



# A New Pathway for Antibiotic Innovation

A Summary of a Conference on Exploring Drug Development for Limited Populations

## Conference overview

On Jan. 31, 2013, The Pew Charitable Trusts hosted a one-day conference, *A New Pathway for Antibiotic Innovation: Exploring Drug Development for Limited Populations*, in Washington, DC, to weigh the merits of a proposed regulatory pathway for antibiotics that target special or limited patient populations: those suffering from serious or life-threatening infections with few or no treatment options. The lack of new antibiotics over the past decade and the rise in resistance have rendered some infections untreatable. The limited population regulatory pathway promises to bring urgently needed medicines to the sickest patients by reducing some of the economic and regulatory barriers to antibiotic innovation. During the conference, about 100 attendees, including government officials, infectious disease physicians, public health specialists, pharmacists, pharmaceutical company representatives, and payors, addressed the various components of the pathway from their points of view.

The meeting was divided into three sessions, each followed by a round-table discussion. During the first session, panelists defined the limited population antibiotic pathway, weighing its potential merits from the health care, regulatory, and business perspective. The second session examined how drugs approved under this pathway might be managed and monitored in various health care settings. In the third session, speakers and panelists explored the roles that payors and reimbursement policies might play in ensuring that limited population antibiotics are used only by patients who need them—those for whom the benefits of the drugs outweigh the potential risks.

Some general themes emerged:

- Payors, health care providers, and pharmaceutical companies generally supported the concept of a limited population regulatory pathway.
- The pathway could increase the feasibility and lower the costs of clinical trials for high-need antibiotics.
- Limited population antibiotics probably would command premium pricing, which could provide a reasonable return on investment for antibiotic developers.
- Premium pricing could ensure that limited population antibiotics are not used indiscriminately, thus preserving the effectiveness of these critical drugs over time.
- A special designation or labeling alone will not curtail unnecessary use of the limited population antibiotics but could signal that these drugs are different from other antibiotics and should be treated accordingly.
- No one called for strict restrictions or penalties on the use of limited population antibiotics, but all participants agreed that stewardship, or proper management, and data-driven use of these drugs would be important for success of the pathway.
- Certification or prequalification may be a way to curtail unnecessary use of limited population antibiotics.
- Monitoring of use will be important for patient safety and perhaps evaluation of antibiotics approved under this pathway.
- Payors probably will reimburse for limited population drugs used in the hospital in the same manner as other drugs, so the extra cost burden of premium pricing may fall on hospitals or patients.
- Payors may desire patient outcome data to support the use and to justify the cost of limited population antibiotics.

# Limited population approval pathway

## Background

As antibiotic-resistant bacterial infections grow 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, and some infections are now untreatable.<sup>1</sup>

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<sup>2</sup> and the President's Council of Advisors on Science and Technology<sup>3</sup> have proposed a regulatory pathway for antibiotics that target special or limited patient populations: those suffering from serious or life-threatening infections with few or no treatment options. The U.S. Food and Drug Administration, or FDA,<sup>4</sup> health professionals,<sup>5</sup> and several companies<sup>6</sup> 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 drugmakers test treatments in 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 that are needed 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 health care 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 foster judicious use and bolster antibiotic stewardship efforts.

An important assumption behind the special labeling of products approved via the proposed pathway is that it would effectively limit use to those for whom the benefits of the antibiotic exceed the risks of potential side effects. Currently, 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. The President's Council of Advisors on Science and Technology and FDA<sup>7</sup> emphasize that the broader health care community, including patients, providers, and payors, would play a role in limiting use of the drugs to patients with acceptable risk. Presumably, approval could be broadened with additional safety and effectiveness data at a later date, if warranted.

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

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

The conference, *A New Pathway for Antibiotic Innovation: Exploring Drug Development for Limited Populations*, was convened 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 strove to address the questions below and craft solutions that will bring lifesaving antibiotics to patients.

### Questions for regulators and antibiotic developers

- What is the limited population regulatory pathway?
- Why is this pathway needed from the regulators' perspective?
- What types of antibiotics may be approved under this pathway and what would the drug labels indicate?
- What are the benefits and risks of 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 affect 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 health care providers

- To what extent does the FDA-approved indication guide how a drug is used clinically? Would prescribers treat limited population antibiotics differently from 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?
- 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 can health care practitioners ensure drugs approved under this pathway are being used in a manner consistent with the approved indication?
- 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 of, reimbursement for, and access to limited population antibiotics change if indications were expanded?
- What remedies could be instituted to curtail inappropriate use if necessary?

The conference was organized into the following three sessions, each of which concluded with a round-table discussion including audience input:

- Session One: Defining the Limited Population Regulatory Pathway: What It Is, What It Does, and Why It Is Needed.
- Session Two: Forging a Societal Compact: Perspectives on How to Ensure Antibiotics Approved Under This Pathway Are Used in a Limited Population.
- Session Three: Lessons Learned, Unanswered Questions, and Charting the Path Forward.

There was much overlap between sessions because the concepts covered are interrelated. Instead of presenting material in chronological order, we synthesized the day's conversation below, organized by topic area.

## Overview of the day's discussions

The conference sessions were moderated by Allan Coukell, Pew's senior director of drug and medical device initiatives.

### The limited population antibiotic pathway: What it is and why it is needed

Robert Guidos, vice president of public policy and government relations for the Infectious Diseases Society of America, began the meeting by describing the limited population regulatory pathway that his organization first proposed in 2012, and the reasons it is needed. He noted that the number of new antibiotics coming to market plummeted over the past decade as resistant infections rose to the point where some are now untreatable.

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Most large pharmaceutical companies also abandoned antibiotic development over that time because of regulatory uncertainty, Guidos said, citing this as proof that more feasible FDA approval pathways are needed. Although he acknowledged that FDA's essential role is to ensure Americans have safe and effective drugs, he concluded that the agency's assessment of benefit versus risk for patients with the most serious infections has been out of balance for some time.

According to Guidos and other panelists, it is nearly impossible to study antibiotics for highly resistant infections in traditional, large-scale clinical trials because of the small number of patients with these serious infections. Under the limited population antibacterial drug pathway, antibiotics would be tested in smaller clinical trials of people with few or no other treatment options. These patients could tolerate more uncertainty about potential side effects of new drugs compared with those who have milder, treatable infections. Products approved under this pathway would be narrowly indicated for use in patients for whom the drugs' benefits have been shown to outweigh the risks, Guidos explained.

## Distinguishing limited population drugs from other antibiotics: Special labeling and premium pricing

Limited population antibiotics would come with a special label putting the health care community on notice about the clinical evidence supporting the use of these drugs, a valuable distinction that would encourage their appropriate use, according to Guidos. But he pointed out that although FDA will play an important role in ensuring that a drug's labeling is informative enough to guide physicians, the agency "will not have a role in authorizing or prohibiting use of approved products within the practice of medicine." Other panelists concurred, stressing that strict restrictions or penalties for off-label use of limited population antibiotics would harm patients and that some scientifically driven empirical use would be acceptable, particularly since few rapid diagnostics exist to identify pathogens quickly, and because the timing of treatment is critical to patients' health.

Some panelists, including Kavita K. Trivedi, a medical epidemiologist with the Healthcare Associated Infections Program for the California Department of Public Health and lead of the California Antimicrobial Stewardship Program Initiative, raised doubts that labeling alone would discourage indiscriminate use of limited population antibiotics. "We have ample evidence that physicians do not read labels," she said. Pranita Tamma, director of pediatric antimicrobial stewardship at Johns Hopkins Hospital, agreed, saying physicians are generally not aware of labeled indications regarding age restrictions, body size for intended use, and other factors. "In pediatrics ... about 80 percent of our drug use is used off-label," she explained. Guidos said there would have to be a comprehensive education program associated with limited population antibiotics to let doctors know that the drugs are different and should be treated accordingly. He envisions FDA, the Centers for Disease Control and Prevention, or CDC, the public health community, and the American Medical Association working together to educate health care providers.

