition to numerous phase I and II trials) to support approval of a new antibiotic (as for other drugs). Such trials are very expensive (e.g., >$50 million-$100 million) and take a long time to complete. Thus, companies will only conduct such studies when the perceived potential market size of a new drug is very large, encompassing both susceptible and resistant bacteria causing common infections. It is not feasible for drugs that treat specific, highly resistant pathogens to be developed using clinical trials conducted at this scale.

The requirement for large-scale clinical trials to support approval is based on the need to provide a very clear understanding of the relative risks and benefits of a new drug to treat common illnesses. In particular, if there are already other therapeutic options available to treat a specific disease that has favorable risk-benefit ratios, the tolerance for safety risks is substantially lower for newly approved drugs to treat the same disease. Thus, drugs developed to treat these diseases generally go through a comprehensive evaluation of risks in the broad disease population likely to use the drug (e.g., to rule out a risk of a low frequency, serious adverse event that would not be acceptable in patients with such disease). These large trials add significant costs and often delay or discourage development, thus depriving those with serious manifestations of the disease and limited treatment options (a population in whom the benefit may justify increased uncertainty about the risk) of viable therapeutic options.

For serious diseases for which few if any acceptable treatments are available, the tolerability for risk is much higher. As an example, before the first HIV drug was approved, even highly toxic drugs were appropriately deemed approvable, because the infection itself caused nearly a 100% mortality rate. As more and more new anti-HIV drugs became approved, the death rate from HIV infection plummeted, and there was an increasingly safe group of antiretroviral drugs already on the market. As such, the tolerability for risk for each successively approved new agent became lower and lower, appropriately so.

Similar to the early years of HIV drug development, the risk-benefit ratio of approved SPLMU drugs will be quite different than for less serious diseases and/or diseases for which numerous available therapies exist. The SPLMU concept enables clinical development programs that are more limited than a traditional development program that would result in use of the drug in a broad population suffering from less serious infections. Also likely to be of great interest to companies, we anticipate, based on our discussions with FDA leaders, that this mechanism could be used to facilitate development of an antibacterial to treat serious infectious diseases due to the same resistant pathogen at multiple disease sites—a critical public health need. Clinical data could be pooled from infections caused by the targeted bacterial pathogen at several different body sites (e.g., pneumonia, bloodstream infection, intra-abdominal infection). Moreover, these data, in combination with data from in vitro studies, animal models of infection (with pharmacokinetic and pharmacodynamic data), human pharmacokinetic and pharmacodynamic
data, and important microbiologic information about the mechanism of action of the new drug and the mechanisms of resistance, could support approval for use in serious infections due to the resistant pathogen. This mechanism also could be considered for developing therapies for multidrug-resistant tuberculosis (MDR-TB)—a critical public health issue because current therapeutic regimens are not very effective.

In addition, the SPLMU Drug designation could be temporary or permanent. If the drug sponsor later went through a traditional study route for an indication for the anti-infective the limited use designation could be removed.

How else will the SPLMU approach help to address antimicrobial resistance?
By helping to limit prescription of drugs approved by the SPLMU mechanism to patients who fall within the special population indicated on the FDA-approved label, the mechanism would protect individual patients outside of the special population from exposure to drugs that may pose an uncertain risk. Furthermore, the SPLMU mechanism also would serve a broader public health purpose for anti-infective therapies as it could be used to help deter development of resistance to important drugs by encouraging their use to only those patients with a highly resistant, target pathogen. Because companies may only market drugs according to their FDA approved indication, the SPLMU mechanism would be a potent means of limiting advertisement/marketing of the drug for a narrow, appropriate use. Such focused marketing would help prevent inappropriate, broader use of such life-saving medications, thereby slowing the spread of resistance and prolonging the drugs’ useful lives.

In addition, the SPLMU mechanism will help to enforce the understanding that anti-infective drugs provide an important societal benefit that necessitates the need for greater societal responsibility. We believe this new approval mechanism will promote the development and implementation of antimicrobial stewardship programs in health care facilities across the United States—a priority for IDSA and the infectious diseases community in general. (See additional discussion about antimicrobial stewardship below.) And, although antibiotics typically are prescribed empirically (i.e., without culture tests being performed to confirm the diagnosis), IDSA anticipates and will help to encourage, along with the health care community and payors, that confirmatory tests are performed in patients prescribed antibiotics approved under the SPLMU mechanism so that the drug can be discontinued in patients found not to be in the indicated population.

