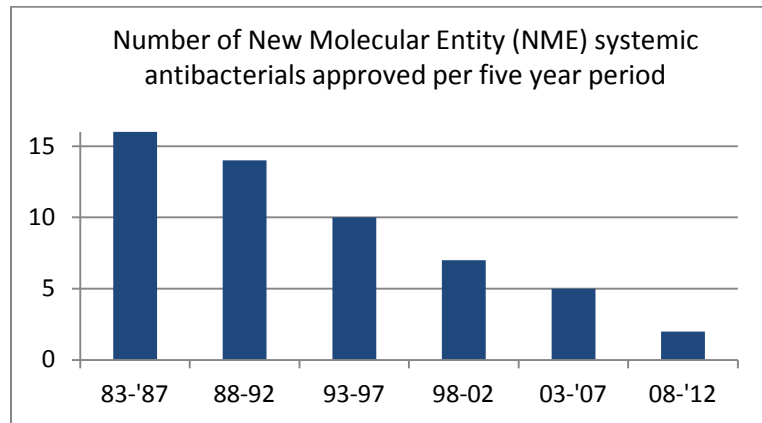




Incentives for Change: Addressing the Challenges in Antibacterial Drug Development

Background

The rate of discovery of new classes of antibacterial drugs has dramatically slowed, and no new class of antibiotics to treat Gram-negative pathogens has been developed since the early 1960s.¹ Between 1983 and 1987, 16 new systemic antibacterial products were approved compared to only two systemic antibacterial products approved since 2008.² Many factors have contributed to this decline, including scientific and regulatory challenges and uncertainty associated with basic and translational research, drug development, and drug approval. Relatively low reimbursement rates combined with the typically short-course and curative nature of these therapies have limited opportunities to generate returns on investment and contributed to the lack of development compared to other therapeutic areas such as chronic diseases and oncology.



Source: IDSA. (2011) Combating Antimicrobial Resistance: Policy Recommendations to Save Lives. *Clin. Infectious Dis.* 52(S5):S397-S428.

Addressing these concerns to improve the antibacterial drug development pipeline will require new ideas and multi-stakeholder commitment to reforming key areas. One area that could have a positive impact is identifying new economic incentives as a means to change the calculus of investment in antibacterial development and related health technologies, such as diagnostics.

Antibacterial products have historically been relatively inexpensive and manufacturers have relied on high-volume, low-cost sales to recoup development costs. This model has led to broad clinical use of antibacterial products, and in some cases inappropriate overuse, which has hastened the emergence of resistant pathogens. As a result, there is a pressing need to create and implement stewardship programs that will curb the widespread use of the products to conserve the utility of new antibacterials. Given the

¹ Spellberg B. (2012). New Antibiotic Development: Barriers and Opportunities in 2012. *Confronting Today's Crisis in Antibiotic Development. Alliance for the Prudent Use of Antibiotics (APUA) Clinical Newsletter* 30(1):8-10. Retrieved February 21, 2013, from http://www.tufts.edu/med/apua/news/newsletter_22_2401405063.pdf.

² IDSA. (2011). Combating Antimicrobial Resistance: Policy Recommendations to Save Lives. *Clinical Infectious Disease* 52(S5):S397-S428. Retrieved February 21, 2013, from http://cid.oxfordjournals.org/content/52/suppl_5/S397.full.pdf+html.

current system for reimbursement, stewardship will likely decrease sales, further undermining developers' ability to support the development of new products and recoup investments. In order to effectively implement any stewardship program, it is essential to develop reimbursement models that can sustain and increase development efforts for new antibacterial products. Experts in this field are researching options that “de-link” reimbursement from unit sales.