Guidos speculated that a number of factors beyond labeling and education programs such as liability concerns would deter physicians from the unnecessary prescribing of limited population antibiotics. By limiting the potential market, narrow indications would also set the stage for premium pricing, reflecting the lifesaving value of the most urgently needed antibiotics. High pricing could in turn help curb the use of limited population antibiotics. Attendees discussed throughout the conference ways to manage and monitor limited population antibiotics.

## Antibiotic development: Keeping up with resistance and patient needs

Building on many of the themes Guidos introduced, Edward Cox, director of FDA's Office of Antimicrobial Products in the Center for Drug Evaluation and Research, provided a historical perspective on antibiotic development, explaining how some infections have become untreatable because of resistance. "If we look at the last five to 10 years, the number of antibacterial drugs reaching approval has decreased significantly," Cox noted. The pipeline has been faltering since the 1990s, he said, but concerns regarding the clinical development of telithromycin, a broad-use oral antibiotic approved by FDA in 2004, caused controversy and uncertainty, further destabilizing the field.

Today there is an urgent need for new antibiotics for patients with few or no available treatment options in order to avoid a situation Cox described as “similar to the pre-antibiotic era.” For many years, he said, the goal of antibiotic makers was to develop drugs for broad use in a variety of different infections. The resulting clinical trials were very large, because the benefit-versus-risk calculation for these drugs needed to account for the full spectrum of patients who might take them—those with mild as well as severe conditions. Although many antibiotics studied this way are still in use, some are not because of serious adverse events detected after the drugs were marketed. The risks might be acceptable for patients with no other options, but not for the broad population of patients for whom the drugs were indicated. According to Cox, the “practical reality of antibacterial drug development based on large development programs that we have seen in the recent past [is] simply not a sustainable model for antibacterial drug development.” Over the past decade, the degree of innovation has not kept up with resistance or patient needs, he explained.



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Edward Cox, Director, FDA Office of Antimicrobial Products

According to Cox, a limited population development pathway could bring urgently needed treatments to market, and companies have expressed renewed interest in developing antibiotics since the concept was first described in 2012. Although he would not offer an opinion on how a limited population regulatory pathway should be implemented, Cox said it would be very important for the field to put something in place quickly. He also noted that FDA rulemaking is a long process. During the question-and-answer period, Cox also emphasized that the regulatory standards of approval would not be lowered under a limited population regulatory pathway and that the same requirement for substantial evidence of safety and effectiveness exists for all drugs approved by FDA. What would be different, he stressed, is the benefit-risk assessment of these products, which would be targeting patients considered to have an “unmet need”: few or no treatment options.

Throughout the day, several panelists urged that careful consideration be given to the definition of unmet need. During the question-and-answer session after the first panel, Cox indicated that there could be reasons beyond resistance that patients require new options to treat infections, such as contraindications to conventional antibiotics because of allergy. John H. Rex, vice president and head of infection development, global medicines for AstraZeneca Pharmaceuticals LP, said any definition of unmet need should include the “absolute requirement” for diversity in antibiotics. “It is really important that we permit drug number two, number three, and number four to get invented,” he explained, “because without that diverse, vibrant pipeline, we will never make it.”

In Cox’s opinion, regulatory approval of limited population antibiotics is not the only goal of this pathway. Getting these drugs to the right patients would be critical from a safety and public health point of view. “A lot of this will be dependent upon the engagement of the health care community to facilitate the appropriate use of these products,” emphasized Cox, adding that payors and health care providers need to be involved in the management and monitoring of limited population antibiotics.

## Makings of a limited population antibiotic: Hypothetical drug models provide frame of reference

After the introductory remarks of Guidos and Cox, Nicole Mahoney, senior officer of antibiotics and innovation at Pew, provided two hypothetical drug models as examples of the types of antibiotics that might be approved under a limited population regulatory pathway. These models included a description of each drug, the target patient population, the potential clinical development program to support approval, the associated costs, and anticipated pricing for the drugs. The hypothetical antibiotics were based on a recently published regulatory framework proposed by members of the pharmaceutical industry and refined based on stakeholder discussions (see Appendix C for more details).<sup>11</sup>

The first drug presented was a broad-spectrum intravenous product for patients with multidrug-resistant strains of *Klebsiella pneumoniae*, *Escherichia coli*, or *Pseudomonas aeruginosa*, a potential total of 75,000 hospital-associated infections. It would be approved for a single infection type based on one Phase 3 clinical trial, small prospective studies, descriptive data in a range of infections, and robust preclinical data. Clinical analyses would include about 500 patients treated with the drug. The second hypothetical drug was for multidrug-resistant *Pseudomonas* infections, estimated to occur in about 10,000 to 54,000 U.S. patients. This antibiotic could be approved based on small prospective studies and descriptive data; a typical Phase 3 study would be infeasible because of the small size of the patient population. Analyses would include about 300 patients treated with the drug. The estimated pricing was much higher than for traditional antibiotics, at \$2,000 to \$10,000 and \$15,000 to \$30,000 for a 10- to 20-day course of hypothetical drugs one and two, respectively (see Appendix C).

The takeaway from the models was that limited population antibiotics would be approved based on less evidence than that required for antibiotics meant for broad populations, and that they probably would command premium pricing. During the question-and-answer session, the industry panelists concurred with the price range Mahoney assigned to the hypothetical drugs, recognizing that they would be more expensive than traditional antibiotics. "I think that it is entirely logical that if you are willing to spend \$15,000 for an antineoplastic that would prolong your life 15 months, that you would spend \$15,000 for an anti-infective that would give you back 60 years of life," Rex said.

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**A limited population approval pathway could help bring high-need antibiotics to market if it lived up to its promise of making clinical testing more feasible.**

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## Benefits and risks from the business perspective: Regulatory uncertainty, pricing, and reimbursement

Drugmakers at the conference said a limited population approval pathway could help bring high-need antibiotics to market if it lived up to its promise of making clinical testing more feasible, less expensive, and perhaps faster than under existing programs. If the pathway achieved these goals, it would provide a valuable incentive for companies that otherwise would be discouraged by challenging clinical trial requirements, lengthy testing timelines, and other factors. Unanswered regulatory questions about the pathway cause concern for drugmakers, who said they do not fully understand the scope of data and types of clinical trials that would be required. According to Christine Welch, vice president for regulatory affairs with Achaogen Inc., a clear regulatory mechanism is crucial for small companies trying to raise capital. "I would find it very difficult today and challenging to persuade investors that we can obtain regulatory approval with small descriptive studies," she said. Achaogen announced plans to conduct a superiority study in patients with highly resistant infections to support approval of one of its new investigational antibiotics.

Clinical development programs are not the only regulatory consideration. Michael N. Dudley, senior vice president for research and development and chief scientific officer of Rempex Pharmaceuticals Inc., emphasized that the regulatory review of chemistry and manufacturing would have to occur within a similar time frame as the clinical safety and effectiveness review in order for the pathway to work from a practical standpoint. “The limited development programs that we are talking about in terms of clinical development place manufacturing activities squarely on the critical path,” he explained. The same is true for the review of automated antibiotic susceptibility tests and associated lab equipment used in hospital laboratories. Although these tests guide antibiotic use by helping doctors predict whether a particular drug will treat an infection effectively, their FDA approval often lags behind new antibiotic approval. According to Dudley, without automated susceptibility tests, some hospitals will not allow new antibiotics on the formulary.

