ENGELBERG CENTER for Health Care Reform at BROOKINGS

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Meeting Summary

Incentives for Change: Addressing the Challenges in Antibacterial Drug Development

Recent reports on the increasing incidence of "superbugs," or untreatable infections, in the scientific literature and mainstream media illustrate the ongoing need for research and investment in new and diverse antibacterial drugs.[1, 2, 3] While there is growing concern about the critical need for new antibacterial drugs, the pace of innovation is not keeping up with the emergence of resistant pathogens.[4] There are a number of factors adversely affecting greater investment in this field, and there is growing concern within the public health community that market-based solutions alone are unlikely to be sufficient to revive the antibacterial drug development pipeline.

Under a cooperative agreement with U.S. Food and Drug Administration (FDA), the Engelberg Center for Health Care Reform (ECHCR) formed the Brookings Council on Antibacterial Drug Development (BCADD) as a collaborative forum to engage stakeholders and identify actionable next steps in this field. As part of the BCADD project, ECHCR convened an expert workshop, "Incentives for Change: Addressing the Challenges in Antibacterial Drug Development," on February 27, 2013. This workshop explored two of the economic factors impacting the development pipeline. The first half of the workshop focused on understanding the effects of various incentives on drug discovery and development and the second half looked at novel reimbursement models that could support appropriate stewardship and expanded investment in antibacterial drug development.

Incentives and the Antibacterial Drug Development Environment

Investment in all areas of biomedical innovation, including antibacterial products, has declined in the last decade.[5] Over the last two decades, there has been a significant shift in the types of companies engaged in developing and sponsoring new antibacterial drug products. Most new research in this field is taking place within small firms, as many of the large pharmaceutical firms have eliminated their antibacterial drug development programs. While smaller firms create a diverse and rich innovation environment, they often struggle to raise the capital needed to bring products through large, late-phase

[1] Szabo L & P Eisle. (2013). CDC sounds alarm on deadly, untreatable superbugs. *USA Today*. 5 March 2013. Retrieved from http://www.usatoday.com/story/news/nation/2013/03/05/superbugs-infections-hospitals/1965133.

[2] Meier B. (2013). Pressure Grows to Create Drugs for 'Superbugs'. *The New York Times*. 2 June 2013. Retrieved February 27, 2013 from http://www.nytimes.com/2013/06/03/health/experts-debate-plan-to-speed-antibiotic-development.html?pagewanted=all.

[3] Centers for Disease Control and Prevention. (2013). Antibiotic Resistance in the United States, 2013. Retrieved September 17, 2013, from http://www.cdc.gov/drugresistance/threat-report-2013/pdf/ar-threats-2013-508.pdf.

[4] Infectious Diseases Society of America. (2011) Combating Antimicrobial Resistance: Policy Recommendations to Save Lives. *Clinical Infectious Diseases* 52(S5):S397-S428.

[5] National Venture Capital Association. (2013). Patient Capital 3.0: Confronting the Crisis and Achieving the Promise of Venture-Backed Medical Innovation. Retrieved September 23, 2013, from http://www.nvca.org/index.php?option=com_content&view=article&id=268&Itemid=103.

clinical trials. In the past, smaller firms would bridge this gap by selling a promising product to a larger firm early in development, look for venture capital investment, or go on the public market. However, due to the recent economic downturn, small companies have become increasingly dependent on product or company buy-outs. This can also be challenging as very few large firms have retained the infrastructure and expertise needed to acquire and bring these products to market.

The threat of drug resistance demands innovative and diverse new classes of antibacterial drugs. Antibacterial drug development presents unique challenges that can make innovation in this field particularly difficult and expensive. For example, due to concerns about accelerating the rate of resistance in pathogens across whole classes of drugs, antibacterial drug developers are unable to rely on the incremental innovation that has driven new drug approvals in other therapeutic areas. However, participants noted that the investment community sees opportunities for small molecule innovation in the antibacterial development space. Small molecule therapies tend to be cheaper to develop and manufacture than most novel biologic drugs and personalized medicines, which is where much of the large pharmaceutical industry has directed its efforts in the last few years. A recent study also found a higher probability of regulatory success for antibacterial drugs compared to other therapeutic areas.[6] Another study found that anti-infectives, including antibacterial products, can be better candidates for transferring late stage results to phase 3 trials and eventual approval than other development areas.[7]

Understanding the effects of incentives on drug development

While incentives can encourage continued and expanded investment in antibacterial drug development, there are questions about the effectiveness of various types of economic incentives. The Interagency Task Force on Antimicrobial Resistance,[8] under the supervision of the Assistant Secretary for Planning and Evaluation, commissioned the Eastern Research Group (ERG) to perform an economic analysis of possible incentives for the development of new antibacterial drugs. A representative from ERG presented some of their preliminary findings at the meeting.

