Duke UNIVERSITY | Duke-Margolis Center *for* Health Policy

Exploring Practical Implementation of Economic Incentives for Antimicrobial Development in the U.S.

Day 1: Expert Workshop
Summary
July 20, 2016

Introduction

Antibiotic-resistant pathogens have become a severe public health concern, and drug-resistant infections are estimated by the CDC to cause over two million illnesses and 23,000 deaths per year in the U.S. Many pathogen strains have developed resistance as a result of inappropriate antibiotic use, and as traditional antibiotics are losing their effectiveness, lack of effective treatments is a major challenge facing healthcare providers. Antimicrobial development is costly as clinical trial design and the lack of sensitive and rapid diagnostics make evaluating a drug against a specific pathogen exceedingly difficult and time consuming. Once an antimicrobial is approved, it typically encounters a weaker market than drugs in other therapeutic areas due to the narrow set of patients for whom they may be clinically appropriate, which limits use and therefore drug sales, and because antimicrobials as a category are priced much lower than drugs for other indications. In addition, the availability of effective generic antibiotics currently on the market makes market entry of new antibiotics even more economically challenging. As a result, few companies invest in antimicrobial development. In order to overcome the drug resistance problem, stakeholders need to create incentives for research and development activities, and to promote stewardship and appropriate use of current and future antibiotics.

Antimicrobial resistance (AMR) is the result of a combination of factors. Antimicrobial overuse and misuse includes prescribing antibiotics for viral infections or minor infections that will likely resolve on their own, patient noncompliance (not completing a full course of antibiotics as prescribed), preventive use of antibiotics in clinical and agricultural settings, including as a growth enhancer in agriculture. AMR also results from a dearth of options for diagnosis and treatment of infections. The antimicrobial drug development market has been failing for decades, discouraging investment in antimicrobial development, resulting in a low number of drugs in the pipeline. New economic incentives are needed to spur antimicrobial development while ensuring appropriate use.

When compared with other categories of drugs, antibiotics face constant challenges from generic drugs, and therefore, might have a longer path to profit and lower returns on investment. It is estimated that a company would need a Net Present Value (NPV) of greater than $100 million to make an investment in antimicrobial development financially feasible[1].

Global consensus on the need for policies that support antimicrobial development incentives is growing, with several groups dedicated to tackling this issue in the U.K. and E.U. Further, more than 80 pharmaceutical and biotechnology companies have signed the Davos Declaration, which calls on governments to help develop new and alternative market structures for antimicrobials. However, the current efforts of the U.S. government to build such market structures have yet to fully impact the

[1] https://www.ohe.org/publications/new-drugs-tackle-antimicrobial-resistance-analysis-eu-policy-options

return for antimicrobials, and there is not yet a path for implementation of a delinkage model, which provides reimbursement to the manufacturer regardless of sales volume, for antimicrobials.

Meeting Objectives

On July 20, 2016, under a cooperative agreement with the U.S. Food and Drug Administration (FDA), the Duke-Margolis Center hosted an expert workshop to address the challenges facing antibiotic research and development, with a focus on evaluating and aligning on several economic incentives that would reward antimicrobial products based on societal value rather than volume sold. This expert workshop involved a broad group of stakeholders to explore several key issues: the increasing threat of antibiotic-resistant pathogens; the financial and technical challenges to antibiotic developers; the inappropriate use of antibiotics; and the unsatisfactory development and utilization of rapid diagnostics. Participants also evaluated major proposed incentive models and assessed their effectiveness in encouraging antibiotic R&D activities within the U.S. Participants at the workshop included small and large drug and device manufacturers, regulatory agents, public and private payers, patient advocates, infectious disease physicians, economists, and public health officials.

Addressing Unmet Need

In 2013, the CDC conducted an assessment of the greatest antimicrobial threats in the U.S. Through this assessment, the CDC developed a tiered list of threats; the most urgent include *Clostridium difficile*, Carbapenem-resistant *Entrobacteriaceae*, and *Neisseria gonorrhoeae*. The purpose of this list was to provide a snapshot of the threats posed by microbial pathogens, and CDC has stated that they will update the list every five years. This list was generated based on infection occurrence, economic impact, and availability of therapeutics, and during the workshop, several outstanding concerns were raised about using such a list for incentivizing drug development. Consequently, the workshop attendees discussed the need for a priority list that could inform future R&D efforts. Furthermore, workshop attendees identified the need to act beyond today and to think proactively by taking into account future unmet need by promoting a diverse drug portfolio. While it is impossible to accurately predict future resistance, participants agreed that any prioritization list should enable a drug development pipeline that is robust and diverse.

