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–Limited Population Approval Pathway: Background

As antibiotic-resistant bacterial infections are growing more common, few new drugs to treat them are reaching patients. Over the past decade, regulatory and economic challenges have contributed to the decline in antibiotic innovation—particularly for drugs that treat resistant infections.[1] To encourage the development of antibiotics that address unmet needs (mainly resistance) and get them to market faster (preferably before widespread resistance develops), the Infectious Diseases Society of America[2] and the President's Council of Advisors on Science and Technology (PCAST)[3] have proposed a regulatory pathway for antibiotics that target special or limited patient populations—namely those suffering from serious or life-threatening infections with few or no treatment options. The U.S. Food and Drug Administration (FDA),[4] health professionals[5] and several companies[6] support the concept.

Antibiotics are typically studied in large patient populations with a wide range of disease symptoms and severity. By contrast, the limited population pathway would let drug makers test treatments in smaller subpopulations with the most serious or life-threatening types of infections. This could make clinical trials shorter and less expensive, though special labeling would reflect the lack of safety and efficacy data for the broader population, yielding three primary benefits. First, the abbreviated process would lower economic and regulatory barriers to the development of antibiotics we need most, providing an incentive for companies that otherwise would be discouraged by prohibitively high development costs, lengthy testing timelines and the slow uptake of new antibiotics by healthcare providers seeking to stall resistance. Second, in limiting the market, narrow indications could create conditions for value-based or premium pricing for high need antibiotics. Third, the special labeling under this pathway may also foster judicious use and bolster antibiotic stewardship efforts.

An important assumption behind the special labeling of products approved via the proposed pathway is that this would effectively limit use to those for whom the benefits of the antibiotic exceed the risks of potential side effects. Currently, the FDA weighs the benefits and risks against the entire population that may use a particular drug. The limited population proposals would stratify patient subpopulations by risk, allowing approval of antibiotics for patients with a severe form of a disease—for example multidrug-resistant pneumonia—but not for use in a broader population of patients with more treatable and less life-threatening forms of the infection. PCAST and the

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[1] The Pew Charitable Trusts, Infectious Diseases Society of America, Pharmaceutical Research and Manufacturers of America, "Reviving the Pipeline of Life-Saving Antibiotics: Exploring Solutions to Spur Innovation," conference proceedings, September 22, 2011, Washington, D.C.,
http://www.pewhealth.org/uploadedFiles/PHG/Content_Level_Pages/Issue_Briefs/AIP_PipelineProceedings_9_web.pdf.
[2] Infectious Diseases Society of America, "Limited Population Antibacterial Drug (LPAD) Approval Mechanism," accessed January 17, 2013,
http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Advancing_Product_Research_and_Development/Bad_Bugs_No_Drugs/Press_Releases/LPAD%20one%20pager.pdf#search=%22lpad%22.
[3] Executive Office of the President, President's Council of Advisors on Science and Technology, "Report to the President on Propelling Innovation in Drug Discovery, Development, and Evaluation," September 2012,
http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-fda-final.pdf.
[4] Derrick Gingery, "Antibiotic Incentives: FDA's Woodcock Says LPAD Could Be Better Than Exclusivity, But Questions Remain," *The Pink Sheet Daily*, April 18, 2013.
[5] American Medical Association House of Delegates, "Establishment of Limited Population Antibacterial Drug (LPAD) Approval Pathway," Resolution 231, June 19, 2013,
http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Advancing_Product_Research_and_Development/Bad_Bugs_No_Drugs/Position_Papers/AMA%20HOD%20resolution%20LPAD(1).pdf#search=%22lpad%22; Infectious Diseases Society of America, "Organizations' Letter to Congress in Support of LPAD Approval Mechanism," April 12, 2012,
http://www.idsociety.org/uploadedFiles/IDSA/Policy_and_Advocacy/Current_Topics_and_Issues/Antimicrobial_Resistance/10x20/Letters/To_Congress/LPAD%20Public%20Health%20Organizations%20Letter.pdf.
[6] Infectious Diseases Society of America, "Limited Population Antibacterial Drug (LPAD) Approval Mechanism Support Letter," April 12, 2012,
http://www.idsociety.org/uploadedFiles/IDSA/News_and_Publications/IDSA_News_Releases/2012/LPAD_Company_Support_Letter_041212_EC.pdf#search=%22lpad%22; Infectious Diseases Society of America, "FDA Prescription Drug User Fee Act (PDUFA) reauthorization legislation, New product approval mechanism for antimicrobials (LPAD)," April 10, 2012,
http://www.idsociety.org/uploadedFiles/IDSA/News_and_Publications/IDSA_News_Releases/2012/20120409%20Basilea%20letter%20%20LPAD.pdf.