In summary, the important benefits of the SPLMU mechanism include:

- Creation of a new anti-infective drug approval pathway that permits a more appropriate risk-benefit ratio for serious infections and will bring lifesaving medicines to those patients most seriously in need of them.

- Empowering FDA to innovate the anti-infective pipeline by providing them flexibility to more rapidly approve urgently needed medicines.

- Rightly leaving in physicians’ hands the power to oversee the use of approved products within the practice of medicine.
A streamlined approval pathway that will enable pharmaceutical companies to study SPLMU drugs in far fewer patients than currently is required, more rapidly, and at significantly less cost.

A likely higher valuation of these precious drugs among payors, providers, patients, and society in general.

Placing the burden of protecting these drugs on those stakeholders best positioned to ensure their appropriate use (e.g., health care providers, health care systems, payors, patients).

Promoting the establishment of critically needed antimicrobial stewardship programs in health care facilities across the United States.

**Institute of Medicine (IOM) Review of FDA Anti-Infective Clinical Trial Design**
In addition to considering the SPLMU mechanism in the context of the GAIN Act and PDUFA, IDSA also recommends that the Subcommittee direct FDA to engage with the Institute of Medicine (IOM) in a process to review the operational feasibility of FDA’s current approaches to the design of anti-infective (including antibacterial, antifungal, and influenza antiviral) drug clinical trials. The IOM could: assess the limitations and strengths of FDA’s current statistical approaches; provide new perspectives on approaches to balancing public health risk vs. benefit of decisions that must be made, even in the face of incomplete or imperfect data, and applied to the evaluation of the safety and efficacy of new anti-infective drugs; and make recommendations leading to more rapid improvements in regulatory science.

**Foundation for the National Institutes of Health (FNIH) Initiative**
In 2010, FDA contacted the Foundation for the NIH (FNIH) Biomarkers Consortium to request its assistance in reviewing and assessing the evidence available for making regulatory decisions for some antibacterial drug clinical trials. Specifically, this initiative is an independent collaboration with academia, industry, IDSA, and others to advance development of antibacterial trial endpoints. The initial focus for this effort is skin infections and pneumonia. Congress should seek out ways to support this and similar initiatives to improve the regulatory pathway for approval of new antimicrobial drugs.

**IV. Antimicrobial R&D: Removing Economic Disincentives**
To fix the broken antimicrobial pipeline and stimulate the development of desperately needed new antimicrobial drugs, IDSA has long advocated that a combination of push and pull incentives will be necessary. The GAIN Act takes an important step in the right direction by providing a type of pull incentive—increased data exclusivity for new antibiotics. However, this incentive, while helpful, alone will not sufficiently raise the net present value (NPV) of antibiotics sufficiently to permit them to compete fairly against other drugs for companies’ R&D investment resources. To that end, IDSA recommends the following incentives be added to the GAIN Act for inclusion in PDUFA:
Push Incentives

Public Private Collaborations
The European Union (EU), through its Innovative Medicines Initiative, is launching a new collaborative research effort focused on antibiotics for serious resistant pathogens. The EU recognizes that the extent of action required to significantly impact the challenges facing the discovery and development of novel antibiotics is too great for any single entity. This new initiative will focus on the discovery and development of antibiotics targeting drug-resistant priority pathogens. IDSA applauds the EU for its leadership and urges Congress to take steps toward a similar, complementary initiative in the U.S. Even if the Subcommittee determines that the GAIN Act cannot be used to establish a public private partnership, surely the legislation can be used at least to designate a lead agency to explore the options in this arena and to report back to Congress on those options within one year. Such options should include the possibility of working jointly with the EU and other countries on a public private collaboration to address this growing global problem. Designating a lead agency to explore these options could be done at little or no cost. If we do not act, we run the risk of further eroding our competitive edge and losing valuable intellectual capital and jobs.