ERG developed a multi-stage decision tree framework to calculate private expected net present value (ENPV)[9] at the initiation of preclinical studies for six bacterial indications (acute bacterial otitis media, acute skin and skin structure infections, community-acquired bacterial pneumonia, hospital-acquired bacterial pneumonia, complicated intra-abdominal infections, and complicated urinary tract infections). ENPV can remain negative if sales are insufficient to generate a positive return on investment (ROI). ERG's initial findings indicated that ENPV (calculated within a 90% confidence interval) varied significantly between indications and was driven largely by market size, leaving the smallest markets with the lowest baseline ENPV. The initial modeling showed that the lower bound of the baseline ENPV was negative for most indications. The two exceptions to this trend were complicated urinary tract infections (cUTI) and acute bacterial skin and skin structure infections.

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[6] Evans R, S Hinds & D Hammock. (2009). Portfolio analysis and R&D decision making. *Nature Reviews Drug Discovery* 8:189-190.

[7] DiMasi J, H Grabowski & J Vernon. (2004). R&D Costs and Returns by Therapeutic Category. *Drug Information Journal* 38:211-223.

[8] Interagency Task Force on Antimicrobial Resistance. (2011) Public Health Action Plan to Combat Antimicrobial Resistance. Retrieved February 27, 2013 from http://www.cdc.gov/drugresistance/pdf/public-health-action-plan-combat-antimicrobial-resistance.pdf

[9] ENPV is the projected difference between the discounted value of the expected costs of an investment and the discounted value of the expected returns. Positive ENPVs indicate a net gain for the investor.

ERG's analysis addressed the proposed incentives' and conservation measures' effects on ENPV for each indication at different phases in drug development. Incentives and conservation measures with similar effects on the parameters of the model were grouped together. For example, various forms of intellectual property protection and market exclusivity were pooled, as they all increased sales through market monopolies.

ERG considered each incentive using a threshold ENPV that reflected a potential positive tipping point for investors, especially small companies. ERG calculated the level of resources needed for each incentive to push ENPV above the threshold value for each indication. Because baseline ENPV varied between indications, reaching the chosen threshold ENPV required incentives of varying magnitude for each indication. Larger incentives were needed to allow indications with the lowest baseline ENPV to reach the threshold. Some incentives, such as reductions in time to market or in the cost of capital, were able to push ENPV above the threshold at very large magnitudes but were not very feasible at a practical level. Incentives such as intellectual property incentives (including patent term extensions, adjustments, and data and marketing exclusivity) were unable to push any of the indications' ENPV above the threshold regardless of the magnitude of the incentive, but the additional exclusivity under the Generating Antibiotic Incentives Now (GAIN) Act was cited by some participants as an important factor in continuing to pursue antibacterial product development.

Timing the delivery of incentives in the value chain is another critical question. At each successive stage of preclinical and clinical testing, the size of the incentive needed to reach the threshold increased due to time discounting. Rewards that occurred earlier in the development cycle could be smaller but would have the same effect on ENPV at time zero as a much larger reward later in the process. For developers, a "step change" in funding requirements occurs around phase 2 in the transition to the more costly phases of drug development. This time is also referred to as innovation's "Valley of Death," where many promising molecules stall because of too few incentives to bring them through expensive phase 3 trials if success is less than certain. Milestone prizes or subsidies during development could encourage companies to bring molecules into preclinical or clinical testing that they might otherwise abandon due to a lack of resources. Front-loaded payouts, however, may also mean financing the development of molecules that fail in later testing. Prizes and awards have the advantage of only paying for successful products.

Certain incentives appeared to have greater value to developers when they were applied later in the product development cycle, such as additional market exclusivity and tax credits to subsidize late-stage clinical trials. ERG's preliminary results indicate that the most significant drivers of ENPV across all indications included the cost of capital, market size, time to market, and phase 3 trial costs. Several participants added that access to capital and regulatory uncertainty play a significant role in industry's decision-making processes about whether to continue to develop a product. Participants expressed hope that subsidizing development costs could encourage companies to invest more in discovery research and that public subsidies could help reduce the ROI required by developers. Participants also supported payouts early in the market lifecycle when antibacterials are otherwise unlikely to generate significant returns, and staged payouts that could be conditioned on stewardship targets. By staging payments over an extended period of time, companies might also be incentivized to invest in preserving product effectiveness or meeting explicit stewardship targets.