Subsequently, the discussion focused on ways to promote a diverse pipeline of antimicrobials. Available incentives would need to ensure that the drugs in development were broad enough to address unknown future needs, while also promoting development of drugs designed to address current, urgent needs. By providing both incentives that can be general, by being applicable to most antimicrobials, and targeted, by being available to antimicrobials that meet specific criteria, the U.S. would be able to react to current threats and to be forward-looking. However, one incentive model will not be able to address both types of development, so multiple options will need to be considered.

Fueling the less than attractive market for antimicrobials is the reluctance from venture capitalists to invest in the antimicrobial development business due to the lack of predictable positive return on investment. Lack of funding makes it very difficult for innovative, small drug manufacturers to enter and survive in this space. Further, large companies have shuttered their antimicrobial divisions because they see greater returns from investments in other disease areas.

While patients across all age groups, locations and medical conditions require antibiotics that are affordable, safe and effective, major challenges remain that are causing an increase in resistance and a dry antimicrobial pipeline.

Stimulating Antimicrobial Development

The antimicrobial drug development market has been considered to be failing because of lack of investment and a lack of innovation in the drug pipeline. Several aspects contribute to this problem, including the need for drug conservation, scientific challenges, availability of low cost and effective generics, and mis-/over-use, which leads to resistance. Sales of drugs for other diseases and conditions are far more lucrative than those targeting bacterial infections; sales of the top cancer drug total more than sales for all antimicrobials. Removing the disincentives to antimicrobial development with targeted economic policies has great potential to rescue this failing market.

Push incentives

One type of incentive that participants discussed was a "push incentive", which provides funds prior to market launch to support drug development. Push incentives have the potential to reduce the initial cost of research and development, and therefore to lower the barrier to entry. These incentives are particularly useful for smaller manufacturers because obtaining investment in antibiotics from traditional sources (venture capital, public offerings) is challenging due to the high risk, low profitability, and lack of predictability. In addition, strong patient advocacy and high sales volumes in other therapeutic areas drives investment to other, more lucrative areas.

To address financial and market issues associated with early antibiotic development, the Biomedical Advanced Research Development Authority (BARDA) has been implementing several measures to promote early research and development. BARDA, an organization within the U.S. Department of Health and Human Services (HHS), is focused on enhancing the U.S. government's ability to develop medical countermeasures to natural and man-made biological threats. In July 2016, BARDA, in cooperation with the National Institutes of Health (NIH), announced one of the largest public-private partnerships in the world, which will aim to move antimicrobial targets from the lab into clinical trials. Additionally, the BARDA portfolio funds all clinical phases of antimicrobial drug development. Between these two programs, BARDA will serve as an incubator for drug developers with funding and support provided from pre-clinical research through clinical trials.

Most participants felt that funds available through the BARDA and NIH programs were appropriate push incentives, and there was less of a need to develop additional push incentives for early development as there was a need to support other parts of the drug development life cycle. Many participants felt that funds should support products all the way through manufacturing. Chemistry, Manufacturing and Control (CMC) is an expensive process, and there is a need for incentives to get antimicrobial companies, particularly small companies who rely on grants and other outside funds for development, through manufacturing and production. While contracting manufacturing to overseas sites creates savings, there could be a trade-off in safety and accessibility.