Other Push Incentives
While exclusivity provides value to companies once a drug is on the market, numerous economic models have indicated that push incentives (i.e., providing value early in R&D) are necessary to spur new antimicrobial development. Such incentives could include tax credits, grants, or other mechanisms of direct funding through the National Institutes of Health and the Biomedical Advanced Research and Development Authority (BARDA). While the Energy and Commerce Committee does not have jurisdiction to pursue all of these options, we encourage Committee Members to indicate their support for exploration of these proposals to colleagues on the House Ways and Means and Appropriations Committees.

Pull Incentives

Exclusivity
The increased exclusivity provided by the GAIN Act attaches to the end of existing Hatch/Waxman data exclusivity and would run concurrent with most antibiotics’ existing patent terms. As such, GAIN will keep competitors off the market only in limited cases when the original drug’s development period took so long that less than 10 years of patent life remains available post-approval. For the average antibiotic, 10 to 12 years of patent time typically remains post-approval. Thus, GAIN’s exclusivity incentive’s primary benefit will be to protect companies from patent infringement suits during the additional 5 years of exclusivity. Such an incentive may be particularly helpful for a company with potentially weak intellectual property rights.

To raise antibiotics’ NPV even further and thus spur antibiotic R&D for the patients who need them, IDSA has proposed that exclusivity also must be applied at the end of all remaining

exclusivity and patent time to keep competitors’ drugs off the market longer. Structured in this manner, IDSA’s exclusivity proposals will likely not score a cost to the federal government for the next decade or two, given the average amount of patent life typically remaining on new antibiotics at the time they are approved. Major companies, including GlaxoSmithKline (GSK) and Pfizer, agree with IDSA’s assessment. To strengthen GAIN’s exclusivity provision, consider the addition of (1), (2), and (3) below in descending order of priority:

(1) A period of exclusivity (e.g., 5 years) that attaches to the end of all existing exclusivity and patent periods, thereby prohibiting the approval of competitors’ drug applications during the protected period. Since the time it was established in 1997, pediatric exclusivity has helped to generate more than 900 pediatric studies, and over 430 products have undergone labeling changes for pediatric use—demonstrating that exclusivity at the end of patent life is a model worth considering. Both GSK and Pfizer have modeled this incentive and agree that it would provide substantial additional benefit over the current GAIN exclusivity provision.

(2) An additional period of exclusivity (e.g., 3 years) that attaches at the end of all existing exclusivity and patent periods if the antibiotic is the first of a new class because, for example, the active moiety of the product achieves its therapeutic effect through a new mechanism of action or targets a site on the infectious pathogen not targeted by products previously approved. For purposes of this new provision, FDA will need to define in regulations the term “antibiotic class” as this term currently is not defined. However, many experts agree only one new class of antibiotic has been approved since the 1970s. New classes of antibiotics can provide valuable new protections against drug-resistant pathogens, and thus, creating new antibiotic classes should be a priority for GAIN.

(3) Any exclusivity period extended pursuant to the GAIN Act should be further extended by additional exclusivity (e.g., 1 year) at the end of all existing exclusivity and patent periods for each subsequent approval an antibiotic receives for treating an additional infection or pathogen where FDA deems the subsequent approval(s) address a critical unmet need. It makes sense to consider limiting this incentive, e.g., no antibiotic could receive more than three such extensions. This incentive will spur companies to conduct additional research on approved antibiotic drugs, thus, providing valuable effectiveness and safety information about how these drugs work in patients suffering these infections; without such additional studies physicians will not have access to this critical information.

V. The Scope of GAIN’s Impact

To address the infections posing the greatest risk to patients (and therefore of greatest concerns to ID physicians), ensure the GAIN Act is applicable to drugs and related diagnostics that treat and detect new infectious pathogens as they emerge, and best fits the way FDA approves antibacterial drugs (currently by indication based on infection and not pathogen). IDSA agrees with others that it would be best to modify the GAIN definition of “qualified infectious disease product.” We propose the following revised definition: “an anti-infective (including antibacterial, antifungal, and influenza antiviral drugs) for human use that meets the statutory definition of a new chemical entity; is indicated for use in a serious or life-threatening
infections; and which demonstrates the potential to address unmet medical needs for such disease or condition.”