Participants noted that a combination of incentives would likely be required to truly reinvigorate the development pipeline. While participants agreed that ERG's model yielded valuable insights, many noted that additional information could further refine the results to reflect the real-world investment

decisions made by companies. Several participants volunteered to share data on the costs for discovery and commercialization as this information could significantly change the effects and magnitudes of incentives on ENPV. Participants also noted that threshold ENPV would vary depending on the characteristics of the individual developers. Different types of incentives may also be necessary to address the needs of different size developers in various phases of the product development lifecycle.

Balancing stewardship, development costs, and reimbursement

Effective stewardship is needed to delay the emergence of resistant pathogens and to preserve the utility of antibacterial products. Traditional stewardship programs aim to ensure the appropriate use of antibacterial products and may involve health care professionals, pharmacies, hospital management, insurers, and their formulary committees. While stewardship programs are needed, they also create disincentives for new research in this field by limiting ROI. Two of the suggestions to address these disincentives include reducing the cost of development through new streamlined regulatory pathways and identifying new reimbursement models that incentivize both new development and stewardship.

Proposed Regulatory Changes

In 2012, the Infectious Diseases Society of America proposed a limited population antibacterial drug (LPAD) designation[10] that they suggest will invigorate development in this field. The LPAD designation was intended to expedite the development and approval of products by allowing them to be studied in and approved for a narrow population of patients with serious infections. Under this proposal, FDA would not have the authority to restrict the use of LPAD products. Instead, ensuring the appropriate use of these products would be managed by the health care community. Special labeling and an LPAD logo would alert prescribers that, given the more targeted clinical trials, the benefits and risks associated with the drug are not well-characterized outside the indicated population, and FDA considers the drug to be inappropriate for broader, "off-label" use. The President's Council of Advisors on Science and Technology (PCAST) made a similar recommendation calling for FDA to develop a "special medical use" (SMU)[11] pathway. The SMU pathway would not be restricted to antibacterial products however, and could be applied to clearly-defined subpopulations of patients in other therapeutic areas. Proponents of these regulatory pathways assert that the targeted and streamlined clinical trials will reduce development costs, making antibacterial drug development more attractive. Some participants noted that reduced clinical trial costs alone would not be sufficient to invigorate the antibacterial drug pipeline, and government intervention might be appropriate given the failure of the market to support antibacterial drug development.

Reimbursement paradigms to support appropriate use of antibacterial drugs

The current reimbursement model for drugs is based on unit sales of a product. Antibacterial drug products are typically used in short courses of treatment, are curative, and have traditionally been reimbursed at low rates per unit. In light of the need to further limit the use of new antibacterial products, this reimbursement model presents a serious challenge for making the development of antibacterials a viable and attractive investment for manufacturers. Companies have few incentives to

[10] Infectious Diseases Society of America. (2012). Limited Population Antibacterial Drug (LPAD) Legislation Would Expedite Development of Much-Needed Antibiotics. Retrieved February 27, 2013, from http://www.idsociety.org/2012_LPAD_Proposal_Backing/

[11] 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 27, 2013 from http://www.whitehouse.gov/sites/default/files/microsites/ostp/pcast-fda-final.pdf

invest in antibacterial research, particularly for products that target drug resistant infections where the potential patient population is small and there is an increased need for strict stewardship. For these reasons, various stakeholders have started to explore new reimbursement mechanisms that create a feasible development business model while "delinking" the ROI from sales volumes. For example, a capitated or license-based model could allow payers to purchase for a flat rate the right to prescribe any amount of a new antibacterial drug, completely separating payments from sales volume. More detailed descriptions of these models can be found in the meeting discussion guide.[12]

Value-Based Pricing

While not explicitly a delinking mechanism, higher, value-based pricing could remove some of the incentive to pursue the low-price, high-volume sales model that has driven the widespread overuse of antibacterial products and accelerated resistance. Higher prices and reimbursement values could also incentivize investment; participants pointed to the orphan and oncology fields as areas where innovation has been driven primarily by insurers' willingness to cover the costs of increasingly expensive medicines. Higher prices have also been cited as a relatively effective means to trigger more restrictive reimbursement policies (e.g., prior authorization) and formulary guidelines, which could also support stewardship.