Regulatory incentives

Congress and regulatory agencies have implemented various initiatives that have been intended to address some of the regulatory challenges associated with antimicrobial development, including the

GAIN Act, the proposed use of a Limited Population Antibacterial Drug (LPAD), and collaborative efforts, such as endpoints development through the Foundation for the National Institutes of Health (FNIH) and the Clinical Trials Transformation Initiative (CTTI) Antibacterial Drug Development Program which aims to streamline and facilitate conduct of clinical trials for antimicrobials, particularly those focused on hospital-acquired and ventilator associated bacterial pneumonia, as a means to incentivize drug development. Although these measures have led to modest progress in antibiotic research, there are still several challenges. These challenges include: 1) new drug candidates targeting highly-resistant bacteria show uncertain safety and efficacy; 2) programs focusing specifically on highly-resistant bacteria have challenges with patient enrollment and, 3) restrictive timing on when patients with hospital-acquired infections can be enrolled in trials. Because of these challenges, many participants felt that proving superiority to existing drugs or treatment of resistant bacterial strains was nearly impossible.

Many participants also had concerns about the lack of process harmonization between the FDA and the European Medicines Agency (EMA). Several factors can create unnecessary duplication during the regulatory process, including differing clinical endpoints, development guidances, definitions and rules, and filing and documentation requirements. Many companies would benefit from standardized process and alignment on Chemistry, Manufacturing, and Controls (CMC) requirements. Therefore, international coordination to standardize the FDA and EMA drug approval processes was identified as a need.

Pull incentives

Over the past few years, government and non-government stakeholders in the U.K., E.U., and U.S. have proposed economic incentives to help drive investment in R&D and to promote stewardship. Some of these models include “pull incentives”, which provide a reward once the product is approved and on the market. In the U.K., the Review on AMR was commissioned by the U.K. Prime Minister in collaboration with the Wellcome Trust, to examine the economic issues surrounding antimicrobial development and drafting recommendations to improve them. In May 2016, the Review on Antimicrobial Resistance released a new report detailing a comprehensive plan aimed at tackling AMR globally. Through the Review on AMR, three factors were identified to improve antimicrobial development: 1) funding for early stage R&D activities; 2) a lump sum payment upon market entry and 3) harmonization of FDA/EMA clinical trial standards. Additional, global coordination was identified crucial to overcoming antibiotic resistance.

In Europe, the European Commission’s Innovative Medicines Initiative (IMI) established DRIVE-AB, a consortium comprised of 23 public and private partners from 12 different countries. The group aims to define “responsible antibiotic use” with both qualitative and quantitative indicators, describe the current antibiotic resistance landscape from clinical and economic standpoints across socioeconomic backgrounds, and work with simulation models to assess the future impact of antibiotic resistance. DRIVE-AB follows three major core principles: to ensure access for patients in need, to promote sustainable use of antibiotics, and to encourage innovation in research. To address both the medical need and drug stewardship, DRIVE-AB has explored a variety of delinkage models, and has published in their preliminary findings report that the market entry reward and the insurance license models were most promising pull initiatives.

A market entry reward is a series of fixed payments to a developer who receives approval for a high-priority drug. This model could be ideal to incentivize antibiotic development, but it was suggested that

might work more effectively with a tiered, or benchmarked, system for how rewards could be distributed. A benchmark market entry reward could 1) incentivize high-priority drug development (such as Gram-negative or oral drugs); 2) show transparency and predictability in measurements and outcomes and 3) encourage further development after initial registration. Payments to the manufacturer could be based on these criteria, with bonus payments for each benchmark that the drug meets. Participants were supportive of this model, but questioned whether it would be feasible to implement in the U.S., particularly if funding were to be dependent on appropriations from Congress.

Another model that was presented was the insurance license model, and the related cap and collar model (see DRIVE-AB report for more details). The insurance model is currently being piloted within the U.K.'s National Health Service. In this model, the payer commits to buying a set number of courses of drug at a certain price. If, at the end of the contracted period, the actual utilization is lower than the agreed amount, the payer will pay up to what the full volume would have cost; if the utilization is higher than the agreed amount, the payer will pay the manufacturer for the extra units of drugs, but only to cover the cost of goods; the manufacturer will not make a profit on the excess sales. In the cap and collar model, the manufacturer can make profit on product above the agreed amount (the collar), but only to a certain volume (the cap). The profits made on any sales over the cap will be split between the payer and the manufacturer. Both versions of this model address two important issues: stewardship, because the manufacturer will have no incentive to sell more drugs than are needed because of the predictable and agreed upon return of investment.

