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IDSA
Infectious Diseases Society of America

April 12, 2012

The Honorable Fred Upton
Chairman
House Energy and Commerce Committee
2183 Rayburn House Office Building
Washington, DC 20515

The Honorable Henry Waxman
Ranking Member
House Energy and Commerce Committee
2204 Rayburn House Office Building
Washington, DC 20515

The Honorable Joe Pitts
Chairman
Subcommittee on Health
House Energy and Commerce Committee
420 Cannon House Office Building
Washington, DC 20515

The Honorable Frank Pallone, Jr.
Ranking Member
Subcommittee on Health
House Energy and Commerce Committee
237 Cannon House Office Building
Washington, DC 20515

RE: Comments on Generating Antibiotic Incentives Now PDUFA Discussion Draft and Request for Meeting

Dear Chairman Upton and Ranking Member Waxman:

The Infectious Diseases Society of America (IDSA) welcomes this opportunity to provide comments on the House Energy and Commerce Committee's U.S. Food and Drug Administration (FDA) Prescription Drug User Fee Act (PDUFA) reauthorization legislation discussion draft, dated March 8, 2012, and particularly on Title VIII—Drug Regulatory Improvements; Subtitle C-- Generating Antibiotic Incentives. **We respectfully request to meet with you to further discuss our comments and answer any questions.**

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, including an increasing number of patients with serious and life-threatening antimicrobial-resistant infections against which we have frighteningly few, and in some cases no, effective therapeutics available. Addressing the dry antimicrobial pipeline and combating antimicrobial resistance have been IDSA's top policy priorities for the past decade and have included our launch of the "Bad Bugs, No Drugs" advocacy campaign in 2003 and recent launch of "the 10 x '20 initiative," which seeks the development of ten new systemic antibacterial drugs by 2020.

IDSA applauds the Committee's efforts to consider strong incentives to spur new antibiotic research and development (R&D) as part of the PDUFA reauthorization legislation. This is an opportunity that we cannot afford to miss. IDSA is pleased to support many provisions in the discussion draft and to offer additional policy proposals for your consideration. **IDSA's highest priority recommendation—establishment of a Limited Population Antibacterial Drug (LPAD) approval mechanism—appears on page 5 of this letter, under our comments on "Sec. 826. Clinical Trials" of the discussion draft.** The LPAD proposal could be included under Section 826 or inserted as a separate section where appropriate.

IDSA has selected the LPAD proposal as our top priority, because we believe that this approval pathway mechanism is a necessary complement to the Committee's discussion draft and the Generating Antibiotic Incentives Now (GAIN) Act and will enable companies to access the economic incentives included in your draft. At least 13 pharmaceutical companies already have endorsed the inclusion of LPAD in PDUFA. For more information on LPAD, please see the attached draft legislative language, one page summary, and frequently asked questions document.

Sec. 821. Extension of Exclusivity Period for Drugs

a. Extension of Exclusivity Period for New Qualified Infectious Disease Products

Comments: Provide exclusivity at the end of all remaining exclusivity and patent time.

It's our understanding that the increased exclusivity provided by the discussion draft attaches to the end of existing Hatch/Waxman data exclusivity and would run concurrent with most antibiotics' existing patent terms. As such, this provision 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, this exclusivity incentive's primary benefit will be to protect companies from patent infringement suits during the additional 5 years of exclusivity.

To provide an economic incentive that would help antibiotics compete internally for companies' R&D resources, IDSA has proposed that exclusivity also must be applied at the end of all remaining exclusivity and patent time (similar to the structure of pediatric exclusivity) to keep competitors' drugs off the market longer and improve the net present value of developing antibiotics. Structured in this manner, IDSA's recommended 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. We have heard from major companies, including GlaxoSmithKline (GSK) and Pfizer, which agree with IDSA's assessment.

b. Definitions of "Qualifying Pathogen" and "Qualified Infectious Disease Product"

Comments: Strongly urge Energy and Commerce Committee to adopt the structure and scope used in the Senate Health, Education, Labor, and Pensions (HELP)

Committee PDUFA draft regarding definitions, protection of designation and flexibility targeting emerging infections, as well as inclusion of "antifungals."