It is IDSA’s understanding that Subcommittee members are considering whether to expand the scope of the GAIN Act to cover antifungal drugs. Fungi can cause serious and life-threatening infections, particularly in cancer patients, HIV/AIDS patients, and the elderly. The costs of treating these infections are skyrocketing, and the morbidity and mortality associated with invasive fungal infections is extremely high. For these reasons, IDSA supports covering antifungals that treat serious and life-threatening infections in the GAIN Act and thus we include them in our proposed revised definition above.

We also have added language to cover influenza antivirals. We realize that this request is new and that Subcommittee members want to keep the GAIN Act definition narrow to address the most urgent needs. However, we want Subcommittee members to be aware that influenza antivirals are desperately needed to reduce the current high levels of influenza-associated morbidity and mortality in the United States. CDC estimates that seasonal influenza epidemics result in an average of more than 200,000 influenza-related hospitalizations and a range of approximately 3,400 to 49,000 influenza-related deaths each year in the U.S. Of particular note, there were 122 pediatric influenza-associated deaths in the U.S. last season, and the number of pediatric deaths ranges from 46 to 153 each year. There also were more than 300 deaths in children from the 2009 pandemic H1N1 in the U.S. We currently have only two effective influenza antivirals available, and one of these drugs is not available to treat many types of patients, including children under the age of five. In addition, there are very real concerns that resistance is developing against these two available drugs in circulating influenza strains. New effective antiviral drugs are urgently needed to prevent severe infections and deaths among large numbers of adults and children during future seasonal outbreaks and pandemics of influenza. IDSA experts are available to discuss with Subcommittee members and staff the state of antibacterial, antifungal, and influenza antiviral drug development and the threats posed by antimicrobial resistance in all three areas.

VI. Incentives for Development of Rapid Diagnostics

Diagnostic tests are a critical part of the solution to the problems of antimicrobial resistance and R&D, and can play a critical role in detecting and identifying emerging infections as well as biothreats. Rapid, highly sensitive, point-of-care diagnostics improve physicians’ ability to effectively treat patients and prescribe antibiotics in a manner consistent with antimicrobial stewardship. We need diagnostic tools to accurately identify serious, drug-resistant bacterial, fungal, and viral pathogens and, importantly, to inform the physician when the pathogen he or she is trying to treat is a virus and therefore untreatable using antibiotics. Thus, diagnostics can be extremely helpful in preserving for a longer window of time the effectiveness of approved antibiotics. Better diagnostics also reduce the costs of new anti-infective development by increasing the number of microbiologically evaluable patients in the clinical trial population. There are currently serious challenges to enrolling eligible patients in clinical trials for new antimicrobials.
Unfortunately, numerous disincentives exist that hamper the development of new diagnostic tests including the expense of collecting clinical specimens against which to validate diagnostics, difficulty in obtaining FDA approval for diagnostic tests, challenges in securing Medicare and private insurance coverage of new diagnostics, and a lack of value-based reimbursements for these tests.

A good first step toward strengthening diagnostics R&D will come from establishing a centralized specimen biorepository to house patients’ clinical specimens (e.g., tissue, sputum, blood, urine) collected during clinical trials. Such a repository would strengthen infectious diseases research and critically needed diagnostics development by reducing redundancies (i.e., eliminate the need for multiple players to collect the same types of specimens numerous times), assuring that quality specimens are collected, and saving valuable time and resources. A similar Cancer Human Bio-Bank (ca-HUB) is being established by the National Cancer Institute (NCI). On this concept, the Institute of Medicine has opined that, “The broader use of high-quality, standardized repositories would speed the pace of scientific and clinical advances at a much lower expense than would be required if new clinical samples had to be collected to study each new concept.” IDSA proposes that the same is true for infectious disease research, particularly related to diagnostics.

IDSA recognizes that the Subcommittee may be hesitant to include a provision in GAIN to create such a repository. However, we firmly believe this idea is worthy of consideration and therefore recommend that the GAIN Act or PDUFA direct the National Institutes of Allergy and Infectious Disease (NIAID), in conjunction with CDC, FDA, and the Assistant Secretary for Preparedness and Response (ASPR), to consult with non-government stakeholders including representatives from diagnostics and pharmaceutical companies, academia, and professional societies to explore the feasibility of creating a biorepository of prospectively collected specimens. In so doing, NIAID and the others should consider whether such a repository would lower the cost of clinical validation of, and otherwise assist with the R&D for, diagnostic tests intended to advance the treatment, detection, identification, prevention, or control of antimicrobial-resistant infections. Consideration of this idea by these agencies could be done at little to no cost. Further, NIAID also should examine the feasibility of making the biorepository self-sustaining by establishing a program under which non-governmental entities could pay a fee for access to each human biological specimen, including costs related to the overall maintenance and operation of the biorepository.