One issue that was discussed was the difficulty in ensuring accessibility for both the market exclusivity reward and insurance. In the case of a drug that sells a high volume of product, generic drug makers will likely fill the void if the developing manufacturer chooses to discontinue the product. However, if the drug is rarely used, or meant as a drug of last resort, than there will be no incentive to continue production once the award period ends. As a result, there is a need to consider how any incentive would impact sustainability and access.

Many participants were also concerned that the market entry reward or insurance models would be difficult to implement within the U.S. healthcare system, and they were eager to consider pull models that could be implemented relatively quickly. Transferable exclusivity vouchers were a model presented at the workshop that could gain support in Congress and be a meaningful incentive for both small and large manufacturers. In this model, the antimicrobial manufacturer would be rewarded with a voucher that would extend exclusivity of a product of their choice for an additional set amount of time after the patent expires. This voucher could be used by the company that received it, or it could be sold to another company. Profits from the sale, or profits from the other drug's extended market exclusivity, would provide the reward for the antimicrobial development. This model would not require upfront government funding, but it could work equally well in promoting stewardship and encouraging medical innovation.

Factors Affecting Implementation

Predictability was identified as pivotal to promote antimicrobial development. Due to the multi-year drug development process, manufacturers need to have a predictable return on investment once their product enters the market. Furthermore, sustainability was also identified as a key factor needed to promote development. Incentives that rely purely on government funds may not attract manufacturers

as the funding would require Congressional appropriations, which are neither predictable nor sustainable due to their dependence on the political climate at the time.

Because of this issue, participants considered alternative options for funding a delinking reward. Antimicrobials have a high societal value, but they are often priced low, and new drugs should be used infrequently. U.S. health systems, including the Centers for Medicare and Medicaid Services (CMS), as well as private insurers, are beginning to move toward value-based, high-quality care. CMS estimates that alternative payment models (APMs) will constitute 30% of the total reimbursement by the end of 2016, and CMS has set a goal of linking 85 percent of all Medicare payments to quality and outcome metrics by the end of 2016. Two prominent examples are Medicare ACOs and the bundled payment model, where payments to hospitals and physicians are tied to the providers' quality and performance measures. Although providers that cover Medicare and Medicaid patients are not yet required to follow strict stewardship protocols and practices, antibiotic use has become a growing concern for health officials, to the point that CMS recently introduced a proposed rule that would require hospitals to implement antibiotic stewardship programs. Recently, CMS has adopted quality measures that focus on preventing healthcare-associated infections (HAIs), and providers would be financially penalized for failing to meet the infection control requirements. Additionally, HHS has taken measures to distribute information on appropriate antibiotic use, and tracked medical claims on the utilization of antibiotics. Data collection will play an important part in implementing stewardship and promoting better value in care. These efforts aim to support the Transforming Clinical Practice Initiative (TCPI) to help physicians make better clinical decisions.

Many private insurers have also begun to implement policies that support value-based care and prescribing. In some instances, insurers have negotiated payments for drugs that are contingent on the drug's efficacy. In these negotiations, the insurer can estimate the cost-benefit ratio based on existing cases of disease. However, estimating the number of people who may use an antimicrobial can be difficult. In regards to the price of new drugs, drug price negotiation often starts years ahead of market entry, which makes it difficult for payers to estimate the value of the product due to the lack of market certainty. Drug manufacturers will redistribute their investment to higher-opportunity medical areas, and if payers can effectively respond to their shift in investment, they will have more leverage in negotiating drug prices with manufacturers.

Promoting Stewardship and Appropriate Use

The importance of appropriate use and the need for any payment models to take stewardship measures into their design was raised often during discussion. The way antimicrobials are currently used and prescribed was identified as a top priority by the attendees; therefore some of the discussion focused on how economic incentives could be tied to proper use. Antimicrobials that enter the market with the help of an incentive should have a longer period of use than those currently on the market as a result of modified prescribing behaviors. One suggestion was to use diagnostic-restricted marketing for the drug, and to utilize penalties or bonuses on use for providers.

Participants discussed how there is a grey area of judgment that exists between "proper" and "improper" use of antimicrobials. As clinical decisions are measured in retrospect, quality and outcome measures do not always represent the medical judgment of physicians. Further, it is difficult to obtain reliable data for outcome measures, and additional quality metrics could be a burden on physicians. The

goals of cost-control and stewardship are often overlapping, because less utilization of antimicrobials will also decrease the expenditure on drugs.