While IDSA understands the desire for predictability engendered in the House list of qualifying pathogens, IDSA prefers the Senate HELP Committee discussion draft's definitions of "Qualified Infectious Disease Product," which limits the incentives only to serious and life-threatening infections and provides a process for selecting pathogens as "Qualifying Pathogens." The Senate draft establishes a process where the Secretary will establish and update the list of qualifying pathogens, in consultation with experts in infectious diseases, which will provide the necessary flexibility to target incentives to areas of unmet medical need and keep pace with emerging infectious threats. The Senate HELP Committee proposal will adjust to successful drug development and emerging pathogens better than a list of qualifying pathogens in statute, as current areas of unmet need will hopefully be addressed over time and new dangerous pathogens for which there are few, if any, satisfactory treatment options will continue to emerge. Further, to ensure predictability, the Senate discussion draft ensures that once a company receives a designation of "qualified infectious disease product," the designation cannot be withdrawn. This provision provides companies with the certainty they need to proceed with R&D, regardless of updates made to the list of qualifying pathogens. We support the idea of creating such a designation and request that the House Energy and Commerce Committee consider including the same predictability in its PDUFA bill.

IDSA also supports the Senate discussion draft's inclusion of antifungal drugs in its definition of "qualified infectious disease product." 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. We ask that the Energy and Commerce Committee include antifungals in its bill.

Moreover, as covered in the Antimicrobial Stewardship section below, the House discussion draft's definition of "qualified infectious disease product" could be further modified to require that a drug sponsor 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.

Sec. 822. Additional Extension of Exclusivity Period for Qualified Infectious Disease Product for which a Companion Diagnostic Test is Cleared or Approved

Comments: Support the provision and exploration of other mechanisms that support diagnostics development and validation (see comments on Section 826 below).

IDSA supports the House provision to provide additional exclusivity to help incentivize diagnostics R&D. 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 detect and 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.

Under our comments for Sec. 8 Clinical Trials, IDSA is proposing a provision to examine the feasibility of a clinical specimen biorepository, which could be particularly useful for diagnostics R&D.

Sec. 823. Priority Review and Sec. 824. Fast Track Product

Comments: Supports sections 823 and 824 and urge inclusion elsewhere in draft of new pathway to get the most needed products to the approval process.

IDSA supports provisions in the discussion draft to grant priority review to qualified infectious disease products and to make qualified infectious disease products eligible for fast track. IDSA has long recognized that antibiotic R&D faces unique regulatory hurdles, and we appreciate the Committee's attention to this issue. However, both of these provisions focus on FDA approval. Unfortunately, many products are not even able to reach this critical juncture due to infeasible clinical trial designs. Under our comments for Sec. 826, IDSA will provide recommendations on this issue, specifically our top priority—the Limited Population Antibacterial Drug (LPAD) approval mechanism—as mentioned above. We raise this issue here because Congress must address the clinical trial problems in a meaningful way in order to allow companies to benefit from the priority review, fast track, and economic incentives provided in the House draft.

Sec. 825. Study on Incentives for Qualified Infectious Disease Biological Products

Comments: Supports Government Accountability Office (GAO) study on biological products, but encourages inclusion of additional GAO studies proposed in the Senate discussion draft.

IDSA supports a GAO study on the need for incentives to support the development of qualified infectious diseases biological products. IDSA also supports GAO studies proposed in the Senate discussion draft on the need for antibiotic and antifungal R&D incentives to help document clinical trial information, including public versus private funding for trials, and regulatory issues, including recommendations to improve the review and predictability of regulatory pathways for qualified infectious disease products. Such information will be valuable as we all continue to work to ensure that biological, antibiotics and antifungals are made available to patients who desperately need them.

Sec. 826. Clinical Trials

a. Review and Revision of Guidelines

Comments: Supports provisions related to review/revision of clinical trial guidances

IDSA supports the Committee's efforts to hasten the review and revision of clinical trial guidances. FDA's current approach to clinical trials design poses significant challenges for antibiotic R&D. In fact, FDA's guidances, in some instances, appear to deviate substantively from standard clinical care and thereby may impede, rather than facilitate, antibiotic drug development. The realities of patient care may not allow compliance with current regulatory guidance.

b. Institute of Medicine Study

Comments: Add a new provision asking the Institute of Medicine (IOM) to assess current statistical approaches, weigh in on risk/benefit analysis and other issues.

IDSA suggests inclusion of an IOM study on the review and revision of clinical trial guidelines, the predictability of regulatory pathways and review, and any outstanding regulatory impediments. Congress should consider commissioning the IOM to review the operational feasibility of FDA's current approaches to the design of antibacterial and antifungal drug clinical trials. The IOM has the necessary scientific expertise and 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.

c. Limited Population Antibacterial Drug (LPAD) Approval Pathway

Comments: Add new approval mechanism for antibacterial drugs to treat the most serious bacterial infections where there exists an unmet medical need.