Payers have also become increasingly willing to peg reimbursement to quality and outcomes measures, rather than using the volume and intensity of services as its benchmark. Ongoing health care and payment reform will likely bolster this trend. As has been noted at this and other meetings on this topic, some stakeholders are willing to support higher pricing for antibacterial products that deliver a measurable value and improvement over existing therapies. Considering that treating resistant infections has been shown to cost up to $30,000 per patient (and the U.S. healthcare system more than 20 billion dollars annually),[13] the value of new antibacterial drugs to treat these infections cannot be overstated. With fewer therapeutic options available than ever before, any new product that can improve outcomes for patients with serious infections is expected to cost significantly more than existing therapies. In discussions about a proposed restricted-use antibacterial drug, stakeholders appeared willing to support pricing on the order of $2,000-30,000 per course of treatment. Depending on the prevalence of resistant infections, such a drug could likely generate up to $500 million in annual U.S. sales.

New antibacterial drugs have entered the market in recent years at significantly higher price points than older therapies, and have been widely accepted and approved for higher reimbursement or add-on payments by payers.[14] Optimer's DIFICID® (fidaxomicin) is the first new treatment for *C. difficile*-

[12] Incentives for Change: Addressing the Challenges in Antibacterial Drug Development; Brookings Institution Workshop Discussion Guide. (2013). Retrieved March 4, 2013 from http://www.brookings.edu/~/media/events/2013/2/27%20bcadd%20meeting/discussion%20guide.pdf

[13] Roberts R, et al. (2009) Hospital and Societal Costs of Antimicrobial-Resistant Infections in a Chicago Teaching Hospital: Implications for Antibiotic Stewardship. *Clinical Infectious Diseases* 49:1175-84. Retrieved February 27, 2013 from http://www.tufts.edu/med/apua/research/completed_projects_4_3378722343.pdf

[14] Medicare Program; Hospital Inpatient Prospective Payment Systems for Acute Care Hospitals and the Long-Term Care Hospital Prospective Payment System and Fiscal Year 2013 Rates; Hospitals' Resident Caps for Graduate Medical Education Payment Purposes; Quality Reporting Requirements for Specific Providers and for Ambulatory Surgical Centers Federal Registry Notice. Retrieved February 27, 2013 from https://www.federalregister.gov/articles/2012/08/31/2012-19079/medicare-program-hospital-inpatient-prospective-payment-systems-for-acute-care-hospitals-and-the#h-142

associated diarrhea to come to market in over 25 years, and has been shown to be better at preventing re-infection than older drugs.[15] Though it costs twice the price of the previous standard therapy, DIFICID® has performed well on the market, and has been awarded a new technology add-on payment (NTAP) bonus under the Centers for Medicare and Medicaid Services' (CMS) reimbursement system. CMS' national coverage determination has also encouraged uptake throughout the health care system.

Along the same lines, a product's "health impact" could serve as a basis for delinking ROI from sales volume under the proposed Antibiotic Health Impact Fund.[16] Developers who voluntarily place products in a fund (rather than seeking high sales volume on the traditional market) would receive prize money based on that product's value to society. If the fund was large enough to incentivize product development, such a system could steer antibacterial innovation towards the greatest unmet needs and encourage manufacturers to preserve their products' efficacies – and therefore the size of their payout – by promoting appropriate use.

Advanced Market Commitments

Guaranteed payments or advanced market commitments could potentially provide an attractive reward for developers that delinks payment from sales volume. Advance market commitments have proven effective at supporting other therapeutic areas and the development of products without strong market incentives. Examples include the GAVI Alliance,[17] which subsidizes vaccines for public sector use in the developing world, and the Biomedical Advanced Research and Development Authority (BARDA),[18] an office within the U.S. Department of Health and Human Services (HHS) that supports the development and purchase of medical countermeasures against chemical, biological, radiological, and nuclear threats through dedicated funding.[19] Participants from industry favored guaranteed payments that began soon after the product entered the market, and estimated the necessary magnitude of the award at $1.75-2.5 billion over five years. There was some discussion that public sources of funding might be needed or appropriate to guarantee that level of reward.