FDA[7] emphasize that the broader healthcare community, including patients, providers, and payors, would play a role in limiting the use of these drugs to patients with acceptable risk. Presumably, approval could be broadened with additional safety and effectiveness data at a later date, if warranted.

While there is some precedent for doing so, it is unclear if the FDA has authority to implement a limited population pathway on its own or if it requires legislative action. The agency is weighing the issue.[8] The proposal has been compared to orphan drug provisions where rare diseases are sometimes approved based on clinical data for small groups of patients.[9] The FDA has the authority to accelerate drug approval and some flexibility in applying statutory requirements when the entire patient population has serious unmet needs.[10] However, the FDA has not established a drug development pathway for subpopulations with serious or life-threatening infections within a broader patient group.

In addition to these policy questions, other issues are unresolved, including the feasibility of a limited population pathway from the implementation, business and clinical perspectives.

Conference Discussion Guide

Pew is hosting this conference to advance the concept of a limited population pathway for antibiotic approval and explore its merits from the business and public health perspectives. With stakeholders, we hope to address the questions below and craft solutions that will bring life-saving antibiotics to patients.

Questions for Regulators and Antibiotic Developers
 ➢ What is the limited population regulatory pathway?
 ➢ Why is this pathway needed from the regulator's perspective?
 ➢ What types of antibiotics may be approved under this pathway, and what would the drug labels indicate?
 ➢ What are the benefits and risks to a limited drug development pathway from a business perspective?
 ➢ How would antibiotics approved under this pathway be priced to make this a viable business model?
 ➢ How might this pathway impact business decisions and investments in antibiotic development?
 ➢ Would companies have an incentive to study limited population antibiotics for expanded indications when appropriate to do so from a public health perspective?
 ➢ Would limited population antibiotics differ from traditional approvals regarding marketing and promotion?
 ➢ How could drugs approved under this pathway be monitored to ensure they are being used in a manner consistent with the approved indication?

Questions for Healthcare Providers
 ➢ To what extent does the FDA-approved indication guide how a drug is used clinically? Would prescribers treat limited population antibiotic differently than other drugs?
 ➢ What factors would influence the availability and use of limited population antibiotics from the clinician and hospital perspective?
 ➢ Under what circumstances would limited population antibiotics be used? For example, would diagnostics be required or would these drugs be used after other treatments fail?
 ➢ What impact would this regulatory pathway have on special populations such as children?
 ➢ Limited population antibiotics may command premium pricing. What are the potential price sensitivities, if any, for hospital formularies and what level of evidence may be required for adoption and use of these products?
 ➢ How could drugs approved under this pathway be monitored to ensure that they are being used in a manner consistent with the approved indication?

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[7] Stephanie Beasley, "Woodcock Floats Obesity Drugs As Candidate For Limited Use Designation," *FDA Week*, March 16, 2012; Janet Woodcock, "Evidence vs. Access: Can Twenty-First-Century Drug Regulation Refine the Tradeoffs?," *Clinical Pharmacology & Therapeutics* 91, no. 3 (2012): 378-380, doi:10.1038/clpt.2011.337.
[8] Nanci Bompey, "FDA Mulls Ways To Move On LPAD Using Current Authority," *FDA Week*, October 4, 2012; "Creating an Alternative Approval Pathway for Certain Drugs Intended to Address Unmet Medical Need," *Federal Register* 78 FR (15 January 2013) p. 3005-3008.
[9] Anna Yukhananov, "Group asks FDA to treat superbugs like rare diseases," *Reuters*, March 8, 2012.
[10] Applications for FDA Approval to Market a New Drug, 21 C.F.R. 314 (2012); Licensing, 21 C.F.R. 601 (2012).

➢ What remedies could be instituted to curtail inappropriate use if necessary?

Questions for Payors
➢ Could insurers (e.g., via reimbursement policies) influence the use of limited population drugs? If so, how?
➢ Limited population antibiotics may command premium pricing. What are the potential price sensitivities, if any, and what level of evidence would insurers require to reimburse for the use of these products? Would they require diagnostics? Would they require evidence that limited population antibiotics are used only after other treatments have failed?
➢ How would the price, reimbursement and access to limited population antibiotics change if indications were expanded?
➢ What remedies could be instituted to curtail inappropriate use if necessary?

Hypothetical Drug Models for Reference

We prepared models to suggest the types of antibiotics that may be tested under a limited population development program. These are hypothetical, not based on any specific investigational drugs, and are intended simply as a discussion tool for this meeting. The models are based on a recently-published regulatory framework proposed by members of the pharmaceutical industry[11] and were refined with expert input.[12] We acknowledge limitations of our methods, particularly regarding the market estimates.