When drug developers contemplate strategies to develop new products, pricing and reimbursement are at the forefront of their minds. In the past, companies had an incentive to sell as much of a drug as possible, but conference participants, including those from industry, acknowledged that this approach is at odds with what is good for society—namely preserving antibiotic effectiveness over time. “This is a classic example of a market failure where it requires an intervention and a new financing model to protect the nation’s long-term health,” said Dudley, whose company is exploring policy solutions that break the link between revenue and the volume of antibiotics sold and introduced one such idea at the conference.<sup>12</sup>

Panelists at the conference generally agreed that the narrow market established by the limited population pathway sets the stage for premium pricing for antibiotics, possibly as much as \$15,000 to \$30,000 per course, as Mahoney proposed. Although the proposed prices are considerably higher than those associated with traditional antibiotics, some argued that they properly represent the lifesaving value of high-need antibiotics and align better with stewardship goals. But drugmakers expressed concern about whether payors would reimburse adequately for limited population antibiotics, particularly in the hospital setting, where they probably would be used most.

Medicare, with 50 million beneficiaries and centralized decision-making, is often used as a baseline for coverage by private payors, according to James Scott, president and CEO of Applied Policy LLP, a health policy and reimbursement consulting company in Alexandria, VA. In the hospital setting, Medicare does not cover costs for specific drugs, instead reimbursing based on diagnosis-related groups, or DRG, that are adjusted according to disease severity. DRG payments “are calculated based on the resources the hospitals presumed to have used to treat a patient of that type,” said Scott. Private payors reimburse using similar mechanisms. The DRG is based on the average cost of care for patients with a particular diagnosis—pneumonia, for example—and does not always reflect higher costs of new technologies, especially during the first two or three years after product launch. To address this deficiency, Medicare created a “new technology add-on payment,” or nTAP, for new drugs and devices with demonstrated value, providing additional reimbursement for a set time period—usually two or three years after market introduction. Scott explained that nTAP could help cover the higher price of limited use antibiotics and should be considered as part of the business strategy for bringing them to market.

Panelists also explored whether reimbursement coverage decisions would affect the prescribing of limited population antibiotics. Some, including FDA and the Infectious Diseases Society of America, have suggested that payors might have a role to play in ensuring that limited population antibiotics are used only in those who truly need them. Payors at the conference emphasized that Medicare and private insurance plans probably would cover limited population antibiotics—even considering the high prices the drugs may command—although, as mentioned above, reimbursement may not pay the full price of the drug in every setting. Like other conference

participants, payors said they recognize that timing is critical for patients with serious infections and that physicians need to treat them quickly. “From the standpoint of being a payor, I do not think we want to get in the way of that,” said H. Eric Cannon, chief of pharmacy at SelectHealth and a director with the Academy of Managed Care Pharmacy. Payors at the conference pointed out that if they wished to manage limited population antibiotic use, they have more tools at their disposal in the outpatient versus inpatient setting, including prior authorization, because drugs are not selectively reimbursed in hospital claims.

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## The narrow market established by the limited population pathway sets the stage for premium pricing for antibiotics.

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Despite the reluctance, the Centers for Medicare & Medicaid Services, or CMS, could use existing authority to influence antibiotic use in hospitals, Scott said. Three mechanisms the agency could employ are national coverage determinations, conditions of participation, and quality measurement programs. Scott deemed national coverage determinations (of whether a service is reasonable or necessary) for antibiotics the least likely tool that CMS might use. He noted that the agency could require antibiotic stewardship programs as a mandatory condition of Medicare participation and that such a requirement could affect the management of limited population antibiotics. The weakness in this approach, he noted, is that CMS would simply verify that facilities had an antibiotic management or stewardship program in place but would not necessarily determine its quality or effectiveness. Potentially more effective are quality measures under the hospital inpatient quality-reporting program, which CMS has already used for antibiotics, according to Scott. Quality measures are developed by professional societies and validated before being adopted by CMS. Although such programs are technically voluntary, hospitals’ Medicare payments are reduced 2 percent across the board if they do not comply with quality measures, he said.

Price was not likely to affect coverage decisions, according to payors at the conference, because by definition, limited population antibiotics would target patients with few or no other treatment options. Furthermore, Medicare, which is expected to be a major payor for limited use antibiotics, is somewhat insensitive to drug price, according to Scott. And although price is a factor in reimbursement decisions of private insurers, it is only one of many that are considered, often after demonstration of benefit. However, the private insurers at the meeting acknowledged that they have a fiduciary responsibility to their clients and said that as health care costs rise, drug pricing may be scrutinized more.

Cannon said the design of benefits is changing so that patients may pay higher deductible and out-of-pocket expenses than in the past. Previously, providers in a hospital would assume drug costs would be fully covered. “In the new world, yes, it will be covered, but the patient may have a \$6,000 or a \$10,000 responsibility that they have to pay,” according to Cannon. The result is an increase in bad debt, which may cause insurers to put systems in place to manage drugs. Insurers are not opposed to high-priced drugs, said Cannon. But along with that, there needs to be some clear education about the benefits of the drug: a) there is no alternative antibiotic; b) patients will be discharged from the hospital quicker; and c) the likelihood of readmission is greatly reduced, he said. He also emphasized the need for continuity in coverage across health care settings, because although limited population antibiotics would probably be administered in the hospital initially, some patients may need to continue therapy after discharge. Reimbursement and patient copays differ between inpatient and outpatient settings.

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## Health outcomes and value of limited population antibiotics should be measured.

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Saira A. Jan, director of clinical pharmacy management with Horizon Blue Cross Blue Shield of New Jersey and a clinical professor at Ernest Mario School of Pharmacy at Rutgers, the State University of New Jersey, concurred. She noted that when deciding whether to include new drugs on their formularies, insurance plans evaluate both FDA approval data and insurance claim-based data provided by covered facilities for information on patient outcomes. Payors at the conference indicated that health outcomes and value of limited population antibiotics should be measured (with data such as length of stay, days on ventilator, or readmission rates), but there was no consensus on what to collect or how the information would factor into reimbursement decisions. Jan said she believes that pharmaceutical companies could play a role in collecting outcomes data through collaborations with health care facilities and that industry's role has evolved over the years. "It is not just identifying a product and launching the product, but also managing the life cycle of the product and seeing how it is being used in order to ensure that the product survives the life span," she said. Although the private payors do not expect limited population drugs to be cost saving, they do anticipate some level of cost-effectiveness. Medicare is more interested in patient outcomes and not necessarily cost, according to Scott, because under current law, "CMS does not consider cost in determining whether or not a treatment is medically necessary." Scott suggested that companies build observational outcomes into clinical trials as part of any drug development program.