Workshop Objectives

Under a cooperative agreement with the U.S. Food and Drug Administration (FDA), the Engelberg Center for Health Care Reform at Brookings formed the Brookings Council on Antibacterial Drug Development (BCADD) as a collaborative forum for thought leaders to identify actionable next steps to promote antibacterial drug development and seek broad stakeholder engagement. BCADD activities are designed to explore collaborative, transparent, and innovative next steps that involve a wide range of stakeholders including government, industry, the clinical community, and the public. While there are many issues that remain to be addressed in this field, this workshop is focused on two critical topics: better understanding the potential role of incentives in drug discovery and identifying potential reimbursement models that can support both stewardship and expanded development for antibacterial drug products.

Incentives and Drug Development

Many incentives to promote research and development for therapeutic areas with poor markets have been explored and, in some instances, implemented, as in the case of neglected tropical diseases and orphan conditions. Incentives can take many forms, but are commonly divided into so-called “push” and “pull” mechanisms. Push mechanisms address the high up-front costs of investing that can serve to deter development, particularly for smaller developers, or help protect those investments. Examples of push mechanisms include public or philanthropic grants to companies, patent protection, tax credits, and partnerships, often combining public and private funding, that can pool risk and resources among companies. Pull mechanisms, on the other hand, provide more attractive rewards for successful development programs. Examples of pull mechanisms include data or marketing exclusivity extensions, advanced market commitments, transferable priority review vouchers or patent extensions, and prize funds. Several push and pull mechanisms will be discussed in further detail below.

Tax credits are available generally to support U.S.-based research and development. Programs such as the Qualifying Therapeutic Discovery Research Project are intended to specifically reward research that addresses an unmet medical need, can lower long-term U.S. health care costs, or advance a cure for cancer.³ Tax relief has also been used to advance clinical research for some of the most neglected research areas, such as for rare conditions (see Orphan Drug Act, below). A similar program for antibacterial products could help reduce the costs of development.

Incentives based around FDA's approval process can accelerate approval and provide additional support during the clinical trial process, which may increase the odds of a successful approval and shorten approval times. Generally, these pathways are employed for novel or much-needed therapies, helping patients awaiting treatments and providing developers with additional time on the market. Several designations aim to hasten product approvals for treatments for serious conditions. These include breakthrough therapies, fast-track products, and products designated for priority review such as

³ Rao A. (2011). R&D Tax Credits: A Tool to Advance Global Health Technologies? Washington, DC: Results for Development Institute. Retrieved February 21, 2013, from <http://healthresearchpolicy.org/assessments/rd-tax-credits-tool-advance-global-health-technologies>.

qualified infectious disease products under the Generating Antibiotic Incentives Now Act (see below).⁴ Additionally, transferable priority review vouchers have also been used to stimulate research for tropical diseases under the assumption that these products are unlikely to be lucrative, and companies with a qualifying project can apply the voucher to the approval of another product with a larger market.

Advanced market commitments (AMCs), or advanced purchase commitments, subsidize the purchase of a product, typically in late-stage development, at a certain price and volume to encourage the developer to bring it to market. The model has been proposed for many areas of unmet medical need where market incentives are lacking, including for vaccines and antibacterial products. The GAVI Alliance (formerly the Global Alliance for Vaccines and Immunisation), for example, has brought together funding from national governments and the Bill & Melinda Gates Foundation to help bring a pneumococcal pneumonia vaccine to market. The subsidy has helped reduce costs for developing country consumers and guaranteed a stable and significant market for developers. AMCs may be able to further influence developer decision-making if implemented earlier in product development.⁵