Additionally, improved infrastructure was also identified as immediate need; however no specific models were proposed during the meeting.

Stewardship and appropriate use are largely dependent on the doctors and staff that administer care, who need to be capable and well-trained in the area of infectious disease. Currently, there is a shortage of medical practitioners who specialize in infectious diseases due to a lack of academic interests and limited financial returns; therefore, there is a need to create an "intellectual pipeline" to develop professionals with strong expertise in infectious diseases research. In order to achieve this goal, academic institutions, hospitals and manufacturers would need to coordinate to develop the appropriate workforce.

Challenges with Diagnostic Development and Uptake

Diagnostics are an important tool for the identification of infections and for the appropriate treatment of patients.

Rapid diagnostics are helpful in improving the clinical outcomes for both inpatients and outpatients. For inpatients, they can help guide the selection and dosage of antibiotics and correctly identifying the cause of disease; for outpatients, they can replace expensive laboratory tests and reduce the prescription cost. However, health providers fail to adopt rapid diagnostics in their antibiotic treatment. One speaker outlined three major challenges for antimicrobial diagnostic development. First, there is difficulty in obtaining meaningful data on patients, and this step can obstruct the initial selection of antibiotics and undermine the management of antibiotic use. Second, the lack of clinical outcomes data makes it difficult to demonstrate the value of rapid diagnostics, and more funding is needed to support outcomes studies. Third, there is no sustainable payment model to reimburse the cost of rapid diagnostics, and the effort to integrate antibiotic tests into current payment framework faces many challenges.

This lack of uptake can be seen as more of an adaptive issue rather than technical challenge. It is often cheaper and less complicated to skip testing and treat empirically due to the low costs of generic drugs. To overcome this adaptive challenge, it is necessary to help physicians understand test results and demonstrate the tests' benefit to improve clinical care.

In addition to the challenges associated with uptake, there are also development challenges, not unlike those for antimicrobial drugs. There are a number of scientific and economic challenges facing a diagnostics R&D company, including high development cost and low returns on investment. Several financial and non-financial solutions were discussed. Non-financial measures could include promoting education, improving clinical research infrastructures, reforming regulatory schemes to optimize utilization, and expanding patent protection. Financial measures could include increasing funding for R&D activities, providing economic incentives to delink profit and volume, and promoting value-based pricing for diagnostic devices. The federal government could also provide improvements by increasing tax credits for diagnostics research and by permanently repealing the device tax.

The Center for Devices and Radiological Health (CDRH) has made several recent efforts to advance regulatory science and provide efficient regulatory pathways for the diagnostics industry. To address

regulatory issues in diagnostics development, CDRH has increased the communication with the community by convening advisory panel meetings, creating research guidelines, and hosting workshops to promote coordinated efforts in diagnostics R&D.

However, several concerns remain. The first concern is the alignment between the rapid diagnostics and the antimicrobial drug; it was discussed the potential need of incorporating rapid diagnostics into value-based payment models. This measure could both offer incentives for developers and promote antibiotic stewardship for physicians. A market entry reward model could incentivize diagnostics development in areas of antibiotic-resistant bacteria. From a public health standpoint, it was also suggested that federal agencies should consider include rapid diagnostics to the surveillance of infectious diseases.

Participants also discussed strategies for building an efficient infrastructure for diagnostics development. The lack of clinical outcomes data can discourage doctors from adopting rapid diagnostics in antibiotic treatment. If rapid diagnostics cannot demonstrate greater efficacy compared to traditional approach, they are unlikely to adopt the new method of antibiotic treatment.

The most important takeaway from this session was that diagnostics have a limited ability to influence stewardship if they are not used or used appropriately. Introduction of new diagnostics will have limited impact if there are not significant behavioral changes by providers, and there need to be provider incentives in place to encourage physicians to not only use the available tools, but to also change their prescribing behaviors based on the results.

Conclusion and Next Steps

Overall, there was a strong emphasis on the need for new incentives that both encouraged development of antimicrobials and promoted their appropriate use. There have been many recommendations made globally, and the U.S. faces the challenge of adapting some of these recommendations for use in a fragmented healthcare system. Even though there is still not a unanimous view on how these policies should move forward in the U.S., there is definitely agreement on the urgency for actions. While there was a strong emphasis on the need for new incentives for development, the need for measures that would control overuse and misuse of antimicrobials was recognized as a high priority.