## Health care providers: Their role in the management of limited population antibiotics

Discussion at the conference indicated that much of the management of limited population antibiotics would fall on health care providers and less on payors. Some participants said they believe that premium pricing would discourage unnecessary inpatient prescribing because it could increase costs to hospitals and possibly patients based on the fact that claims are paid at a set rate based on the DRG. The discussion proceeded under the general assumption that the cost of a course of treatment with a limited population antibiotic would start at about 10 times more than existing antibiotics. It is not clear whether a less marked price difference would remove the impetus to avoid routine first-line use of these drugs. The price of antibiotics has generally gone down in recent years, because few new antibiotics have been approved, and the commonly prescribed drugs are generics. Because of this trend, "adding a new, very expensive class of drugs will clearly be a culture shock for institutions," said Steven C. Ebert, clinical manager at Meriter Hospital and clinical professor of pharmacy at the University of Wisconsin, Madison. Hospitals have assumed the cost of high-priced cancer drugs and antivirals, panelists noted, but these drugs were also managed through carefully constructed guidelines and, in some cases, prior authorization. While acknowledging that antibiotics are different in that they must be administered quickly, and therefore some empirical use would occur, Ebert said: "With these high-cost antibiotics, I think there is going to be an enhanced need to require some type of documentation of the need to initiate or to continue those particular agents."

Those involved in stewardship programs, however, were skeptical that price alone would affect use, pointing to difficulties in managing traditional antibiotic use across health care settings, especially long-term care facilities. According to Tamma, "most physicians are unaware of the cost of drugs." From her perspective, good stewardship programs, in addition to price, could be a powerful deterrent to unnecessary use. Stewardship, she said, "involves someone or a group of people, often pharmacists and physicians working together closely with clinicians, to optimize the selection, the dose, the route, and duration of antibiotics as well as being cognizant of adverse drug events that can occur with antibiotics."

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## Stewardship programs, in addition to price, could be a powerful deterrent to unnecessary use.

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According to Tamma, physicians and pharmacists at her hospital work together to select appropriate antibiotics for patients on a case-by-case basis, reassessing appropriateness of the treatment after 48 or 72 hours based on available microbiology data and clinical information. At that time, they could decide to discontinue treatment or switch to a different antibiotic. She said a similar approach could be taken for the management of limited population antibiotics, and that, without such a system, these drugs may be overprescribed and misused. Ebert pointed out, however, that in some cases, a lack of clear microbiology data would make it difficult to justify de-escalation of antibiotic therapy—for example, in a case where a patient had a severe infection but a culture was negative. Even when cultures confirm that a patient is infected with a pathogen that is susceptible to conventional antibiotics, it may be hard to persuade doctors to make a switch, he said.

Effective stewardship of limited population antibiotics at the facility level would require a broad, multi-stakeholder strategy, including input from formulary committees, according to Ebert and Matthew Bidwell Goetz, chief of infectious diseases for the Veterans Affairs Greater Los Angeles Healthcare System and a professor of clinical medicine at the David Geffen School of Medicine at the University of California, Los Angeles. They said such committees generate treatment guidelines and protocols to inform the appropriate use of antibiotics. They may face challenges in setting guidelines for limited population antibiotics, in part because they lack rapid diagnostics to pinpoint the cause of infections in most cases, but they could review and revise them based on outcomes reported at their facilities.

Panelists proposed other management tools for consideration: aggressive education of all health care stakeholders, including the full range of potential prescribers, pharmacists, hospital administrators, and patients; consent forms; and precertification of institutions where drugs approved through the pathway would be prescribed.

### Tracking use of limited population antibiotics: Informing stewardship and assessing the pathway

Ebert and Goetz noted the value of monitoring the use of limited population antibiotics to help inform stewardship efforts. Monitoring could also help FDA and others assess the utility of the limited population regulatory pathway and the way antibiotics approved in this manner are used in practice. Conference participants outlined several potential systems to track use of the drugs. Registries were suggested as a viable option, but high costs were a concern from the pharmaceutical company perspective, and panelists noted that these systems are also expensive for hospitals. The FDA Sentinel reporting system was mentioned as a potential mechanism for monitoring adverse events linked to limited population antibiotics, but this might be a general indicator of usage patterns and not a tool that institutions could employ to benchmark use. Finally, electronic health records and the CDC's National Healthcare Safety Network antibiotic usage module were discussed as potential tools for tracking antibiotic usage, although neither of these tools has been widely adopted.

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Monitoring could also help FDA and others assess the utility of the limited population regulatory pathway and the way antibiotics approved in this manner are used in practice.

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## Lessons learned, unanswered questions, and charting the path forward

Coukell began the third and final session of the conference by asking three rapporteurs whether the conference made the limited population regulatory pathway concept clearer and whether important questions remain.

Mahoney reiterated that Pew's interest was to determine whether the limited population regulatory pathway seemed feasible from a business and public health perspective and concluded that it could help bring high-need antibiotics to market if outstanding questions were addressed. She explained that to gauge the potential return on investment, businesses and their investors need clarity on the types of clinical trials that may be required under the pathway and the level of reimbursement that might be expected for limited population antibiotics. Businesses are also concerned about "how much time it would take to implement something like this," whether by legislative or regulatory means, and "that should be a consideration moving forward," she said.

Mahoney emphasized that the trade-off for an expedited approval pathway is that limited population antibiotics would not be used broadly, but acknowledged that the drugs might be used as first-line therapy in some cases. "One thing that came across loud and clear is that penalties for off-label use is probably not a decent solution and that there has to be some flexibility in rational use of limited pathway antibiotics," she said. Health care providers could ensure proper stewardship of critical antibiotics, curtailing use when necessary based on microbiology data, she said.

John Powers, associate clinical professor of medicine at George Washington University and the University of Maryland School of Medicine, advised that stakeholders assess how the limited population pathway fits with existing regulatory pathways such as accelerated approval and emphasized the need for clear definitions of terms such as "risk," "serious," and "life-threatening." He cautioned that FDA should carefully consider the amount of evidence it will require for approval of antibiotics under this pathway. "It seems to me pretty inherently logical that one cannot have a lifesaving drug if the drug is not demonstrated to save lives," he said. Demonstrating an impact on morbidity or mortality, according to Powers, "really justifies going down this pathway in the first place, and that defines the benefit that the payors are looking for in terms of justifying a cost."

Powers also stressed the need for good diagnostics in developing limited population antibiotics and for limiting their usage by practitioners who are accustomed to empirical therapy. He speculated that companies might not have incentives to develop diagnostics for fear of losing market share but said alternative business and reimbursement models could improve the situation.

David M. Shlaes, owner of Anti-Infectives Consulting LCC, acknowledged that there is "a disconnect between a limited antibiotic development label and pathway and empiric use." But this is true for all antibiotics, for which 80 percent of use in the hospital is empirical, he said. Shlaes emphasized that physicians would prescribe limited use antibiotics when local epidemiological data or other information warranted. Still, he said, limited population antibiotics fit the basic tenets of stewardship programs better than traditional antibiotics, and he called the high price a "self-policing policy" that would result in increased scrutiny on prescribing and discourage use of these drugs. Finally, Shlaes stressed the need for data mining and predictive modeling as well as prospective observational studies to provide outcomes data for payors on the potential benefits of limited population antibiotics.

# Appendix A

## Agenda

Jan. 31, 2013  
The Pew Charitable Trusts  
901 E St. NW, 10th Floor  
Carolinas Room  
Washington, DC 20004

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- 8-8:30 a.m.                      **Registration and continental breakfast**
- 8:30-8:45 a.m.                      **Welcome and introduction**  
**Moderator:** Allan Coukell, senior director, drugs and medical devices,  
The Pew Charitable Trusts
- Session 1:                              **Defining the limited population regulatory pathway: What it is, what it does,  
and why it is needed**
- 8:45-9:45 a.m.                      **Presentations**
- **Robert Guidos**, J.D., vice president, public policy and government relations, Infectious Diseases Society of America.
  - **Edward Cox**, M.D., M.P.H., director, office of antimicrobial products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration.
  - **Nicole Mahoney**, Ph.D., senior officer, antibiotics and innovation, The Pew Charitable Trusts.
  - **John H. Rex**, M.D., FIDSA, FACP, vice president and head of infection development, global medicines, AstraZeneca Pharmaceuticals LP.
  - **Michael N. Dudley**, Pharm.D., FIDSA, senior vice president, research and development, and chief scientific officer, Rempex Pharmaceuticals Inc.
  - **Christine Welch**, M.S., RAC, vice president, regulatory affairs, Achaogen Inc.
- 9:45-10:25 a.m.                      **Expert round-table discussion (moderated)**  
Discussion questions
- 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 of 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 affect 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?