A combination of push incentives and AMCs may help further accelerate product development, especially for smaller companies that cannot afford as much risk. Initiatives undertaken in the last decade by the U.S. Department of Health and Human Services (HHS) make use of a hybrid model to stimulate research and development and create a government-funded market for countermeasures against chemical, biological, radiological, and nuclear bioterrorism agents. The **Project BioShield Act** of 2004 (P.L. 108-276) and the 2006 **Pandemic and All-Hazards Preparedness Act (PAHPA)** (P.L. 109-417) authorized \$5.6 billion over 10 years to support the late stage development and purchase of medical countermeasures against bioterrorism threats for the Strategic National Stockpile.⁶ Overseen by the Biomedical Advanced Research and Development Authority, provisions also provide expanded authority to the NIH and FDA to expedite research and licensure of medical countermeasures and authorize prize payments to support mid-stage product development for meeting certain targets.⁷ Though purchasing has been somewhat limited in scope and not all products have received regulatory approval, the program has supported the development of nine products against *Bacillus anthracis* (anthrax), botulism, smallpox and radio-nuclear exposure.⁸ PAHPA is currently up for reauthorization and has passed in the House of Representatives (H.R. 307).

The **Orphan Drug Act** (P.L. 97-414) supports research and development for treatments for orphan conditions, or those affecting fewer than 200,000 people in the United States. Designed to encourage investment in products with very limited markets, the program has helped develop more than 400 drugs

⁴ FDA. Fast Track, Accelerated Approval and Priority Review: Accelerating Availability of New Drugs for Patients with Serious Diseases. Retrieved February 21, 2013, from <http://www.fda.gov/forconsumers/byaudience/forpatientadvocates/speedingaccesstoimportantnewtherapies/ucm128291.htm>.

⁵ Mossialos E et al. (2010). "Advanced market commitments." Policies and incentives for promoting innovation in antibiotic research. Copenhagen: World Health Organization, European Observatory on Health Systems and Policies. p. 95-100. Retrieved February 21, 2013, from http://www.euro.who.int/__data/assets/pdf_file/0011/120143/E94241.pdf.

⁶ Managed by the Centers for Disease Control and Prevention and HSS, the Strategic National Stockpile is the United States' national repository of antibacterial drugs, chemical antidotes, antitoxins and other critical medical and surgical supplies for dealing with bioterrorism, pandemic threats, and other public health emergencies.

⁷ Russell P. (2007). Project BioShield: What It Is, Why It Is Needed, and Its Accomplishments So Far. *Clinical Infectious Disease* 45 (Supp. 1):S68-S72. Retrieved February 21, 2013, from http://cid.oxfordjournals.org/content/45/Supplement_1/S68.full.

⁸ Cohen J. (2011). Biodefense: 10 years after. Reinventing Project BioShield. *Science* 333(6047):1216-1218.

and biologic products since its enactment in 1983.⁹ Companies with products receiving Orphan Drug designations receive seven years of marketing exclusivity, tax incentives, grants for drug development, fast-track designation, access to Investigational New Drug consultations, and a waiver for PDUFA user fees. The Orphan Drug program also offers a 50 percent credit on expenses related to clinical testing for orphan drug candidates.

Enhanced market exclusivity provisions have already helped to stimulate research for less attractive markets, such as for orphan drugs, pediatric indications, and first-to-file generic drugs. The **Generating Antibiotics Incentives Now (GAIN) Act**, incorporated under the Food and Drug Administration Safety and Innovation Act in 2012, guarantees an extra five years of marketing exclusivity for new antibacterial products meeting the requirements for qualified infectious disease products (QIDPs). This exclusivity is in addition to standard or orphan drug exclusivity, and therefore could extend up to 12 years after approval. QIDPs will also receive Priority Review and Fast Track designation.

The Eastern Research Group (ERG) has been contracted by HHS to perform an economic analysis of possible incentives for the development of new antibacterial drugs. The analysis includes a number of indications, such as acute bacterial otitis media, acute skin and skin structure infections, community acquired pneumonia, complicated intra-abdominal infections, complicated urinary tract infections, and hospital acquired bacterial pneumonia. To assess the current state of investment in antibacterial research and development for areas of unmet medical need, ERG developed an economic model to calculate the **expected net present value** (ENPV) for prospective new drugs for each indication under various market conditions. For this analysis, the ENPV is defined as the total value of expected revenues over the product life cycle minus the costs of drug development.