One recognized key to success will be rewarding antimicrobial development based on the drug's value to society rather than the volume of drug sold. However, implementation of this de-linkage approach in the U.S. will need to align with current U.S. trends toward value-based payments. Utilizing a system that promotes value could also encourage greater use of diagnostics, which may reduce inappropriate use of existing antimicrobials.

As next steps, the Duke-Margolis team will work with the Antimicrobial Advisory Group to develop a more detailed look at these incentives and possible paths to implementation. In November, Duke-Margolis will host a public meeting to solicit broader feedback on incentives, implementation method, and funding options.

Day 2: Antimicrobial Advisory Group Meeting
Summary
July 21, 2016

On July 21, 2016, the Duke-Margolis Center hosted a meeting with the Antimicrobial Advisory Group to discuss in-depth criteria that antimicrobial development incentives should meet, and practical

considerations that would make economic incentives feasible and financially sustainable. Experts from different stakeholder groups discussed a variety of incentive measures designed to encourage antimicrobial development, focusing primarily on "pull" incentives that reward manufacturers economically upon a drug's approval. Participants evaluated a variety of incentive models, including market entry rewards, an "insurance" model, higher reimbursement, and transferrable exclusivity. The meeting ended with a discussion on possible funding options to support antimicrobial development incentives.

Project Timeline

The meeting started with a debrief about next steps and timeline associated with the project. In the next few months, the Duke-Margolis Research staff will work closely with the Advisory Group to evaluate implementation and funding of each potential incentive model in order to develop policy recommendations. In the late fall, Duke-Margolis will host a large public meeting to share the group's proposals and to gather broader stakeholder feedback. The ultimate goal is to publish, by the end of 2016, several white papers analyzing economic incentives to reward drug research and development, addressing incentive payment options, and providing policy recommendations.

The Advisory Group was also made aware of several external events that will be held later this year to address antimicrobial-related issues. PACCARB will hold the next meeting on September 19-20, 2016 to discuss policy recommendations for antimicrobial research. The UN General Assembly, planned on September 21, 2016, will also address antimicrobial resistance issues. Lastly, the ESCMID-ASM Conference on Antimicrobial Resistance, scheduled for September 21-23, 2016 in Vienna, Austria, will also discuss antimicrobial issues relevant to the group's interests.

Core Principles and Emerging Themes

The Advisory Group started the morning conversation by discussing what core principles should be used to evaluate the most promising economic incentives to support antimicrobial development while also ensuring appropriate use. The member of the Advisory Group identified predictability as one of the major core principles. The members stressed the importance of predictable returns to drug manufacturers as must-have for any potential model. Subsequently, patient access and affordability were additional core principles that the members of the Advisory Group proposed to add to the list. Development in areas of unmet medical need was identified as a key requirement for any potential incentive, as well as promoting appropriate use and rigorous stewardship programs. Lastly, the consideration of incentives that could be successful under the current political climate and market conditions was emphasized.

Stewardship and responsible use was also a topic of discussion as any incentives should promote sustainability and expand the life span of antimicrobials. Incentives should also be used to ensure prevention of inappropriate use.

Antimicrobial resistance is not an issue confined to the U.S.; several countries face the same challenges and several groups within the U.K. and Europe have invested a large quantity of resources to explore ways to combat resistance and stimulate development in areas of unmet medical need. Therefore, it was suggested that the Advisory Group coordinate closely with the global community as new economic incentives are explored.

The Advisory Group discussed the challenges associated with the quality and availability of data as it is very difficult to gather clinical data on drug use, and there is very limited evidence on the optimal dose and regimen. Often, the data gathered is not sufficient to satisfy providers or payers. Therefore, the quality and availability of data have posed a great challenge for stakeholders.

Promoting antimicrobial development also requires the engagement of several regulatory and legislative players. During the discussion, it was recognized that the CDC antimicrobial resistance list is a powerful tool to determine the priority of current medical needs; however, it does not capture future threats, and may need to be modified to serve as a R&D prioritization list for new drug development.