VII. Antimicrobial Stewardship and Appropriate Use

Antimicrobial stewardship refers to coordinated interventions designed to improve and measure the appropriate use of antimicrobials by promoting the selection of the optimal antimicrobial drug regimen including dosing, duration of therapy, and route of administration. The major objectives of antimicrobial stewardship are to achieve best clinical outcomes related to antimicrobial use while minimizing adverse events and the emergence of antimicrobial resistance. Antimicrobial stewardship also may reduce excessive costs attributable to suboptimal antimicrobial use. As the Subcommittee considers providing greater federal support to incentivize new antibiotic R&D, it is equally important to safeguard that investment with policies
to ensure that antibiotics do not rapidly become obsolete due to the overuse that drives resistance.

Next week IDSA, the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS) will release a policy statement on antimicrobial stewardship that will put forth our joint position on antimicrobial stewardship. However, IDSA’s fundamental position already has been made public. We recommend that all health care facilities, including hospitals, long-term care facilities, long-term acute care facilities, ambulatory surgical centers, and dialysis centers be required to develop and implement an antimicrobial stewardship plan as a condition of participation in Medicare and Medicaid. IDSA recognizes that the Subcommittee does not have sole jurisdiction over Medicare, but we encourage you to consider ways to promote the appropriate use of antibiotics through the GAIN Act. Specifically, IDSA recommends that the following language regarding antimicrobial stewardship be added to the GAIN Act:

“The Secretary shall, in cooperation with CDC and CMS, promote measurement of antibiotic usage across all health care settings and support adoption and implementation of comprehensive antimicrobial stewardship programs across all health care settings to promote the appropriate use of antibiotics. Flexibility in program requirements must be allowed based on facility size and type.”

Moreover, GAIN’s definition of “qualified infectious disease product” could be further modified to require a drug sponsor to provide to FDA during the drug review process a plan for educating health care providers in all health care settings on the drug’s appropriate use and to reinforce precautions to reduce the risk of resistance.

**VIII. Conclusion**

In conclusion, IDSA thanks the Subcommittee once again for its leadership and focus on antimicrobial resistance and the dry anti-infective pipeline. These are complex, multi-faceted problems that require a combination of policy solutions, including regulatory improvements, push and pull economic incentives, new diagnostics tests, and establishment of antimicrobial stewardship programs in each health care facility to ensure the continued development and long-term utility of antimicrobial drugs. IDSA looks forward to continuing to work with the Subcommittee to enact the strongest possible package of solutions through the GAIN Act and PDUFA.
February 22, 2012

Dear U.S. House Leaders:

We, the undersigned organizations representing patients, health care providers, health systems, veterans, women’s health, children’s health, seniors, and other key stakeholders urge you to address the serious and growing problems of antimicrobial resistance and the dry pipeline for antibiotic research and development (R&D) in upcoming Food and Drug Administration (FDA) user fee legislation. A growing number of patients are suffering from and succumbing to antimicrobial-resistant infections, because we have too few, and in some cases no, antibiotics to treat them. Ironically, as the number of patients succumbing to resistant infections rises, the number of new antibiotics in development is plummeting.

If Congress does not enact strong solutions, we face a future that resembles the days before these miracle drugs were developed, one in which people died of common infections, and where many medical interventions that we take for granted—including care for premature infants, surgery, cancer chemotherapy, organ transplantation, and even dentistry for some patients—become impossible. Antimicrobial resistance also is placing a significant burden on our health care system—costing over $20 billion annually in health care costs according to one study. To save patients’ lives, we support U.S. efforts that strive to achieve the laudable goal of approving ten new systemic antibiotics by 2020. Read more about The 10 x ’20 initiative (http://www.idsociety.org/10x20) on the Infectious Diseases Society of America’s website.
In 1990, there were nearly 20 pharmaceutical companies with large antibiotic R&D programs. Today, alarmingly, only a few companies remain. Not only does the tumbling private investment in antibiotics R&D jeopardize the development and availability of sorely needed new antibiotics in the United States, it also drains indispensable jobs and intellectual capital as companies seek to do business in other countries. For example, the regulatory environment for antibiotics in the European Union (EU) is viewed much more favorably by pharmaceutical companies and antibiotic public/private collaborations are being pursued as part of the EU’s Innovative Medicines Initiative.1