The model is based on a multi-stage decision tree framework, in which there are a series of decision nodes. At each node, there is an expected probability of success and marginal ENPV. The ENPV uses the private opportunity cost of capital (also referred to as the private rate of discount) to account for changes in the value of money over time. Key variables for determining the costs of development are phase duration time, probability of success for each phase, cost of capital, and pre-clinical and clinical trial costs as well as costs of a number of product supply chain activities that occur concurrently with different stages of clinical development. Key variables determining the future revenues are the projected market size, product launch success probability, sales of comparable drugs, and time before generic entry (i.e., length of exclusivity periods).

The base expected net present value estimates are then recalculated incorporating the impact of conservation and development incentives. Conservation incentives are assumed in the model to lower ENPV by reducing expected market size. On the other hand, development incentives are assumed to increase ENPV by lowering development costs, time to market, and cost of capital.

ERG generated a comprehensive list of incentives based on a review of the literature and input from experts. The criteria for inclusion was designed to maximize the usefulness and manageability of the modeling exercise and included (1) whether it is under HHS regulatory authorities; (2) if it could be analyzed within the model ENPV framework; (3) if it would promote development of a new molecular entity; (4) if it would promote appropriate use; (5) if it would be practical to implement; (6) if it creates market distortion; (7) if it impacts access and/or affordability; and (8) the magnitude of transaction costs

⁹ FDA. Developing Products for Rare Diseases & Conditions. Retrieved February 21, 2013, from <http://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm#>.

it would impose. The incentives were grouped based on how they affected the model parameters. For example, incentives that lower phase 3 clinical trial costs were grouped together. The incentive analysis involved solving for the level of each type of incentive to meet a set private ENPV target by indication using the decision-tree model developed.

The decision-tree EPNV model is constructed to allow users to input incentive-specific variables, such as reduction in FDA approval time or a decrease in clinical trial cost. Key variables related to incentives are parameterized to allow experimentation with many different scenarios and considering combinations of incentives. HHS plans to use the model to do flexible policy analysis of the impact on proposed incentives on development.

Reimbursement Models

Given the emergence of resistant pathogens, the need to preserve the effectiveness of existing antibacterial drugs and ensure mechanisms to protect new products is critical. Stewardship initiatives will need to holistically address the challenges of promoting appropriate prescribing and infection control. At the same time, new models of reimbursement may be needed to support appropriate clinical use as well as provide incentives for developers to revitalize the antibacterial pipeline.

Limited-Use Paradigms

Proposals to develop a regulatory pathway which limits use for antibacterial products have been discussed over the past several years and have been recently highlighted as a potential solution to lower development costs. Representatives from pharmaceutical development firms and the Infectious Disease Society of America (IDSA) have put forth similar models to address the pitfalls of late-stage antibacterial development. The IDSA's "Limited Population Antibacterial Drug" (LPAD) designation has been proposed to address the challenges of antibacterial trial design, stewardship, and investment by approving new antibacterial products for a narrow, well-defined indication based on data from smaller—and potentially cheaper and shorter—clinical trials.¹⁰ The risks associated with an LPAD-approved drug may be less well characterized in a broader disease population than those developed in traditional phase 3 trials. Given the higher level of uncertainty with these products, an LPAD-approved drug would be appropriate only for "the most serious infections where there exists an unmet medical need (i.e., where insufficient satisfactory therapeutic options exist)" and where patients may be willing to accept a higher degree of uncertainty. Narrower indications within specified populations, less well characterized risk profiles, and premium pricing could also help prevent overprescribing and use of LPAD-approved drugs as a broad-spectrum antibacterial drugs.