The U.S. regulatory environment—specifically lack of feasible and predictable antibacterial approval pathways—is the primary reason that the few pharmaceutical companies still investing in antibiotic R&D report they plan to focus future efforts on markets outside of the United States. These findings underscore the need to establish a feasible and predictable approval pathway to advance R&D of desperately needed new antibiotics. In fact, such a new pathway will be necessary to allow companies to access the other economic incentives included in the House discussion draft. 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 patients with the most serious bacterial infections, FDA's risk-benefit equation has been out of balance.

The LPAD approval mechanism would provide an important new approval pathway for antibacterial drugs that treat patients with the most serious infections where there exists an unmet medical need (i.e., where insufficient satisfactory therapeutic options exist). It is not feasible for antibacterial drugs that treat serious infections due to highly resistant bacterial pathogens to be developed using traditional, large scale clinical trials due to the limited numbers of patients in which such serious infections occur. Instead, under the LPAD mechanism, a drug's safety and effectiveness would be studied in substantially smaller, more rapid, and less expensive clinical trials—much like the Orphan Drug (OD) Program permits for other rare diseases. LPAD products then would be narrowly indicated for use in small, well-defined populations of patients for whom the drugs' benefits have been shown to outweigh their risks. For patients with serious infections and insufficient therapeutic options, a greater degree of uncertainty about overall risk associated with a drug can be tolerated. The LPAD mechanism will not be used to approve antibacterial products that treat more common infections or where sufficient alternative therapeutic options exist.

The LPAD designation (which the company will seek in advance and FDA will approve), a description of the indicated population, the rationale for limiting use, and an LPAD logo would appear in LPAD products' labeling. Through this information, FDA would be providing notice to the health care community, providers, and payors that these products carry less precise estimates of risk and, as a result, the drugs' marketing and use should be limited to the indicated population. LPAD products' limited use also would help slow the rate at which resistance to these drugs develops—an important goal of the medical, public health, and patient communities. Of critical importance, the LPAD mechanism ensures that clinical decision-making remains in physicians' hands. FDA will have no role in regulating use of approved products within the practice of medicine. However, FDA will be able to monitor LPAD products' safe use through its existing Sentinel System.

Find more information about LPAD**, including draft legislative language**, in the enclosure documents. Please note that the LPAD mechanism previously was referred to as Special Population Limited Medical Use (SPLMU) drug approval mechanism before the concept was narrowed specifically to focus only on antibacterial drugs.

d. Centralized Specimen Biorepository to Ease Diagnostic R&D

Comments: Add language directing federal agencies to explore the feasibility of creating a biorepository of prospectively collected specimens, similar to NCI's Cancer Human Bio-Bank.

As mentioned above, diagnostics provide tremendous value in improving patient care, facilitating the appropriate use of antibiotics, and helping to identify patients for antibiotic clinical trials. 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 Committee may be hesitant to include a provision in the PDUFA V legislation to create such a repository due to the potential cost. Although such an effort likely would have initial set up costs, we believe it then could be self-sustaining. We firmly believe this idea is worthy of consideration and therefore, we recommend an immediate no-cost alternative, i.e., Congress direct the National Institutes of Allergy and Infectious Disease (NIAID) to use the next year, 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. 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. For additional information, please see draft legislative language and a summary of this proposal enclosed.

Additional Recommendations

a. Public Private Collaborations to Address Scientific Challenges

Comments: Add provision to designate a lead federal agency to explore Public Private Collaborations and report back to Congress.

The European Union (EU), through its Innovative Medicines Initiative, is launching a new collaborative research effort focused on antibiotics for serious resistant pathogens.[1] The EU recognizes that the extent of action required to significantly impact the scientific challenges facing the discovery and development of novel antibiotics is too great for any single entity. Furthermore, the diversity of skill sets required to tackle these challenges requires contributions from a number of key stakeholders. For example, the lack of a robust pipeline illustrates the

scientific challenges that the industry faces and consequently a framework for sharing knowledge and resources across companies, government agencies and academia is needed to increase the success of antibiotic R&D. 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 Committee determines that PDUFA legislation cannot establish a public private partnership, surely the legislation can at least 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.

b. Antimicrobial Stewardship
Comments: Add provision directing the Secretary to promote measurement of antibiotic usage and support adoption of stewardship programs appropriate to facility size and type.

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 Committee 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.