Finally, the Advisory Group reflected on the last session of the 7/20 Expert Workshop, which focused on the use of antimicrobial diagnostics. It was recognized that the challenge facing rapid diagnostics is more "social science" issue than lack of "technical innovation". Acknowledging that it is difficult to incentivize doctors to change their behaviors and adapt to a new treatment approach, it was suggested to focus on coordinating priorities, setting up appropriate incentive structures, and creating effective models to facilitate the physicians' adaptation of rapid diagnostic techniques.

Prioritizing Economic Incentives

Economic Incentives – Market Entry

The first incentive discussed was the market entry reward, which provides an inventive to the developer by awarding a large, monetary reward upon launch of an antimicrobial product. This sum can be paid out over time, and the drug would need to meet certain criteria to be eligible. One obstacle to this incentive is identifying the funding to support it. Several groups have proposed that the magnitude of the reward should be between $1-4 billion; therefore, a government would be the most practical source of funds, which, in the U.S., would need to be appropriated by Congress. However, although many members of Congress understand the need for novel antimicrobials, the current partisan divide, budget deficit, and competing funding interests would make it difficult for Congress to reallocate money to antimicrobial development. It was suggested to engage patients and health providers in advocacy efforts, and to engage in a massive public awareness campaign about the issue's importance in order to make an appropriation from Congress feasible.

Seeking private investment for antimicrobial development also faces multiple challenges. Investors need reassurance of outcomes and they expect predictable and relatively quick financial returns on their investment; therefore, an award payout that is dependent on meeting predetermined milestones years after drug launch might not be an attractive incentive. The manufacturer needs assurance that funds will be awarded before committing to development.

The meeting then discussed approach and timing for the market-entry reward. Staggering the payments rather than paying in one lump sum seemed to be the most feasible approach because it would provide predictability to the manufacturer while also maintaining accountability in continued manufacturing of the product. Under this model, drug developers would receive the reward in regular intervals over a certain period of time. Another possible approach is the "milestone award", which is a set amount paid to the manufacturers when they deliver on specific milestones.

Some issues with this model remain. For example, members brought concerns about the manufacturer's commitment to continued manufacturing of the drug once the reward payments end. One unresolved issue is what would happen in the long term to a drug in this model.

Economic Incentives – Insurance Model

The meeting also evaluated the strengths and weaknesses of the insurance model. The goal of the insurance model is to improve the financial predictability for drug developers by transferring a portion of financial risk to payers, while promoting conservation of antimicrobial use. This model acknowledges the need to be prepared in case of an outbreak or development of resistance, but does not reward the manufacturer for producing and selling more than is actually needed.

The insurance model is currently being piloted with the U.K.'s National Health Service (NHS). In this model, the payer and manufacturer agree upon a fixed number of courses of drugs to supply each year. If the actual utilization of drug is under the agreed amount, the payer reimburses the remaining number of courses produced by the manufacturers. On the other hand, if the utilization turns out to be above the agreed amount, providers will pay the manufacturer for the extra units of drug, while the manufacturer will provide a rebate to the payer for any profit above unit cost. This arrangement provides financial predictability for manufacturers, but also ensures that the manufacturer has no incentive to market the drug, and therefore limits high-volume, and potentially inappropriate, use.

This model could face multiple challenges in the U.S. Unlike the U.K.'s single-payer system, the U.S. has a multi-payer system and a fragmented insurance market. Therefore, it might be difficult to negotiate on a yearly basis pricing and volume with several different payers. The Advisory Group suggested a variety of strategies to overcome this challenge like:

- Developing a repeatable negotiation model applied to a broad range of payers;
- Promoting coordinated efforts among payers and providers in antimicrobial payment;
- Applying a PCORI-style, per-member per-month (PMPM) reimbursement model;
- Developing a centralized system that negotiates with payers or provider (e.g. group purchasing organizations)

One major concern with this model's implementation in the U.S. (where negotiations would take place with multiple payers rather than the government), would be the potential lack of incentive for private payers to purchase the drugs from manufacturers. If payers end up buying the drug and not using it, during the next negotiation cycle the payers may negotiate for lower volumes or lower prices. The payers may also choose not to buy in and instead rely on other payer companies to do the purchasing. In this case, the payer would bear little risk.