Representatives of the pharmaceutical industry have proposed a similar approval pathway ("tier C") that also uses restricted trial size to approve products for a limited, pathogen-specific indication.¹¹ Much like orphan drugs, antibacterial products could be approved based on studies of only a few hundred patients, assuming the drug underwent rigorous pharmacokinetic and pharmacodynamic evaluations. The rest of the evidence could be gathered from small comparative studies that merged clinical datasets for the pathogen across multiple body sites. An intermediate tier was also proposed requiring a single

¹⁰ Infectious Disease Society of America. (2012). Limited Population Antibacterial Drug (LPAD) Approval Mechanism. Retrieved 18 January 18, 2013, from http://www.idsociety.org/uploadedFiles/IDSA/News_and_Publications/IDSA_News_Releases/2012/LPAD%20one%20pager.pdf.

¹¹ Rex J *et al.* (2013). A comprehensive regulatory framework to address the unmet need for new antibacterial treatments. *The Lancet Infectious Diseases*, early online publication, 15 January 2013. doi:10.1016/S1473-3099(12)70293-1.

standard phase 3 randomized controlled trial and several smaller trials. The European Medicines Agency has already developed a pathogen-specific guidance, and a draft guidance is expected from FDA in 2013 as stipulated in the GAIN Act.

On February 4, 2013, FDA held a public hearing to gather input on the creation of an alternative approval pathway for serious or life-threatening conditions of unmet medical need, which was propelled by the recommendations of the President's Council of Advisors on Science and Technology in their September 2012 report.¹² While there was no consensus as to whether smaller trials would shorten time to market or be simpler to design and execute, rethinking the drug approval and clinical trials processes could help limit clinical trial failures, costs, and regulatory uncertainty across therapeutic areas of current unmet medical need.

Proposed Delinking Mechanisms

Though industry has traditionally relied on high-volume, low-cost sales to recoup their investments in antibacterial drug development, future stewardship initiatives may attempt to significantly limit sales volume for novel and first-in-class antibacterial drugs. Several proposals for reimbursing novel antibacterial products have been put forward that attempt to provide fair and even attractive return on investment while supporting stewardship through lower sales volume.

A **price-based model** would reimburse drug developers at a higher rate than they are currently. Rather than relying on sales volume to drive return on investment, higher reimbursement rates could meet sales targets through fewer prescriptions and potentially even grow the market if reimbursement rates were sufficiently high. Premium pricing could potentially serve to prevent physicians and payers from supporting the use of novel antibacterial products as first-line therapies and help preserve their utility. High prices are common for other drugs with limited usage that meet a critical medical need, such as orphan and oncology indications, and could garner support for limited population designations.

Reimbursement models that value antibacterial drugs in accordance with their utility and importance to society, with the price hike additionally helping to curb overprescribing, have also been discussed. Antibacterial reimbursement rates could be benchmarked to the unmet need or social burden resulting from infectious diseases, typically measured in disability- or quality-adjusted life years (DALYs or QALYs). This approach is similar to the justification for the pricing of oncology drugs that add months or years of life. An inability to treat both routine and complicated infections would drastically burden society and could have wide-ranging effects on the practice of medicine. Depending on the valuation of a DALY, the market for a new antibacterial could be between \$73–183 billion for the United States and Canada.¹³

A **value-based evaluation model** takes this concept one step further and attempts to reimburse based on a new antibacterial product's health impact. The **Health Impact Fund (HIF)** is a proposed pay-for-performance mechanism that encourages drug developers to sell their products globally at the cost of

¹² President's Council of Advisors on Science and Technology. (2012). Report to the President on Propelling Innovation in Drug Discovery, Development and Evaluation. Retrieved February 21, 2013 from <http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-fda-final.pdf>.

¹³ Kesselheim A & K Outterson. (2011). Improving Antibiotic Markets for Long Term Sustainability. *Yale Journal of Health Policy, Law & Ethics* 11(1):101-67.

production in exchange for 10 years of annual reward payments.¹⁴ Payments would be offered as a share of the fund based on the product's proportional health impact compared to all other HIF-registered products. Because payments would be benchmarked to the health impact and effectiveness of the drug, the model translates well to antibacterial stewardship. More innovative products would merit greater reward and developers could be incentivized to preserve antibacterial drugs' utility to reap the maximum payments. They could therefore have a more direct stake in promoting good prescribing practices and infection control. While this model has been proposed, it has not been established and would require significant upfront investment.