In March 2012, the Society for Healthcare Epidemiology of America (SHEA), and the Pediatric Infectious Diseases Society (PIDS) released a policy statement on antimicrobial stewardship that outlines our joint position on antimicrobial stewardship footnote the ICHE article (should be public access). We recommend that all health care facilities develop and implement an antimicrobial stewardship plan. Specifically, IDSA recommends that the following language regarding antimicrobial stewardship be added to the discussion draft:

> *"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."*

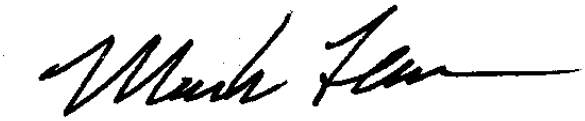
Moreover, the discussion draft's definition of "qualified infectious disease product" could be further modified to require a drug sponsor to provide to FDA during the drug review process a plan for educating health care providers in all health care settings on the drug's appropriate use and to reinforce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

Conclusion

Once again, IDSA commends the Committee and the sponsors of the GAIN Act for seeking to address the dry antibiotic and antifungal pipelines through the Prescription Drug User Fee Act (PDUFA) reauthorization legislation. Numerous provisions included in the discussion draft will begin to address these crises. IDSA looks forward to working with you to strengthen this proposal with additional policies to bring needed antimicrobials to patients and help protect these new investments from the development of resistance.

For further information, please contact Robert Guidos, JD, IDSA's vice president of public policy and government relations at rguidos@idsociety.org.

Sincerely,



Mark A. Leasure
Chief Executive Officer

Enclosures:
1. Limited Population Antibacterial Drug (LPAD) draft legislative language
2. LPAD one page summary
3. LPAD frequently asked questions
4. Clinical specimen biorepository draft legislative language
5. Clinical specimen biorepository summary

Cc: Rep. Phil Gingrey
Rep. Gene Green
GAIN Act Co-sponsors

Enclosure 1

DRAFT LEGISLATIVE LANGUAGE*
LIMITED POPULATION ANTIBACTERIAL DRUGS

SEC. XXX. DRUGS FOR LIMITED USE IN PATIENTS WITH SERIOUS OR LIFE-THREATENING BACTERIAL INFECTIONS

(XX) ANTIBACTERIAL DRUGS FOR LIMITED USE IN POPULATIONS OF PATIENTS WITH SERIOUS OR LIFE-THREATENING INFECTIONS

(1) IN GENERAL.—The Secretary may approve a drug under section 505(c) or section 351 of the Public Health Service Act as a limited population antibacterial drug if:

(A) the drug is intended for the treatment of a serious or life-threatening infectious disease caused by one or more bacterial pathogens,

(B) the drug demonstrates the potential to address an unmet medical need,

(C) the benefits of approving the drug in a population of patients with such infection outweighs the risks and accepting greater known risk or uncertainty about potential risk associated with the drug in the population is justified by the severity of the infection and the unmet medical need; and

(D) all of the requirements of section 505(c) or section 351 of the Public Health Service Act are met.

(E) The authority to approve limited population antibacterial drugs may not be delegated below the level of the Director, Center for Drug Evaluation and Research, or the Director, Center for Biologics Evaluation and Research.

(2) CONDITIONS OF APPROVAL.—Approval of an antibacterial product for use in a limited population under this subsection shall be subject to the following requirements:

(A) All labeling for a drug approved under this subsection shall prominently and conspicuously bear the words “Limited Population Antibacterial Drug” or a symbol, designated by the Secretary, that conveys that the drug was approved for limited use in said population, or both.

(B) The Indication section of the labeling for a drug approved under this subsection shall state, “This antibacterial drug has been approved for use in a limited population of patients with serious or life-threatening infections where limited alternative therapies are available. The safety and efficacy of the drug has not been established beyond this limited population. Therefore the drug should only be used in patients whose clinical

condition warrants treatment with this drug." A description of the population to which the approval is limited shall be included in the Indication section.

(C) The sponsor shall submit copies of all promotional materials related to the product during the preapproval review period and, following approval for such period thereafter as the Secretary determines to be appropriate, at least 30 days prior to dissemination of the materials. This limitation shall be lifted upon approval of a supplemental application that expands the use of the drug to a population for which no limitations on use are required.

(3) REQUEST FOR DESIGNATION.—A sponsor of a new antibacterial drug may request the Secretary to designate the drug as potentially eligible for limited population status. A request to designate a drug as potentially eligible for such status may be made concurrently with, or at any time after, submission of an application for the investigation of the drug under section 505(i) or section 351(a)(3) of the Public Health Service Act.

(4) DESIGNATION.—Within 60 calendar days after the receipt of a request under subparagraph (3), the Secretary shall determine whether the drug that is the subject of the request has the potential to be approved as a limited population antibacterial drug, and if so, the Secretary shall designate the drug as such.

