

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.