10:25-10:45 a.m.

Q & A (audience)

10:45-11:00 a.m.

Coffee break

Session 2:

**Forging a societal compact: Perspectives on how to ensure antibiotics approved under this pathway are used in a limited population**

Part 1:

**Role of health care providers and institutions in use of limited population antibiotics**

11:00-11:40 a.m.

**Presentations**

- **Matthew Bidwell Goetz, M.D.**, chief of infectious diseases, Veterans Affairs Greater Los Angeles Healthcare System; professor of clinical medicine, David Geffen School of Medicine at UCLA.
- **Steven C. Ebert, Pharm.D., FCCP, FIDSA**, clinical pharmacy specialist, clinical manager, Meriter Hospital; clinical professor of pharmacy, University of Wisconsin, Madison.
- **Kavita K. Trivedi, M.D.**, medical epidemiologist, Healthcare Associated Infections Program and lead, California Antimicrobial Stewardship Program Initiative, California Department of Public Health.
- **Pranita Tamma, M.D., M.H.S.**, director of pediatric antimicrobial stewardship, Johns Hopkins Hospital.

11:40 a.m.-12:20 p.m.

**Expert round-table discussion (moderated)**

Discussion questions

- To what extent does the FDA-approved indication guide how a drug is used clinically? Would prescribers treat limited population antibiotics differently from 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?
- What remedies could be instituted to curtail inappropriate use if necessary?

12:20-12:40 p.m.

Q & A (audience)

12:40-1:40 p.m.

Lunch, Café 9, ninth floor (provided)

Part 2:

Role of payors in use of limited population antibiotics

1:40-2:10 p.m.

Presentations

- James Scott, J.D., president and CEO, Applied Policy LLP.
- Saira A. Jan, M.S., Pharm.D., director of clinical pharmacy management, Horizon Blue Cross Blue Shield of New Jersey; clinical professor, Ernest Mario School of Pharmacy, Rutgers, the State University of New Jersey.
- H. Eric Cannon, Pharm.D., FAMCP, chief of pharmacy, SelectHealth; director, Academy of Managed Care Pharmacy.

2:10-2:50 p.m.

Expert round-table discussion (moderated)

Discussion questions

- 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?

2:50-3:10 p.m.

Q & A (audience)

3:10-3:20 p.m.

Coffee break

Session 3:	Lessons learned, unanswered questions, and charting the path forward
3:20-4:20 p.m.	<b>Rapporteur summaries</b> <ul style="list-style-type: none"><li>• <b>Nicole Mahoney, Ph.D.</b>, senior officer, antibiotics and innovation, The Pew Charitable Trusts.</li><li>• <b>John Powers, M.D., FACP, FIDSA</b>, associate clinical professor of medicine, George Washington University School of Medicine and University of Maryland School of Medicine.</li><li>• <b>David M. Shlaes, M.D., Ph.D.</b>, owner, Anti-Infectives Consulting LLC.</li></ul>
4:20-4:30 p.m.	<b>Wrap-up</b>
4:30-6:30 p.m.	<b>Reception, Café 9, ninth floor</b>

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## Appendix B

### Speaker biographies

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#### **H. Eric Cannon, Pharm.D., FAMCP**

Director, Academy of Managed Care Pharmacy

Chief of Pharmacy, SelectHealth

H. Eric Cannon is chief of pharmacy for SelectHealth, an Intermountain Healthcare company, and has responsibility for SelectHealth Prescriptions, a full-service pharmacy benefit management group.

Dr. Cannon has worked in pharmacy for more than 20 years, with experience in hospital, retail, long-term care, and home health settings. He is an active member of the Academy of Managed Care Pharmacy, where he has chaired the legislative committee and serves on the board of directors. Dr. Cannon is on the board of directors for the Utah Lung Association. He was recently awarded the recognition of fellow of the Academy of Managed Care Pharmacy.

At SelectHealth Prescriptions, Dr. Cannon works to develop, implement, and administer many first-of-their-kind programs to improve clinical quality, control costs, and optimize outcomes in the Intermountain system. He has published numerous articles and research studies in peer-reviewed literature, and has been involved in projects to reduce medication errors and adverse events. Dr. Cannon served on the Institute of Medicine of the National Academies Committee, Preventing Medication Errors. He received his Doctor of Pharmacy degree from Idaho State University.

#### **Allan Coukell, B.Sc.Pharm.**

Senior Director, Drugs and Medical Devices

The Pew Charitable Trusts

Allan Coukell oversees medical programs, including The Pew Charitable Trusts' prescription project, the drug safety project, the antibiotics and innovation project, the medical device initiative and innovate FDA, and other activities related to medical products and services.

Mr. Coukell practiced as a clinical pharmacist in oncology at the Victoria Hospital and London Regional Cancer Center in London, Ontario, and served subsequently as a senior medical writer and editor with Adis International, publisher of the peer-reviewed journals *Drugs*, *Drugs & Aging*, and *PharmacoEconomics*, among others. He also spent a decade in journalism and received an Edward R. Murrow Award for hard news reporting.

Mr. Coukell serves as the consumer representative on the FDA Cardiovascular and Renal Drugs Advisory Committee. He received his Bachelor of Science degree in pharmacy from the University of Manitoba, Canada.

## **Edward Cox, M.D., M.P.H.**

Director, Office of Antimicrobial Products  
Center for Drug Evaluation and Research, FDA

Edward Cox is currently the director of the Office of Antimicrobial Products within the Office of New Drugs, Center for Drug Evaluation and Research, U.S. Food and Drug Administration.

Dr. Cox completed an internship and residency in internal medicine at the Hospital of the University of Pennsylvania in Philadelphia, and went on to complete a fellowship in infectious diseases at the National Institute of Allergy and Infectious Diseases at the National Institutes of Health in Bethesda, MD. He is board certified in internal medicine and infectious diseases. Following two years in private practice in infectious diseases, Dr. Cox joined FDA as a medical officer in the Division of Special Pathogen and Transplant Products in 1998. He subsequently served as a medical team leader before being appointed as deputy director of the Office of Drug Evaluation IV in 2003.

Dr. Cox received his undergraduate degree in chemistry from the University of North Carolina, Chapel Hill, and his medical degree from the University of North Carolina School of Medicine.

## **Michael N. Dudley, Pharm.D., FIDSA**

Senior Vice President, Research and Development, and Chief Scientific Officer  
Rempex Pharmaceuticals Inc.

Michael N. Dudley has more than 30 years of experience in anti-infective drug research and development, with experience in the discovery and the preclinical and clinical stages in both academia and industry. He is senior vice president, research and development, and chief scientific officer for Rempex Pharmaceuticals Inc. in San Diego. Prior to co-founding Rempex, Dr. Dudley held a similar position in Mpex Pharmaceuticals Inc. and was vice president of preclinical and clinical sciences at Diversa Corp. and vice president of pharmacology and microbiology at Essential Therapeutics/Microcide Pharmaceuticals Inc.