(5) ADVICE.—The Secretary shall provide prompt advice to the sponsor of a drug designated as potentially eligible for limited population status as the sponsor plans its development program to obtain the necessary data for approval and any additional studies that would be required to expand the use to a broader population.

*Formerly known as "Special Population Limited Medical Use [SPLMU] Drugs"; now narrowed to cover only antibacterial drugs only and now known as "Limited Population Antibacterial Drugs"

Enclosure 2

Limited Population Antibacterial Drug (LPAD) Approval Mechanism

Background: The Need for a New FDA Approval Pathway for High-Priority Antibiotics

As the number of patients succumbing to antibiotic-resistant infections rises, the number of new antibiotics in development has plummeted. These findings underscore the need for antibiotic incentives and a feasible approval pathway to advance research and development (R&D) of desperately needed new antibiotics. 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 patients with the most serious bacterial infections, FDA's risk-benefit equation has been out of balance. The U.S. regulatory environment is the primary reason that the few pharmaceutical companies still investing in antibiotic R&D report they plan to focus future efforts on markets outside of the United States.

The LPAD Approval Mechanism

The LPAD approval mechanism would provide an important new approval pathway for antibacterial drugs that treat patients with the most serious infections where there exists an unmet medical need (i.e., where insufficient satisfactory therapeutic options exist). It is not feasible for antibacterial drugs that treat serious infections due to highly resistant bacterial pathogens to be developed using traditional, large scale clinical trials due to the limited numbers of patients in which such serious infections occur. Instead, under the LPAD mechanism, a drug's safety and effectiveness would be studied in substantially smaller, more rapid, and less expensive clinical trials—much like the Orphan Drug (OD) Program permits for other rare diseases. LPAD products then would be narrowly indicated for use in small, well-defined populations of patients for whom the drugs' benefits have been shown to outweigh their risks. For patients with serious infections and insufficient therapeutic options, a greater degree of uncertainty about overall risk associated with a drug can be tolerated. The LPAD mechanism will not be used to approve antibacterial products that treat more common infections or where sufficient alternative therapeutic options exist.

The LPAD designation, a description of the indicated population, the rationale for limiting use, and an LPAD logo (similar to the logo pictured above) would appear in LPAD products' labeling. Through this information, FDA would be providing notice to the health care community and payors that these products carry less precise estimates of risk and, as a result, the drugs' marketing and use should be limited to the indicated population. LPAD products' limited use also would help slow the rate at which resistance to these drugs develops—an important goal of the medical, public health, and patient communities. Of critical importance, the LPAD mechanism ensures that clinical decision-making remains in physicians' hands. FDA will have no role in regulating use of approved products within the practice of medicine. However, FDA will be able to monitor LPAD products' safe use through its existing Sentinel System.

Dr. Janet Woodcock, director, FDA's Center for Drug Evaluation and Research, has stated that two companies have expressed interest in pursuing the LPAD mechanism, if the pathway is established. Woodcock also said the LPAD mechanism provides a potential way forward for companies to pursue urgently needed antibacterial drugs. IDSA knows at least seven companies with products that would fit under the LPAD mechanism and help the patients who desperately need access to these drugs**.**

Antibiotics are typically priced far below their true value to society. As with OD designations, an LPAD designation is expected to increase the price of these drugs, compared with traditionally approved antibiotics, making investment in LPAD antibiotics more attractive to pharmaceutical companies. The drugs' higher price, in turn, will encourage payors, the health care community and providers to play a more active role ensuring LPADs are used as indicated, which will help preserve the drugs' effectiveness.
Finally, the LPAD designation could be temporary or permanent. If the drug sponsor later went through a traditional study route for an additional broad indication, the LPAD designation would be removed.

Enclosure 3

Limited Population Antibacterial Drug (LPAD) Approval Mechanism
Frequently Asked Questions

Why is a new approval pathway for high priority antibacterial drugs necessary?
There is an urgent need for new antibacterial therapies to treat patients with serious or life-threatening infections who lack satisfactory therapeutic options, usually because of pathogens' resistance to available therapies. This situation requires new thinking and immediate action. The Food and Drug Administration (FDA) has an essential role to play in ensuring that medicines taken by Americans are safe and effective. But, the agency also has a responsibility to work with drug sponsors to ensure that patients with serious or life-threatening diseases or conditions have access to life-saving, innovative therapies. To date, when it comes to antibacterial drugs, and particularly products needed to treat the most serious bacterial infections, FDA's risk-benefit equation has been out of balance. During a September 2011 policy meeting in Washington D.C., representatives from the few pharmaceutical companies still investing in antibacterial R&D said they are considering focusing their future efforts on European, Asian, and Latin American markets and not on the United States, due primarily to the lack of feasible and predictable regulatory approval pathways for these drugs.