Rempex Pharmaceuticals' Rewarding Antibiotic Development and Responsible Stewardship (RADARS) proposal[20] combines existing reimbursement mechanisms within CMS with other public funding to guarantee an annual minimum payment to drug developers. Under the proposal, CMS would provide a higher reimbursement level for new products through an NTAP for qualifying antibacterial drugs (e.g.,

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[15] Cornely O, et al. (2012). Treatment of First Recurrence of Clostridium difficile Infection: Fidaxomicin Versus Vancomycin. Clinical Infectious Disease 55(Suppl 2):S154–S161. Retrieved September 20, 2013, from http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3388030/pdf/cis462.pdf.

[16] Outterson K, T Pogge & A Hollis. (2011). Combating Antibiotic Resistance through the Health Impact Fund. Boston University School of Law, Law and Economics Research Paper No. 11-30. Retrieved 02/26/2013 from http://ssrn.com/abstract=1866768 or http://dx.doi.org/10.2139/ssrn.1866768.

[17] GAVI Alliance. (2013). Pneumococcal AMC process & design evaluation. Retrieved September 24, 2013, from http://www.gavialliance.org/results/evaluations/pneumococcal-amc-process---design-evaluation/.

[18] Biomedical Advanced Research and Development Authority. http://www.phe.gov/about/barda/Pages/default.aspx

[19] Project BioShield Act of 2004. Pub. L. No. 108-276. Retrieved September 24, 2013, from http://www.gpo.gov/fdsys/pkg/STATUTE-118/pdf/STATUTE-118-Pg835.pdf.

[20] Burgess D. "Rewarding Antibiotic Development and Responsible Stewardship (RADARS)." Incentives for Change: Addressing the Challenges in Antibacterial Drug Development. The Brookings Institution, Washington, DC, 27 February 2013. Presentation. Available at http://www.brookings.edu/~/media/events/2013/2/27%20bcadd%20meeting/presentation.pdf.

qualified infectious disease products under the GAIN Act), while HHS would cover any additional cost of meeting a guaranteed annual minimum for the first five years the product was on the market. A similar program could guarantee minimum payments in the private system through a public funder to ensure that developers were being adequately compensated, without creating an incentive to use antibacterial products inappropriately. Additionally, these payments or a proportion of the payment could be conditioned on meeting stewardship targets.

Strategic Reserve

The proposed "Strategic Antibiotic Reserve" would reward developers of products likely to generate very low sales on the market, including antibacterial drugs indicated only for extremely rare infections, or those reserved long-term until the failure of other available therapies. The reserve would be most appropriate for products that effectively generate no sales, and might easily outlive their patent rights or market exclusivity. The reserve could also be used if multiple therapies for the same bacterial indication entered the market at the same time in order to stagger their market entry. Incentivizing developers to keep their products off the market in this manner would likely require substantial reward payments, but could completely delink rewards from unit sales while compensating developers and preserving the utility of new antibacterial drugs.

Potential Next Steps

Long-term, systematic solutions to the tensions inherent between antibacterial drug development and appropriate use will require broad stakeholder engagement and innovative thinking to ensure the sustained effectiveness of and market for antibacterial drugs. As discussed above, higher pricing appears to be a potential short-term solution to support appropriate use and incentivize development. Reorienting the health system towards incentivizing quality and patient outcomes can also help change the market prospects of new antibacterial drugs. Health systems are already working to incorporate infection prevention, quality measures, and good prescribing practices into their reimbursement structures, and models from other countries indicate that stewardship programs and educational campaigns can reduce inappropriate prescription rates and rates of resistance.[21, 22] It is urgent that stewardship programs are implemented and strengthened across clinical settings to not only promote appropriate use of new products, but to also preserve the effectiveness of the treatments available today.

Diagnostics

A major roadblock to appropriate use of antibacterial therapies is the lack of rapid, accurate diagnostics for antibacterial infections. In the case of acute, serious infections, antibacterial drugs are often prescribed empirically in the absence of confirmatory diagnostic evidence. New diagnostic technologies will be critical to ensuring antibacterial therapies are used appropriately, that drug development and clinical trials can be made more targeted and efficient, and that effective policies (in hospitals, outpatient settings, formularies, etc.) are put in place to support appropriate use. Unfortunately, there

[21] Subuncu E, et al. (2009) Significant Reduction of Antibiotic Use in the Community after a Nationwide Campaign in France, 2002-2007. *PLoS Medicine* 6(6): e1000084. Retrieved February 27, 2013 from http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000084