Prior to his work in the pharmaceutical industry, he held a full-time academic appointment at Roger Williams Medical Center in Providence, RI. He was also professor of pharmacy and chairman of the Department of Pharmacy Practice at the University of Rhode Island College of Pharmacy and adjunct professor of medicine, Brown University School of Medicine. Dr. Dudley has published more than 100 scientific papers and book chapters describing the evaluation and clinical use of anti-infective agents and treatment of infectious diseases. He has served as a consultant on several advisory boards for the pharmaceutical industry, and as an editor for *Antimicrobial Agents and Chemotherapy* (1995-2002), where he remains on its editorial board. He has served as voting member and adviser of the Antimicrobial Susceptibility Testing Subcommittee of the Clinical Laboratory Standards Institute since 1996.

He completed undergraduate work at Pepperdine University and received his Doctor of Pharmacy degree from the University of California, San Francisco.

## **Steven C. Ebert, Pharm.D, FCCP, FIDSA**

Clinical Pharmacy Specialist, Clinical Manager, Meriter Hospital  
Clinical Professor of Pharmacy, University of Wisconsin, Madison

Steven C. Ebert is clinical manager in infectious diseases at Meriter Hospital and clinical professor of pharmacy, University of Wisconsin, Madison. His practice and research interests are antimicrobial resistance, antimicrobial pharmacokinetics/pharmacodynamics, and appropriate utilization of health care resources.

Dr. Ebert has served as a member of the board of directors of the Pharmacy Society of Wisconsin; as chairman of the Wisconsin Antibiotic Resistance Network, or WARN; and as president of the Society of Infectious Diseases Pharmacists. He also served as a member of the FDA Anti-Infective Drug Advisory Committee. Dr. Ebert has published more than 50 original research articles, review articles, and book chapters on optimizing antimicrobial use and administration.

He received his bachelor's degree in pharmacy from the University of Wisconsin, and his doctorate in pharmacy from the University of Texas, Austin.

## **Matthew Bidwell Goetz, M.D.**

Chief of Infectious Diseases, Veterans Affairs Greater Los Angeles Healthcare System  
Professor of Clinical Medicine, David Geffen School of Medicine, UCLA

Matthew Bidwell Goetz is professor of clinical medicine at the David Geffen School of Medicine at UCLA, and chief of Infectious Diseases at the Veterans Affairs Greater Los Angeles Healthcare System. In addition, he is a member of the VA National HIV/AIDS Technical Advisory Group, the VA National Hepatitis C Technical Advisory Group, the VA National Medical Advisory Panel, the VA Infectious Diseases Field Advisory Committee, and the VA Antimicrobial Stewardship Task Force. He is also a former member of the FDA Anti-Infective Drug Advisory Committee.

Dr. Goetz is actively engaged in projects related to antimicrobial stewardship sponsored by the VA and the Centers for Disease Control and Prevention. He is the author of more than 100 peer-reviewed articles.

He received his medical degree from the Tufts University School of Medicine.

## **Robert Guidos, J.D.**

Vice President, Public Policy and Government Relations  
Infectious Diseases Society of America

Robert Guidos is vice president of public policy and government relations for the Infectious Diseases Society of America, or IDSA, which represents more than 10,000 infectious disease physicians and scientists in the United States and abroad who are devoted to patient care, research, education, disease prevention, and public health. Mr. Guidos works with infectious diseases and other health care experts/organizations to develop sound, science-based legislative and regulatory policy. His team activates advocacy campaigns to carry IDSA's messages to the public as well as to policymakers in the U.S. Congress, FDA, CDC, National Institutes of Health, and in other countries.

Prior to his post at IDSA, Mr. Guidos did legislative work for FDA's commissioner and for the U.S. secretary of health and human services. He served as a Brookings Institution congressional fellow in 1998. His scientific, legal, legislative, and health policy experience has enabled him to work effectively with policy leaders in government; the medical, scientific, public health, and international health communities; representatives from the pharmaceutical, biotechnology, and diagnostic industries; patient advocates; and the media.

Mr. Guidos received his bachelor's degree in chemistry from Gannon University in Erie, PA, and his J.D. degree from the University of Pittsburgh School of Law, and he was a U.S. Peace Corps volunteer in Kampala, Uganda.

## **Saira A. Jan, M.S., Pharm.D.**

Director of Clinical Pharmacy Management, Horizon Blue Cross Blue Shield of New Jersey  
Clinical Professor, Ernest Mario School of Pharmacy, Rutgers, the State University of New Jersey

Saira A. Jan serves dual roles as director of clinical pharmacy management at Horizon Blue Cross Blue Shield of New Jersey, or BCBSNJ, and as clinical professor at the Ernest Mario School of Pharmacy at Rutgers. For more than 15 years, she has led a wide array of administrative, clinical, academic, and research programs, using a collaborative approach to medication utilization.

Dr. Jan's leadership and clinical influence at Horizon BCBSNJ have resulted in a variety of cross-divisional medical policies, utilization management programs, and pharmacy-based disease state management programs. She directs clinical initiatives in formulary management, is the chair of the Horizon BCBSNJ Pharmacy and Therapeutics Committee, and works closely with the organization's business units and clinical quality and medical management divisions. Dr. Jan also leads Horizon's medication therapy management program for Medicare Part D and Special Needs Populations and serves on several national committees focused on evidence-based medication management. She has secured pharmaceutical industry cooperation in research and program development initiatives.

Dr. Jan received her master's degree in pharmacology from St. John's University and her doctorate in pharmacy from Rutgers.

## **Nicole Mahoney, Ph.D.**

Senior Officer, Antibiotics and Innovation  
The Pew Charitable Trusts

Nicole Mahoney is the senior officer for antibiotics and innovation at The Pew Charitable Trusts, which addresses the growing public health challenge of multidrug-resistant infections by supporting policies that stimulate and encourage the development of antibiotics to treat life-threatening illnesses.

Before joining Pew, Dr. Mahoney served as an FDA commissioner's fellow in the Office of Antimicrobial Products, analyzing the regulatory pathway for all new antibacterial drugs reviewed by the agency between 1980 and 2011. Prior to that, she was a technology development associate at the National Institute of Allergy and Infectious Diseases, providing patentability and marketability assessments for new technologies and negotiating agreements for research and the exchange of resources (equipment, funds, reagents) between the institute and partner organizations. She also was an American Association for the Advancement of Science policy fellow at the National Institutes of Health and the National Science Foundation.

Dr. Mahoney received her doctorate in biochemistry from the Albert Einstein College of Medicine and completed postdoctoral training at the University of California, San Francisco.

## **John Powers, M.D., FACP, FIDSA**

Associate Clinical Professor of Medicine  
George Washington University School of Medicine and University of Maryland School of Medicine

John Powers is a physician/investigator on faculty as an associate clinical professor of medicine at the George Washington University School of Medicine. Before that, he was the lead medical officer for Antimicrobial Drug Development and Resistance Initiatives at FDA and co-chair of the federal Interagency Task Force on Antimicrobial Resistance. Prior to joining FDA, Dr. Powers served as an assistant professor in the Division of Infectious Diseases at the University of Maryland School of Medicine, and is still on the faculty. He actively cares for patients weekly in clinic and attends on the infectious diseases inpatient service. Dr. Powers has been an investigator on more than 50 clinical trials. He has particular expertise in the design, conduct, and analysis of clinical trials and has published on various aspects of their design.

Dr. Powers received his bachelor's degree and graduated magna cum laude from the University of Pennsylvania. He received his medical degree and residency training from Temple University School of Medicine, where he also served as chief resident. He completed his infectious disease training at the University of Virginia School of Medicine.