Antibiotics’ R&D poses unique scientific, regulatory and economic challenges. One company reports that over a 10 year period, it took 72 lead candidate antibiotic compounds in the early discovery phase to yield one FDA-approved product; other drug categories only took 15 leads to yield an FDA approval. Antibiotics also provide less financial reward for companies as they are used for a short duration, typically are priced low, and must be held in reserve to protect against the development of drug resistance, rather than used widely as most other drugs are.

We are encouraged that Congress has shown a strong interest in addressing the antibiotic crisis, as evidenced by the development of a U.S. Senate working group, past hearings in the U.S. House of Representatives, and pending antibiotic R&D incentives legislation. We call upon Congress to follow through with action that will spur new antibiotic R&D. A combination of push and pull incentives is needed to sufficiently raise the net present value of antibiotics so that they may compete on a level playing field with other drug categories for companies’ R&D resources.

It is also vitally important for Congress to incentivize the development of new related diagnostics, and we are pleased that pending antibiotic R&D incentives legislation begins to address this issue. Better diagnostics can reduce the costs of new antibiotic development by identifying patients who are eligible for clinical trials. Diagnostic tests also are important for conducting surveillance for the patterns of antimicrobial resistance and recognizing emerging drug resistance. In addition, rapid diagnostic tests improve physicians’ ability to prescribe antimicrobial drugs appropriately, which is critical to limit the development of resistant bacteria and preserve these important drugs’ effectiveness for as long as possible. Congress should strengthen federal efforts to promote the appropriate use of antibiotics in health care facilities.

We are gravely concerned about the increasing number of patients with serious, life-threatening infections who cannot be treated due to a lack of effective antibiotics. These cases result in longer hospital stays, readmissions, increased healthcare costs and even deaths. Losing antibiotics entirely—which is where we are heading without urgent action—will undermine the way medicine is practiced and have devastating consequences for patients. We have an obligation to our children and grandchildren to invest in the development of new antibiotics and related diagnostic tests and to preserve antibiotics’ effectiveness for the long term.

Sincerely,

Alliance for Aging Research
Alliance for the Prudent Use of Antibiotics
American Academy of Allergy, Asthma and Immunology
American Academy of Neurology
American Academy of Ophthalmology
American Academy of Orthopaedic Surgeons
American Academy of Otolaryngology-Head and Neck Surgery
American Academy of Pediatrics
American Association of Hip and Knee Surgeons
American Association of Neurological Surgeons
American College of Emergency Physicians
American College of Medical Quality
American College of Rheumatology
American College of Surgeons
American Congress of Obstetricians and Gynecologists
American Geriatrics Society
American Physical Therapy Association
American Public Health Association
American Society for Microbiology
American Society of Hematology
American Thoracic Society
American Urological Association
Association for Professionals in Infection Control and Epidemiology
Center for Hospital Innovation and Improvement
Children’s Hospital Association
Coalition of State Rheumatology Organizations
Congress of Neurological Surgeons
Department for Professional Employees of AFL-CIO
First Focus
Food Animal Concerns Trust
Heart Rhythm Society
HIV Medicine Association
Immune Deficiency Foundation
Infectious Diseases Society of America
National Alliance to Advance Adolescent Health
National Association of County and City Health Officials
National Association of Nurse Practitioners in Women’s Health
National Association of Pediatric Nurse Practitioners
National Association of Veterans' Research and Education Foundations
National Coalition of STD Directors
National Family Planning & Reproductive Health Association
National Foundation for Infectious Diseases
Pediatric Infectious Diseases Society
Premier
Renal Physicians Association
Society for Healthcare Epidemiology of America
Society of Infectious Diseases Pharmacists
Society of Critical Care Medicine
Treatment Action Group
Trust for America’s Health

[A similar letter has been sent to U.S. Senate leaders]