What is the LPAD mechanism, how does it work, and what's its value over the status quo?
The LPAD approval mechanism will provide an important new approval pathway for antibacterial drugs that treat patients with the most serious infections and where there exists an urgent unmet medical need (i.e., where insufficient satisfactory therapeutic options exist). It is not feasible for antibacterial drugs that treat serious infections due to highly resistant bacterial pathogens to be developed using traditional, large scale clinical trials due to the limited numbers of patients in which these serious infections occur. Under the LPAD mechanism, a drug's safety and effectiveness could be studied in substantially smaller, more rapid, and less expensive clinical trials—much like the Orphan Drug (OD) Program permits for other rare diseases. LPAD products then would be narrowly indicated for use in small, well-defined populations of patients for whom the drugs' benefits have been shown to outweigh their risks. For patients with serious infections and insufficient therapeutic options, a greater degree of uncertainty about overall risk associated with a drug can be tolerated. The LPAD mechanism will not be used to approve antibacterial products that treat more common infections or where sufficient alternative therapeutic options exist. Of tremendous value, the LPAD approval pathway will reestablish an appropriate balance in FDA's antibacterial risk-benefit decision-making and will create a predictable, measured, and feasible approval pathway that will lure companies back into antibacterial R&D.

What do the FDA and antibacterial pharmaceutical companies think about the LPAD mechanism?
Over the past decade, FDA has failed to fully appreciate, prioritize, and address the unique challenges facing antibacterial product development. The lack of a clear antibacterial approval pathway, coupled with economic disincentives, has brought antibacterial development to its knees. Companies need consistency, feasibility, predictability, and timeliness in order to make investment decisions. Today, FDA appears to better appreciate the dire public health crisis that patients are facing and is revisiting how it has approved antibacterial drugs and particularly products that treat the most serious infections. LPAD is one of the concepts that

FDA is considering, and, thus far, seems to be very receptive to the idea. In a March 30, 2012 congressional briefing, Dr. Janet Woodcock, director, FDA's Center for Drug Evaluation and Research, said the LPAD mechanism provides a potential way forward for companies to pursue urgently needed antibacterial drugs. She also said two companies have expressed interest to FDA about pursuing the LPAD mechanism, if the pathway is established. IDSA knows at least seven companies with products that would fit under the LPAD mechanism and which would help the patients who desperately need access to these drugs**.** Antibacterial companies also are lining up in support of the LPAD pathway. IDSA has received letters of support from seven companies and other companies are beginning to weigh in. Through the LPAD mechanism, these companies see a possible end to the infeasible regulatory hurdles that many have faced over the past decade.

How much clinical trial data will be needed to secure LPAD "limited" approval? Upon what evidence would LPAD approvals be based?
This is a question of the risk-benefit assessment of the LPAD product, population and indication. As always, FDA will make approval decisions based on the law i.e., the drug must be safe and effective for the indicated population. Thus, the trial size will be determined by an assessment of many factors, including the new drug, the severity of the target infection, and the sufficiency of the therapeutic options available to treat the infection. In IDSA's opinion, for drugs needed to treat rare infections caused by resistant bacteria, trial size may be extremely small—as it would be for any rare disease. Some studies may need to be as small as 30 to 100 patients infected with the resistant form of the bacteria. Depending on the study design, some LPAD studies could be further supplemented with patients that have the same bacteria, but in forms that are susceptible to existing approved drugs. In this way, the company working with FDA can show the drugs are safe and effective for the indicated population.

Would the LPAD proposal change FDA's current approval standards?
No. LPAD drug sponsors still will need to demonstrate to FDA's satisfaction that these drugs are safe and effective for their intended uses and that the drugs' benefits outweigh the risks for approving them for the indicated populations (the same as current approval standards). The LPAD concept mirrors existing orphan drug law, permitting approval for small, well-defined populations of patients with serious diseases where there exists an urgent unmet need for new therapeutic options.

Will LPAD permit the FDA to regulate the practice of medicine?
Definitely, no. Of critical importance, the LPAD mechanism ensures that clinical decision-making remains in physicians' hands. FDA will have no role in regulating use of approved products within the practice of medicine. This position is embodied in FDA laws and regulations and consistent with statements made by FDA leadership about the LPAD mechanism. The Infectious Diseases Society of America (IDSA) and greater medical community oppose any efforts that would undermine physicians' ability to practice medicine.