The proposed regulatory approval framework mentioned above consists of four levels or "tiers" of evidentiary data, bounded by "Tier A" requiring proof of effectiveness from two adequately powered large studies (perhaps over 1,000 patients total) to support each target disease and "Tier D" with approvals based on the "animal rule" for situations where human trials are impossible or unethical. Two additional levels provide a middle ground between the data collected under Tier A and D and potential options for developing limited population antibiotics. A "Tier B" approach may support approval of narrow-spectrum antibiotics with some activity against more common bacteria based on one large randomized controlled study of a specific disease and confirmatory data from small open-label trials of patients with a range of infections caused by uncommon or resistant pathogens. Under "Tier C," small, open-label studies and descriptive data (perhaps from less than 500 patients total) from patients with a range of infections (not just one disease) could support approval of antibiotics targeting serious or life-threatening resistant infections for limited populations with few or no other treatments options. Under this proposal, the appropriate tier is selected based on the unmet need for the antibiotic, followed by the strength of preclinical data and the feasibility of clinical trials. For example, a Tier C pathway may be appropriate for rare or uncommon infections where it would be difficult to recruit enough patients for a traditional drug development program.[11] Tier B and C labels would emphasize the risks and limitations of the small clinical datasets underpinning approval of the products and promote their appropriate use.

Scenario 1: Hypothetical Drug B is a drug based on the "Tier B" proposal. *The development goal under Tier B is to conduct feasible trials that focus on the drug's activity against resistant pathogens. Tier B includes one phase 3 trial that meets the current guidelines and statistical requirements for a single infection type, small prospective studies and descriptive data in a range of infections, and robust preclinical data. In this case, the drug candidate is a broad-spectrum IV drug that will be developed initially for a limited population of patients with*

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[11] John H. Rex et al., "A comprehensive regulatory framework to address the unmet need for new antibacterial treatments," *The Lancet Infectious Diseases* 12 (Jan 2013), doi:10.1016/S1473-3099.

[12] Additional recommendations for clinical trials include the European Medicines Agency guidance for testing antibiotics where only limited data can be generated and the Infectious Diseases Society of America's suggestions for organism-specific studies of drugs to treat resistant pathogens. European Medicines Agency, "Addendum to the note for guidance on evaluation of medicinal products indicated for treatment of bacterial infections (CPMP/EWP/558/95 REV 2) to address indication-specific clinical data," draft, March 2010, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2012/07/WC500129443.pdf; Infectious Diseases Society of America, "White paper: recommendations on the conduct of superiority and organism-specific clinical trials of antibacterial agents for the treatment of infections caused by drug-resistant bacterial pathogens," *Clinical Infectious Diseases* 55(8) (Aug 2012): 1031-46.

multidrug-resistant infections. Presumably, the labeled drug indications could be expanded based on additional data.

Drug B: Broad-spectrum IV drug initially developed for a limited population of patients with infections caused by multi-drug resistant strains of *Klebsiella pneumoniae*, *Escherichia coli*, or *Pseudomonas aeruginosa*.

Potential U.S. market: 75,000 multi-drug resistant hospital associated infections out of 500,000 total.[13]

Clinical Trials:
1) Phase 3 randomized, non-inferiority study (meeting standard requirements) against a comparator for treatment of Complicated Intra-Abdominal Infections. Expected enrollment of few patients with highly resistant infections. Efficacy analyses of test of cure in patients with confirmed bacterial pathogen.
2) Open-label studies of several conditions when multi-drug resistant *Enterobacteriaceae* species or *Pseudomonas* is suspected or proven.
3) Other studies: Phase 1 trials; preclinical microbiology data; animal safety data; animal infection models for efficacy exposure range.

Analyses would include about 500 patients treated with Drug B and a safety database of 700 across studies.

Projected R&D budget: <$150 million for preclinical-Phase 3 program.

Label: Drug B has been approved for use in a limited population of patients with serious or life-threatening infections where few alternatives are available. The safety and efficacy of the drug has not been established beyond this limited population.

Drug B is indicated for the treatment of Complicated Intra-abdominal Infections (cIAI) proven or suspected to be caused by Drug B-susceptible strains of *Klebsiella pneumoniae*, *Escherichia coli*, or *Pseudomonas aeruginosa*. It was studied in a single trial for patients with cIAI and is only indicated where other therapy is not available or inappropriate (because of resistance, for example).

Drug B is indicated for the treatment of Hospital Acquired Bacterial Pneumonia, Ventilator Associated Bacterial Pneumonia and Complicated Urinary Tract infections proven or strongly suspected to be caused by Drug B-susceptible strains of *Klebsiella pneumoniae*, *Escherichia coli*, or *Pseudomonas aeruginosa*. Drug B was studied in a very limited number of patients with these conditions. Assessment of efficacy was based in part on attaining drug levels associated with therapeutic effect in cIAI and animal models of infection. Drug B is only indicated in situations where other therapy is not available or inappropriate.