## **John H. Rex, M.D., FIDSA, FACP**

Vice President and Head of Infection Development, Global Medicines  
AstraZeneca Pharmaceuticals LP

John H. Rex is vice president and head of infection development, global medicines of AstraZeneca Pharmaceuticals LP.

Dr. Rex served on the faculty of the University of Texas Medical School at Houston from 1992 to 2002, where his work focused on laboratory studies of novel antifungal agents, clinical trials of novel antifungal agents, and hospital epidemiology. In 2003, he moved to AstraZeneca Pharmaceuticals, where he and his colleagues have undertaken creation of candidate antibiotics via multiple approaches to partnership, creative risk-sharing, licensing deals, acquisitions, and internal program progression. His contributions have helped the AstraZeneca infection program grow from a single product in late life cycle management to a strongly supported and diversified program featuring products in all phases of clinical development, registration, and post-approval commercialization.

In addition, Dr. Rex has been the industry representative on the FDA Anti-Infective Drug Advisory Committee, is vice chair of the Area Committee on Microbiology for the Clinical Laboratory Standards Institute, and is a highlights adviser for *Nature Reviews Microbiology*. He also sits on Wellcome Trust's Seeding Drug Discovery Committee, serves on several editorial boards, was formerly an editor for *Antimicrobial Agents and Chemotherapy*, and is an emeritus editor for Doctor Fungus, a nonprofit website devoted to dissemination of information about medical mycology.

Dr. Rex received his medical degree from Baylor College of Medicine, trained in internal medicine at Stanford University Hospital, and trained in infectious diseases at the National Institute of Allergy and Infectious Diseases.

## **James Scott, J.D.**

President and CEO  
Applied Policy LLP

James Scott, president and CEO of Applied Policy LLP, founded the company to apply his in-depth and insider knowledge of federal health policy to help health care providers and companies succeed. Immediately prior to founding the firm, Mr. Scott oversaw optimal Medicare coding, coverage, and payment for all pharmaceutical products manufactured by Hoffmann-La Roche Inc. While at Roche, he also worked to resolve Medicare and Medicaid reimbursement issues at the federal level and was the company's principal contact with the Centers for Medicare & Medicaid Services.

Mr. Scott served as the senior legislative adviser at CMS, advising the administrator on congressional intent in implementing the Medicare Modernization Act of 2003 and engaging members of Congress in the implementation of the act. Before that, he was an assistant counsel in the U.S. Senate's Office of the Legislative Counsel, where he was a principal drafter of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 and other Medicare legislation.

Mr. Scott received a bachelor's degree in political science from James Madison University in Harrisonburg, VA, and received his Juris Doctor, magna cum laude, from Catholic University's Columbus School of Law in Washington.

## **David M. Shlaes, M.D., Ph.D.**

Owner

Anti-Infectives Consulting LLC

David M. Shlaes has had a 30-year career in anti-infectives spanning academia and industry with a long-standing scientific interest in antimicrobial resistance.

In 1991, he was appointed professor of medicine at Case Western Reserve University. In 1996, Dr. Shlaes became vice president for infectious diseases at Wyeth Research for six years, assuming responsibility for strategic direction. He also was a member of the Forum for Emerging Infections of the National Academy of Sciences for seven years. In 2002, Dr. Shlaes became executive vice president, research and development for Idenix Pharmaceuticals Inc. in Cambridge, MA, focused on the discovery and development of antivirals. In 2005, he left Idenix to form a consulting company for the pharmaceutical industry, Anti-Infectives Consulting LLC. He was an independent director for Novexel SA, an anti-infectives biotech firm in Paris recently sold to AstraZeneca UK Ltd., and he consults for a number of other anti-infective-focused biotechs, including Nabriva Therapeutics AG in Vienna and Actelion Pharmaceuticals Ltd. in Basel, Switzerland, as well as several large pharmaceutical companies. Dr. Shlaes frequently works with venture capital firms in the evaluation of anti-infective companies. He is an editor for *Antimicrobial Agents and Chemotherapy*, a member of the NIH Drug Discovery and Mechanisms of Antimicrobial Resistance Study Section, and the Antibacterial Drug Development Task Force of the Brookings Institution.

Dr. Shlaes received his doctorate in microbiology from Case Western Reserve University, where he also earned a medical degree.

## **Pranita Tamma, M.D., M.H.S.**

Director of Pediatric Antimicrobial Stewardship

Johns Hopkins Hospital

Pranita Tamma is a faculty member at Johns Hopkins University's Division of Pediatric Infectious Diseases and directs the Pediatric Antimicrobial Stewardship Program at Johns Hopkins Hospital.

As director of the Pediatric Antimicrobial Stewardship Program, Dr. Tamma spends a fair portion of her day educating prescribers about optimizing selection, route, dose, interval, and frequency of antibiotics; developing guidelines for appropriate and judicious use of antibiotics; and monitoring patient outcomes after implementation of these practices. Her research focuses on comparative effectiveness studies related to antibiotic use.

Dr. Tamma received her medical degree from SUNY Downstate in Brooklyn, NY, and completed her pediatrics residency and infectious diseases fellowship at Johns Hopkins Hospital. She has a master's degree in public health from the Bloomberg School of Public Health.

## **Kavita K. Trivedi, M.D.**

Medical Epidemiologist, Healthcare Associated Infections Program  
Lead, California Antimicrobial Stewardship Program Initiative, California Department of Public Health

Kavita K. Trivedi, a medical epidemiologist, created, manages, and leads the California Antimicrobial Stewardship Program Initiative at the California Department of Public Health. She also leads the California Department of Public Health in investigating outbreaks and inquiries regarding infection control and prevention in health care settings in California.

Before that, Dr. Trivedi was the medical director of the Downtown Clinic, a multidisciplinary clinic for homeless veterans in San Francisco. Thereafter, she served as an Epidemic Intelligence Service officer in the U.S. Public Health Service with the CDC.

Dr. Trivedi received her medical degree from Stanford University School of Medicine and completed her residency in internal medicine at the University of California, San Francisco.

## **Christine Welch, M.S., RAC**

Vice President, Regulatory Affairs  
Achaogen Inc.

Christine Welch is vice president of regulatory affairs at Achaogen Inc., a small biotech company focused on the discovery and development of new antibiotics for the treatment of serious Gram-negative bacterial infections.

She has more than 20 years of industry experience in global regulatory affairs and drug development gained in both large pharmaceutical and small biotech companies, including SmithKline Beecham Pharmaceuticals, Gilead Sciences Inc., and Alexza Pharmaceuticals Inc. She has been involved in a wide range of regulatory affairs activities from investigational new drug filings to global marketing approvals across a variety of products in the infectious diseases, respiratory, psychiatric, and neurological therapeutic areas. She was previously an independent regulatory affairs consultant in Great Britain, specializing in providing global regulatory and filing strategies. Her early career was spent as a clinical biochemist at Scotland's Western General Hospital in Edinburgh and Yorkhill Hospital in Glasgow.

Ms. Welch received her bachelor's degree in biochemistry from the University of Liverpool and her master's degree in clinical biochemistry from the University of Newcastle-upon-Tyne, both in the United Kingdom. She holds a regulatory affairs certification from the University of California, Santa Cruz.