[22] Goossens H, et al. (2011, June) *Achievements of the Belgian Antibiotic Policy Coordination Committee (BAPCOC)*. Poster presented at the 3rd Edition of the World HAI Forum on Healthcare-Associated Infections, Annecy, France. Retrieved February 27, 2013 from http://www.biomerieux-diagnostics.com/upload/Herman%20Goossens%20Belgium-1.pdf

is little public funding available for diagnostics research, and although the pharmaceutical industry has helped subsidize costs for some diagnostics developed in tandem with particular drugs, broader solutions may be needed. A participant noted that while the market for diagnostics is currently very weak, that could change as new antibacterials enter the market at higher price points. For instance, more expensive drugs are likely to have additional prior-authorization requirements which may include confirmation of the pathogen's susceptibility.

Outcome-oriented drug development

In order to focus development towards unmet needs and clinical outcome improvements, participants agreed that better planning and data could help support innovation and early uptake of new products. Target product profiles could help guide investment decisions, and participants drew analogy to the targeted market for orphan drugs, which address a narrow medical indication and provide a clear benefit and value to patients. Although orphan drugs are expensive, the high prices are justified by the drugs' impacts, and payers have been willing to cover the costs of orphan drugs.

Similar outcome data on new antibacterial drugs could support uptake of new products and speed payers' coverage determinations. Drug developers are already involving payers earlier in the development process and building outcomes and quality metrics into clinical trials to provide payers the necessary evidence to make earlier coverage decisions. Coverage with evidence development,[23] in which CMS requires ongoing data collection as a condition of a national coverage determination, could be used to gather more information on patient outcomes while supporting earlier access to new promising therapies. Such postmarket studies could be especially important for new antibacterial drugs approved under limited labels for small populations. And though still in a pilot phase, the FDA/CMS parallel review process has supported rapid coverage decisions on new devices and saved the developer the burden of doing additional trials.[24] A similar program for drugs could help developers build appropriate outcome measures into clinical trials, in consultation with CMS and FDA.

Research infrastructure

One of the major challenges for reinvigorating the antibacterial development pipeline is the loss of antibacterial research infrastructure and expertise over the last few decades in most major pharmaceutical firms. As discussed by some participants in venture capital, small biotech companies are increasingly relying on acquisition to bring their products through late phase development; most lack the resources to do it themselves even though they are now responsible for the majority of antibacterial discovery research.[25] Without action today to rebuild lost research and development infrastructure and expertise in large firms or substantial investment in the research capacity of small firms, innovation could continue to stall.

Piloting Incentives

[23] The Centers for Medicare and Medicaid Services may mandate the collection of additional patient data to supplement standard claims data for some products as a condition of a national coverage determination, where more data is needed on a new product's effectiveness.

[24] Ray T. (2013, April 3). Exact Sciences Discusses Benefits of Taking Cologuard through FDA/CMS Parallel Review Pilot. *Genomeweb*. Retrieved September 23, 2013, from http://www.genomeweb.com/clinical-genomics/exact-sciences-discusses-benefits-taking-cologuard-through-fdacms-parallel-review.

[25] Dutton G. (2013, August 14). Biopharmas Drive Antibiotic Development. Genetic Engineering & Biotechnology News. Retrieved September 23, 2013, from http://www.genengnews.com/insight-and-intelligenceand153/biopharmas-drive-antibiotic-development/77899874/.

Based on comments from stakeholders, incentives play a significant role in industry's decisions about whether to engage in drug discovery initially and how far to continue with product development. As mentioned before, ERG's preliminary findings illustrate that relatively small incentives given earlier in the development process may have a considerable effect on continued development of drugs through early phases of clinical trials and on to approval. Pilots of early incentive mechanisms combined with different reimbursement models may be an effective means to invigorate new development in antibacterial drug development.

Enhanced stakeholder communication

Finally, participants identified the need for better communication to stakeholders about recent changes in thinking about antibacterial drug development. Participants stressed that FDA has already begun to review and clarify requirements for antibacterial drug approval, and that proposals for single pathogen and limited population pathways were being seriously evaluated, including through soliciting public comment. Developers also indicated that FDA has been flexible in evaluating applications, which should be communicated throughout industry as companies consider investing or rebuilding antibacterial research and development infrastructure. Participants felt that these messages needed to be communicated more broadly throughout industry to help reinvigorate the pipeline.