Projected pricing: $2,000 to $10,000/10-20 day course

Scenario 2: Hypothetical Drug C is a drug based on the "Tier C" proposal. *The tier C approach may be suitable in situations where a typical phase 3 study is not feasible, for example, due to the number of patients needed to ensure an adequate study population. The development goal is to treat infections caused by resistant strains of the target pathogen. This approach relies on small prospective studies and descriptive data focused on specific pathogens in a range of infections. In this case, the drug candidate is a narrow-spectrum IV drug with activity limited to Pseudomonas aeruginosa.*

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[13] The number of hospital acquired *Klebsiella pneumoniae*, *Escherichia coli*, or *Pseudomonas aeruginosa* infections was estimated based by multiplying the reported number of hospital acquired infections (1.7 million according to Klevens RM, Edwards JR, Richards CL, Jr., et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. *Public Health Rep* 2007; **122**(2): 160-6) by the percentage of *Klebsiella pneumoniae*, *Escherichia coli*, or *Pseudomonas aeruginosa* isolates submitted to the US National Healthcare Safety Network between 2009-2010 (8%, 12% and 7.5%, respectively according to: Dawn M. Sievert et. al. Antimicrobial-Resistant Pathogens Associated with Healthcare-Associated Infections: Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. *Infection Control and Hospital Epidemiology*, 2013; 34(1): 1-14). The number of multi-drug resistant infections was assumed to be approximately fifteen percent (based on CDC estimates from 2008, http://www.cdc.gov/hai/organisms/gram-negative-bacteria.html).

Potential U.S. market: About 20,000[14] to 54,000[15] multi-drug resistant Pseudomonas infections out of about 136,000 to 540,000[13]cases total.

Clinical Trials:
1) Small, prospective, open-label, randomized study of Drug C against best comparator for treatment of *Pseudomonas* infections across sites (Hospital Acquired Bacterial Pneumonia, Ventilator Associated Bacterial Pneumonia, Complicated Urinary Tract Infections and Complicated Intra-abdominal Infections). Efficacy analyses focus on demonstration of numerically similar outcomes in patients with culture-proven *P. aeruginosa* at multiple infection sites showing a trend towards improvement (not statistical significance) with Drug C over the comparator.
2) Open-label, non-comparative study of Drug C for patients that cannot be enrolled in the first study and have few treatment options.
3) Observational study of (inadvertent) ineffective therapy for the target pathogen.
4) Other Studies: Phase 1 studies in healthy volunteers and special populations; preclinical microbiology data; animal safety data; animal infection models for efficacy exposure range.

Analyses would include about 300 patients treated with Drug C and a safety database of 400 across studies.

Projected R&D budget: <$100 million for preclinical-Phase 3 program.

Label: Drug C has been approved for use in a limited population of patients with serious or life-threatening infections where limited or no alternative therapies are available. The safety and efficacy of the drug has not been established beyond this limited population.

Drug C is indicated for the treatment of Hospital Acquired Bacterial Pneumonia, Ventilator Associated Bacterial Pneumonia, Complicated Urinary Tract Infections and Complicated Intra-abdominal Infections proven or strongly suspected to be caused by Drug C susceptible strains of *Pseudomonas aeruginosa*. Because data for drug C in these infections are limited, drug C should only be used if other alternatives are known or suspected to be less suitable.

Projected pricing: $15,000 to $30,000/10-20 day course

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[14] The number of hospital acquired *Pseudomonas* infections was estimated based by multiplying the reported number of hospital acquired infections (1.7 million according to Klevens RM, Edwards JR, Richards CL, Jr., et al. Estimating health care-associated infections and deaths in U.S. hospitals, 2002. *Public Health Rep* 2007; **122**(2): 160-6) by the percentage of *Pseudomonas* isolates submitted to the US National Healthcare Safety Network between 2009-2010 (7.5% according to: Dawn M. Sievert et. al. Antimicrobial-Resistant Pathogens Associated with Healthcare-Associated Infections: Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2009–2010. *Infection Control and Hospital Epidemiology*, 2013; 34(1): 1-14). The number of multi-drug resistant infections was assumed to be approximately fifteen percent (based on CDC estimates from 2008, http://www.cdc.gov/hai/organisms/gram-negative-bacteria.html).
[15] The methods and references for this estimate can be found here: Lew Barrett, "Antibiotic Markets and SPLU – Guest Blogger – Lew Barrett," *Antibiotics – The Perfect Storm* (blog), March 20, 2012, http://antibiotics-theperfectstorm.blogspot.com/2012/03/antibiotic-markets-and-splu-guest.html.