Proposals for **payer-based reimbursement models** create a set return on investment that is not driven by prescription volume. Two examples are a capitation model, in which the payer reimburses for the use of the drug per patient per month, and a licensing model in which a payer could license products at a monthly or yearly rate for any number of patients. Reimbursement rates would still have to prove attractive to the developer, but could be "delinked" from individual unit sales. Payer-based models have potential for further supporting stewardship, for instance, by reimbursing only for on-label or other appropriate use, and requiring prequalification of centers to grant licenses.

An alternative compensation model, such as a centrally-managed and -financed **Strategic Antibiotic Reserve** may also support stewardship.¹⁵ Novel first-in-class antibacterial drugs may need to be reserved for extremely limited usage, or reserved completely for decades, to preserve their effectiveness. Drugs reserved in this manner could easily outlive their patent life and exclusivity however. This is particularly true if several classes of antibacterial products are developed around the same time and reserved strategically for serial release. Preserving new drugs' effectiveness is a critical task for public health policy-makers but could dramatically undermine companies' market-based profits. Developers would be compensated in exchange for voluntarily placing their new products in the reserve, helping to preserve the effectiveness of valuable antibacterial resources. Payments would likely need to be on the order of a billion dollars annually in order to properly incentivize developers and could also be value-based to better reward truly innovative products.¹⁶

Rempex Pharmaceuticals recently presented a potential reimbursement model named **Rewarding Antibiotic Development and Responsible Stewardship** at an event sponsored by the Pew Charitable Trusts. Rempex's model proposes that HHS would administer and fund a development guarantee program. Under this program, developers would receive a minimum revenue stream for the first five years a new antibacterial drug is on the market. Eligible products would be selected by HHS or FDA and could potentially include products approved through an alternative pathway such as LPAD or with a QDIP designation. Payments to developers would reduce the risks of development by ensuring a set return on investment, and in exchange, developers would agree to not market their product through their sales force. Medical science liaisons would be used to assist with awareness and appropriate prescribing.

¹⁴ Outterson K, T Pogge & A Hollis. (2011). Combating Antibiotic Resistance Through The Health Impact Fund. Boston Univ. School of Law, Law and Economics Research Paper, No. 11-30 (June 21, 2011). Available at SSRN: <http://ssrn.com/abstract=1866768>.

¹⁵ Kesselheim A & K Outterson. (2011) Improving Antibiotic Markets for Long Term Sustainability. *Yale Journal of Health Policy, Law & Ethics* 11(1):101-67.

¹⁶ Ibid.

This process could also make use of a reimbursement model similar to the Centers for Medicare and Medicaid Services' New Technology Add-On Payment (NTAP). Under this scheme, NTAP payments would cover the difference between the higher costs expected for limited use antibacterial products and the average costs for antibacterials included in current diagnosis-related reimbursement levels. These payments would continue for a period of 10 years. Hospital reimbursement would be conditional on appropriate prescribing and stewardship practices. For example, HHS might reimburse only use consistent with pre-approved stewardship programs and require documentation to support this. As described above, if payments to the drug developer for actual drug usage are less than the guaranteed minimum in the first five years, HHS would pay the drug developer the difference between the guaranteed amount and the amount received.

Future policies and programs will need to mediate the conflicting requirements of ensuring the economic feasibility of new antibacterial research and development while at the same time preserving the effectiveness of antibacterial products. Addressing these economic challenges will be essential if there is going to be meaningful progress revitalizing the antibacterial drug development enterprise. This workshop will support the development of pragmatic proposals for the larger stakeholder community to consider.