What safeguards would be in place to help ensure LPAD products are used as intended, their safety is monitored, and that effective antimicrobial stewardship takes place?
LPAD product's narrow indications will ensure LPAD drug sponsors will narrowly market these precious drugs. This will protect patients outside of the indicated population from exposure to

risk and also will slow the development of drug resistance to LPAD products. Drug sponsors will be required to submit promotional materials on LPAD products to FDA both pre- and post-approval to ensure the companies are marketing their drugs consistent with the drug's narrow indication. FDA will be able to monitor LPAD products' safety through its existing surveillance mechanisms, including the agency's Sentinel System, the same as for all other regulated products.

Further, the LPAD designation, drug labeling, and logo would serve as FDA's notification to providers, the health care community, payors and patients that the risk profile of LPAD products are less well characterized than traditionally approved antibacterials due to their more limited clinical database and as a result the drugs should be used narrowly in the indicated population. We believe physicians, once educated about the purpose of LPAD products will choose to use these drugs as intended, because it is in the best interests of their patients and society as a whole. We also believe payors and health care facilities will do their part to discourage inappropriate uses of these valuable drugs particularly as the drugs' narrow indications are likely to be make them more expensive than other antibacterials.

IDSA also will do its part to educate physicians about the appropriate use of LPAD products through the development of clinical practice guidance documents. Importantly, we believe the LPAD mechanism will promote the establishment of antimicrobial stewardship programs in health care facilities across the country—a high priority for IDSA—as facilities work to figure out how to best utilize this important new category of drugs.

Finally, the health care system is evolving in other ways that will further support the appropriate use of LPAD drugs. More integrated delivery systems with electronic health records will make it much easier to monitor and control prescribing practices, not to mention competition among health plans based on cost accountability.

Enclosure 4

SEC. 1. REPOSITORY OF INFECTIOUS DISEASES SPECIMENS.

(a) AMENDMENT.—Part B of title IV of the Public Health Service Act (42 U.S.C. 284 et seq.) is amended by adding at the end the following:

"SEC. 409K. INFECTIOUS DISEASES SPECIMEN BIOREPOSITORY

"(a) IN GENERAL.—The Secretary, acting through the Director, in consultation with the Director of the Centers for Disease Control and Prevention, the Assistant Secretary for Preparedness and Response, and the Commissioner of the Food and Drug Administration, shall consult with non-government stakeholders including representatives from diagnostics and pharmaceutical companies, academia, and professional societies to explore the feasibilty of creating, either directly or by contract, a biorepository of prospectively collected specimens to assist with lowering the cost of clinical trials of, and otherwise assisting with the research and development for, qualified diagnostic tests or other activities intended to advance the treatment, detection, identification, prevention or control of antimicrobial-resistant infections;

"(b) Self-Sustaining Capacity. — In examining the feasibility of a biorepository under (a), the Secretary shall also examine the feasibility of a self-sustaining biorepository in which the Secretary establishesa 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;

"(c) REPORT.

"(1) IN GENERAL.—Not later than one year after the date of the enactment of this section, the Secretary, shall submit to the appropriate committees of Congress a report regarding the biorepository. Such report

shall contain the potential establishment of such biorepository and the feasibility of making such biorepository self-sustaining.

"(c) DEFINITIONS.—In this section:

"(1) BIOREPOSITORY.—The term 'biorepository' means a shared respository of human biological specimens, containing infectious pathogens, collected for medical or research purposes that includes biorepository data.

"(2) BIOREPOSITORY DATA—The term `biorepository data'—

"(A) means data associated with a human biological specimen stored in a biorepository collected for medical or research purposes; and

"(B) includes patient health information and demographic data associated with a specimen.

"(3) DIAGNOSTIC TEST.—The term 'diagnostic test' is a device as defined by section 201(h) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321)."(3) HUMAN BIOLOGICAL SPECIMEN.—The term 'human biological specimen' means any human body fluid, tissue, blood, or cell; and any material derived from any human body fluid, tissue, blood, or cell.

"(4) QUALIFIED DIAGNOSTIC TEST.—The term 'qualified diagnostic test' means a diagnostic test that is approved after the date of enactment of this Act under section 510 or 515 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360; 21 U.S.C. 360e), including a point-of-care diagnostic test, for treating, detecting, preventing, or identifying an infectious pathogen.

Enclosure 5

Self-Sustaining Infectious Disease (ID) Clinical Specimen Repository

What is a Clinical Specimen Repository?

