

Docket No. FDA-2012-N-1248
Statement of the Infectious Diseases Society of America (IDSA)

**Modified from Comments Delivered at the Food and Drug Administration's (FDA)
February 4, 2013 Hearing on "Creating an Alternative Approval Pathway for
Certain Drugs Intended to Address Unmet Medical Need" as presented by
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As the number of patients succumbing to antibiotic-resistant infections continues to rise, the number of new antibiotics in development has plummeted. Over the past decade, we have witnessed company after company withdrawing from this critical area of medicine, while the death toll climbs. For more information about this crisis, see www.AntibioticsNow.org. Today, there likely are only four large companies and few dozen small companies still actively engaged in the antibiotics research and development (R&D) enterprise, and there are persistent rumors that additional companies might withdraw. This is unacceptable. The U.S. cannot afford to lose additional companies and to see additional sets of antibiotic experts left jobless by another eliminated program. The current situation is a disaster for patients, public health, and national security. We must act now to address this crisis.

The establishment of a Limited Population Antibacterial Drug (LPAD) approval mechanism for antibiotics that address the most urgent unmet needs (i.e., multi-drug resistant infections, etc.) is an essential part of the solution. The LPAD approval mechanism, which IDSA proposed to Congress in 2012, is a game changer that will save lives. IDSA supports creation of the LPAD program preferably through legislation as this appears to be the most accelerated, efficient and least uncertain pathway forward. However, the Food and Drug Administration (FDA) should not wait for such legislation to be enacted before moving forward to create the LPAD mechanism to the extent possible under FDA's existing statutory authority.

In addition to creating new economic incentives, such as the 5-year exclusivity incentive Congress enacted last year as part of the FDA Safety and Innovation Act (FDASIA), we urgently need feasible FDA approval pathways to advance development of critically needed antibiotics. 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 outside of the United States. 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 with the need to provide patients in desperate need with access to beneficial products. To date, when it comes to antibiotics, and particularly antibiotics needed to treat patients with the most serious bacterial infections, FDA's benefit-risk equation has been out of balance.

LPAD will rebalance the benefit/risk equation and provide an important new approval pathway option for companies interested in and able to develop antibacterial drugs that treat the most serious infections where insufficient satisfactory therapeutic options currently exist. At least 15 companies and 24 medical and public health organizations including the American Medical Association (AMA) have lined up with IDSA in support of LPAD's creation.

Why do we need LPAD? 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. Examples of these 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 gram-negative bacterial strains are resistant to all antibiotics, except perhaps tigecycline or colistin (both drugs have toxicity issues), and increasingly to these drugs as well.

For serious diseases for which few if any acceptable treatments are available, the tolerable level of uncertainty regarding a potentially life-saving drug's effectiveness and safety profile is much greater. 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 were 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 benefit-risk ratio of approved LPAD drugs will be quite different than for antibiotics approved under traditional development programs where the drug is indicated for use more broadly.

Under the LPAD approval mechanism, an antibacterial drug's safety and effectiveness would be studied in substantially smaller, more rapid, and less expensive clinical trials—much like the Orphan Drug Program permits for other rare diseases. LPAD products then would be narrowly indicated to be marketed to and used in small, well-defined populations of patients for whom the drugs' benefits have been shown to outweigh their risks. Many bacterial diseases have a broad spectrum of severity. The LPAD 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, the patients, 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. The LPAD mechanism will not be used to approve antibacterial products that treat more common, less serious infections or infections where sufficient alternative therapeutic options exist.

If a company chooses to seek an LPAD designation for its antibiotic and FDA approves the designation and ultimately approves the drug, then the drug's label would include the special LPAD designation, a description of the indicated population, the rationale for limiting the indication, and a special LPAD logo. Through this high profile, new label, FDA would provide notice to the health care community, providers, payors and patients that these products carry greater uncertainty, that is, less precise estimates of risk, and, as a result, the drugs' marketing and use should be limited to the indicated population. An added benefit, LPAD products' limited marketing and use would help slow the rate at which resistance to these drugs develops—an important goal of the medical, public health, and patient communities.