## Appendix C

Pew prepared models to suggest the types of antibiotics that may be tested under a limited population development program. These are hypothetical, are 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<sup>13</sup> and were refined with additional information and expert input.<sup>14</sup> We acknowledge the 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 more than 1,000 patients total) to support each target disease, and Tier D, with approvals based on the so-called animal rule for situations in which human trials are impossible or unethical and evidence from animal studies are used to support FDA approval. 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 from patients (perhaps from fewer than 500) with a range of infections (not just one type of condition) could support approval of antibiotics targeting serious or life-threatening resistant infections for limited populations with few or no other treatment 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 when it would be difficult to recruit enough patients for a traditional drug development program.<sup>15</sup> Tier B and C labels would emphasize the risks and limitations of the small clinical data sets underpinning approval of the products and promote their appropriate use.

## Scenario 1: Hypothetical Drug One 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 intravenous drug that will be developed initially for a limited population of patients with multidrug-resistant infections. Presumably, the labeled drug indications could be expanded based on additional data.

### Drug One:

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

### Potential U.S. market:

75,000 multidrug-resistant hospital-associated infections out of 500,000 total.<sup>16</sup>

### Clinical Trials:

1. Phase 3 randomized, non-inferiority study (meeting standard requirements) against a comparator for treatment of complicated intra-abdominal infections, or cIAI. 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 multidrug-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 One and a safety database of 700 across studies.

**Projected R&D budget:** Less than \$150 million for preclinical-Phase 3 program.

## Label:

Drug One 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 One is indicated for the treatment of cIAI proven or suspected to be caused by Drug One-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 One 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 One-susceptible strains of *Klebsiella pneumoniae*, *Escherichia coli*, or *Pseudomonas aeruginosa*. Drug One 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 One is only indicated in situations where other therapy is not available or inappropriate.

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

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## Scenario 2: Hypothetical Drug Two 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, because of 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*.

### Potential U.S. market:

About 20,000<sup>17</sup> to 54,000<sup>18</sup> multidrug-resistant *Pseudomonas* infections out of about 136,000<sup>19</sup> to 540,000<sup>20</sup> cases total.

### Clinical Trials:

1. Small, prospective, open-label, randomized study of Drug Two 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 *Pseudomonas aeruginosa* at multiple infection sites showing a trend toward improvement (not statistical significance) with Drug Two over the comparator.
2. Open-label, noncomparative study of Drug Two for patients who 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 Two and a safety database of 400 across studies.

**Projected R&D budget:** Less than \$100 million for preclinical-Phase 3 program.

### Label:

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

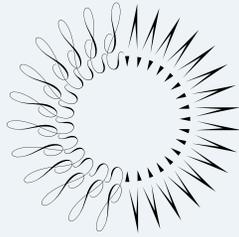
Drug Two is indicated for the treatment of hospital-acquired bacterial pneumonia, ventilator-associated bacterial pneumonia, complicated urinary tract infections, and complicated intra-abdominal infections proven or strongly suspected to be caused by Drug Two susceptible strains of *Pseudomonas aeruginosa*. Because data for Drug Two in these infections are limited, Drug Two should only be used if other alternatives are known or suspected to be less suitable.

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

## Endnotes

- <sup>1</sup> 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, Sept. 22, 2011, Washington, DC, [http://www.pewhealth.org/uploadedFiles/PHG/Content\\_Level\\_Pages/Issue\\_Briefs/AIP\\_PipelineProceedings\\_9\\_web.pdf](http://www.pewhealth.org/uploadedFiles/PHG/Content_Level_Pages/Issue_Briefs/AIP_PipelineProceedings_9_web.pdf).
- <sup>2</sup> Infectious Diseases Society of America, "Limited Population Antibacterial Drug (LPAD) Approval Mechanism," [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](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).
- <sup>3</sup> 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>.
- <sup>4</sup> Derrick Gingery, "Antibiotic Incentives: FDA's Woodcock Says LPAD Could Be Better Than Exclusivity, But Questions Remain," *The Pink Sheet Daily*, April 18, 2013.
- <sup>5</sup> 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](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](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).
- <sup>6</sup> 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](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](http://www.idsociety.org/uploadedFiles/IDSA/News_and_Publications/IDSA_News_Releases/2012/20120409%20Basilea%20letter%20%20LPAD.pdf).
- <sup>7</sup> 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.
- <sup>8</sup> Nanci Bompey, "FDA Mulls Ways to Move on LPAD Using Current Authority," *FDA Week*, Oct. 4, 2012; "Creating an Alternative Approval Pathway for Certain Drugs Intended to Address Unmet Medical Need," *Federal Register* 78 FR (Jan. 15, 2013): 3005-8.
- <sup>9</sup> Anna Yukhananov, "Group Asks FDA to Treat Superbugs Like Rare Diseases," Reuters, March 8, 2012.
- <sup>10</sup> Applications for FDA Approval to Market a New Drug, 21 C.F.R. 314 (2012); Licensing, 21 C.F.R. 601 (2012).
- <sup>11</sup> John H. Rex et al., "A Comprehensive Regulatory Framework to Address the Unmet Need for New Antibacterial Treatments," *The Lancet Infectious Diseases* 12 (January 2013), doi:10.1016/S1473-3099.

- <sup>12</sup> During the conference, Rempex introduced a proposed incentive program to break the link between revenue and the volume of antibiotics sold. The plan, Rewarding Antibiotic Development and Responsible Stewardship, or RADARS, is designed to provide a guaranteed return on investment for urgently needed antibiotics and to promote their stewardship. Slides from the presentation can be found here: <http://www.pewhealth.org/other-resource/a-new-pathway-for-antibiotic-innovation-exploring-drug-development-for-limited-populations-85899450008>.
- <sup>13</sup> Rex et al., "A Comprehensive Regulatory Framework to Address the Unmet Need for New Antibacterial Treatments."
- <sup>14</sup> Additional recommendations for clinical trials include the European Medicines Agency guidance for testing antibiotics when 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](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) (August 2012): 1031-46.
- <sup>15</sup> Rex et al., "A Comprehensive Regulatory Framework to Address the Unmet Need for New Antibacterial Treatments."
- <sup>16</sup> The number of hospital-acquired *Klebsiella pneumoniae*, *Escherichia coli*, or *Pseudomonas aeruginosa* infections was estimated by multiplying the reported number of hospital-acquired infections—1.7 million, according to R.M. Klevens et al., "Estimating Health Care-Associated Infections and Deaths in U.S. Hospitals, 2002," *Public Health Reports* 122 no. 2 (2007): 160-6—by the percentage of *Klebsiella pneumoniae*, *Escherichia coli*, or *Pseudomonas aeruginosa* isolates submitted to the U.S. National Healthcare Safety Network in 2009 and 2010. Those percentages were 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*, 34 no. 1 (2013): 1-14. The number of multidrug-resistant infections was assumed to be approximately 15 percent, based on CDC estimates from 2008, <http://www.cdc.gov/hai/organisms/gram-negative-bacteria.html>.
- <sup>17</sup> The number of hospital-acquired *Pseudomonas aeruginosa* infections was estimated by multiplying the reported number of hospital-acquired infections—1.7 million, according to R.M. Klevens et al., "Estimating Health Care-Associated Infections and Deaths in U.S. Hospitals, 2002"—by the percentage of *Pseudomonas aeruginosa* isolates submitted to the U.S. National Healthcare Safety Network in 2009 and 2010 (7.5 percent, 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"). The number of multidrug-resistant infections was assumed to be approximately 15 percent, based on CDC estimates from 2008, <http://www.cdc.gov/hai/organisms/gramnegative-bacteria.html>.
- <sup>18</sup> 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, March 20, 2012, <http://antibiotics-theperfectstorm.blogspot.com/2012/03/antibiotic-markets-and-splu-guest.html>.
- <sup>19</sup> See Endnote 17.
- <sup>20</sup> See Endnote 18.



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