A clinical specimen repository is a facility that collects, catalogs, and stores samples of biological material, such as urine, blood, tissue, cells, DNA, RNA, and protein, from humans for laboratory research. Medical information also may be stored along with a written consent to use the samples in laboratory studies. Clinical specimens already frequently are collected during clinical trials. Preserving these specimens for future use 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 quality specimens are collected, and saving valuable time and resources. A clinical specimen repository could house clinical specimens obtained, for example, from phase II or phase III clinical trials of drugs or devices.

How would an ID Clinical Specimen Repository Work?

Initially, federal funds would be needed to establish and house the repository. The National Institute for Allergy and Infectious Disease (NIAID) is best situated to take the lead. To ensure usability in multiple instances, samples would be collected prospectively through clinical trials, etc. (including through the new NIAID supported clinical trial infrastructure focused on antibiotic resistant bacterial infections), with defined protocols and linked to all available patient clinical data. The repository could allow researchers — both government-funded and industry-based — to access samples without having to conduct new clinical trials to obtain specimens.

Companies, including those developing diagnostics, that wish to access the repository would pay a fee to do so. NIAID would collect the fees and, ultimately, the fees would entirely sustain the maintenance of the repository.

A central repository would represent a significant advance over current sample collection where each facility or company exclusively collects and owns all samples and no cross-validation is possible.

A similar Cancer Human Bio-Bank (ca-HUB) is being established by the National Cancer Institute (NCI). On the concept of the cancer specimen respositories, IOM 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." We propose the same is true for infectious disease research.

How Could an ID Clinical Specimen Repository be Useful in Combatting Antimicrobial Resistance and Infectious Disease?

Prospectively archived infectious disease (ID) specimens would be highly valuable for the development of rapid point-of-care molecular diagnostic devices capable of detecting pathogenic organisms from patient samples. Rapid diagnostic tests improve physicians' ability to prescribe antibiotics in a manner consistent with antibiotic stewardship. Better diagnostics reduce the costs of new antibiotic 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, including a lack of rapid diagnostics to identify patients with particular resistant infectious.

The existing rapid influenza point-of-care tests have only limited clinical utility, especially for detection of novel influenza A viruses. Additional investments are needed to facilitate the development of

advanced diagnostics for influenza. Inexpensive, accurate diagnostic tests that can provide results in a timely manner can guide laboratory, clinical and public health responses.

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 and challenges in securing Medicare and private insurance coverage of new diagnostics. A respository could serve as an essential component of clinical validation for new diagnostics and could reduce overall diagnostic development time. Efforts must be made to encourage research and development of new diagnostics, and a repository that would allow access to high quality clinical infectious disease specimens would be an important tool to ease research burdens.

Has a Clinical Specimen Repository Been Useful in Other Areas of Medical Research?

Yes. A 2010 Institute of Medicine (IOM) report titled "A National Cancer Clinical Trials System for the 21st Century: Reinvigorating the NCI Cooperative Group Program," found that "The Cooperative Groups have a history of collecting biospecimens from the diverse populations of patients who participate in their clinical trials and maintaining them in repositories with detailed information about patient characteristics, treatment, and outcome. These resources have proven immensely valuable in the development of molecular-based classification schemes and diagnostic tests that now guide decisions on the most appropriate therapy for numerous types of cancer."

ca-HUB aims to modernize the field of cancer specimen biobanking by developing an infrastructure for collaborative biospecimen collection and research including through the production of evidence-based biospecimen standard operating procedures. NCI currently is developing ca-HUB which is expected to be implemented in 2012-2014. ca-HUB will make the resulting data, analysis, policy documents, and scientific tools publicly available to enable the community to collect biospecimens fit for specific scientific purposes. The primary operating components of caHUB will consist of medical research and health care institutions for biospecimen collection, a pathology reference center, core biospecimen processing and analysis operation, a comprehensive and highly integrated informatics platform (e.g. , including patient clinical data, patient consent, biospecimen handling data, and molecular analysis), and a research and development program integrating the efforts underway within NCI's Biospecimen Research Network and NCI's Innovative Molecular Analysis Technologies Program.

The caHUB network will make biospecimens available to a larger scientific community and assure quality control of biospecimens. Such assurance will come through the adoption of national standard operating procedures for collecting, processing, and storing biospecimens and better guidance and educational opportunities for biobank personnel and managers.

CA-HUB also will serve a critical role in coordinating a systematic approach to biospecimen science. CA-HUB will work to facilitate communication and coordination across sectors through an extensive network of partners which includes government agencies, private industry, and non-profit and advocacy organizations.NCI has allocated $23.5 million that the institute received from the American Recovery and Reinvestment Act (ARRA) of 2009 for development of caHUB.