Why would companies pursue a product that would have more limited use? Currently antibiotics are typically priced far below their true value to society. As with Orphan Drug designations, an LPAD designation is expected to increase the price of these drugs, markedly, 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 narrowly as indicated, which also will help preserve the drugs' effectiveness over time. Pricing LPAD drugs at a premium is easily justified based on the severity of the target disease, the limited availability of alternative therapies, and by granting the patient potentially decades more of quality life due to the effective therapy. In addition, because multi-drug resistant infections are more expensive to take care of than susceptible infections, LPAD's premium cost will be offset by reducing the excess healthcare costs due to resistance.

Of critical importance, the LPAD mechanism ensures that clinical decision-making remains in physicians' hands. Off-label use of antibiotics typically occurs when physicians are confronted by problems that on-label drugs are not equipped to handle. For example, let's say an antibiotic that treats KPC *Klebsiella* in the lung and blood is approved via LPAD. A patient develops a KPC *Klebsiella* infection in the brain. The patient's physician is best placed to determine whether, in their clinical judgment, the LPAD drug could be a life-saver in treating the brain infection. In IDSA's discussions with FDA officials about LPAD over the past year, the agency has strongly signaled they have no interest in taking actions to regulate the practice of medicine, penalize physicians who might prescribe LPAD drugs off-label, or otherwise implement restrictions on off-label use. From IDSA's perspective, such actions would not be tolerable. If we want to reduce inappropriate antibiotic use, the key is NOT to create enforcement mechanisms that target off-label use, it is to control the label, as LPAD does, to ensure that on-label marketing is more narrowly targeted. 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. However, FDA will be able to monitor LPAD products' safe use through its existing Sentinel System or other similar mechanisms.

Moreover, off-label use of LPAD drugs can be minimized through the use of:

- the high-profile LPAD label, which will indicate to hospital formularies, providers, payors and others that these drugs possess safety and effectiveness profiles that are more uncertain than antibiotics approved under the traditional approval mechanism;

- educational campaigns about LPAD drugs coordinated by FDA and the Centers for Disease Control and Prevention (CDC) in collaboration with LPAD manufacturers, payors, and professional societies such as IDSA, AMA, the Society for Healthcare Epidemiology of America (SHEA), and the Society of Infectious Disease Pharmacists (SIDP);
- Antimicrobial Stewardship programs, which IDSA, SHEA and others have said should be mandated by the Centers for Medicare and Medicaid Programs (CMS) for all healthcare facilities as a condition of participation in the Medicare and Medicaid programs.

A further benefit, we anticipate the LPAD approval mechanism, including the premium price of these drugs, will promote the development and implementation of Antimicrobial Stewardship programs in health care facilities as well as the development and use of point-of-care diagnostic tests to confirm whether the targeted pathogen is present in patients for whom LPAD antibiotics have been empirically prescribed so that the drug can be discontinued in patients where the LPAD drug's use may be inappropriate. Both stewardship and diagnostics will continue to promote LPAD product's appropriate use and limit the development of resistance to these drugs. Also, as most LPAD agents likely will be parenteral, that is not available in pill form, there will be no opportunity for these drugs to be used broadly outside of a hospital or specialized health care facility to treat common outpatient infections off-label.

In summary, the creation of the LPAD approval mechanism will:

- establish a new anti-infective drug approval pathway that permits a more appropriate benefit-risk ratio for serious infections and will bring lifesaving medicines to those patients most desperately in need of them;
- empower FDA to innovate the antibiotic pipeline by providing them flexibility to more rapidly approve urgently needed medicines;
- rightly leave in physicians' hands the power to oversee the use of approved products within the practice of medicine;
- provide a streamlined approval pathway that will enable pharmaceutical companies to study LPAD drugs in far fewer patients than currently is required, more rapidly, and at significantly less cost;
- ensure a higher valuation of these precious drugs among payors, providers, patients, and society in general;
- ensure the burden of protecting these drugs is on those stakeholders best positioned to ensure their appropriate use (e.g., health care providers, health care systems, payors, patients); and
- foster further establishment of antimicrobial stewardship programs in health care facilities across the United States as well as promote the development of critically needed point-of-care diagnostic tests.

IDSA looks forward to working with FDA, Congress, manufacturers, patients and other stakeholders to advance the development of LPAD agents, which are desperately needed to save lives.