Some members of the group suggested that varying the length of the development contract could address this issue and reduce risk for the manufacturer. One option would be to consider a long-term contract that would cover the entire patent life of an antimicrobial drug. Another option would be to renegotiate the contract after two to three years rather than every year.

The Advisory Group also discussed how this model could and would be adaptable and sustainable for multiple drugs. It was recognized that there could be competition between similar drugs, which could ultimately drive prices down and therefore lower return on investment for manufacturers.

Economic Incentives – High Reimbursement

The Advisory Group discussed the impact of reimbursing antimicrobial products at higher prices. It was recognized that on the supply side, higher prices would incentivize manufacturers to introduce more drugs to the market while potentially tempering stewardship protocols and responsible use of

antimicrobials. On the demand side, higher prices could drive up the out-of-pocket cost and limit patient access to drugs. There is currently nothing stopping antimicrobial producers from charging higher prices for their products, so some members asserted that this model has been already in place. However, the desired outcome of more antimicrobial development is not observed.

From a physician perspective, higher prices could discourage doctors from using antimicrobials appropriately. Unlike drugs for other diseases, antimicrobials are usually prescribed to patients before a diagnosis is made. Consequently, because many antimicrobials are paid for by Diagnosis-Related Groups (DRG), providers will tend to use the lowest-priced drug available to save costs. If the antimicrobial price is too high, hospitals will simply choose not to use them, and patients will not be treated with the right drug at the appropriate time.

However, the high reimbursement model can possibly work if the provider is insensitive to high-price drugs. For example, it was suggested that if intravenous antimicrobials could be moved out of the DRG category and included in Medicare Part B coverage, physicians would not be discouraged from using antimicrobials appropriately. However, this method would not address outpatient issues, which constitute a large portion of antimicrobial use.

Funding Options

The meeting concluded by discussing several options to fund the economic incentives discussed during the previous session. The Advisory Group discussed the possibility of charging a "user fee" for all antimicrobial use, but there was some disagreement on the scale of the population impacted by the fee. Some argued that only outpatient and non-human use scripts should be charged because it will create a non-regulatory incentive for the appropriate use of antimicrobials. Others believe that all patient scripts need to be charged, because health care is a public good and everyone should pay their fair share.

Another funding option discussed during the meeting was the transferrable exclusivity voucher. Under this model, an antimicrobial drug developer would be awarded a transferrable voucher that grants extended exclusivity to another drug. The length of additional exclusivity would be capped once sales reached a set revenue, which was suggested by some to be $1 billion. Compared with other options, transferrable exclusivity vouchers could be a desirable alternative because:

- It would not require an annual appropriation from the government, and thus would have a low Congressional Budget Office (CBO) score
- It would encourage medical innovation because only specific, novel drugs would receive such an incentive
- It could generate money for manufacturers because several months of delayed generic entry could translate into a large amount of money for the company
- Vouchers would be a predictable reward to manufacturers.

However, transferrable exclusivity vouchers could have some negative effects. First, vouchers are a mechanism to subsidize one category of drugs at the expense of other categories, and therefore it will make other groups of drugs more expensive. Second, as vouchers are transferable to non-antimicrobial drugs, the government would provide advantage to therapeutics that are already successful in the market place. Third, vouchers, without modification, do not explicitly promote stewardship or encourage responsible use of antimicrobials.

Several measures were proposed to offset the negative effects of exclusivity vouchers. The value associated with the exclusivity voucher could be limited to a certain amount. The government could impose stringent criteria on manufacturers before granting the voucher, and marketing restrictions could be implemented. Lastly, the government could take measures to ensure patient access would not be affected by the rising prices.

Transferrable exclusivity vouchers could also be used as a reward for manufacturers, or as a way to fund a market entry reward. In the latter case, rather than awarding vouchers to a company after product launch, the government would sell one to three vouchers worth $1 billion per year. The funds generated from this sale could then be applied as a cash reward for another drug product.

Finally, a combination of payment options can be used to provide funds for the delinking rewards. This combination might include a small tax on antibiotic use, a population-based fee from private and public payers, and one auctioned transferable exclusivity voucher. The advantage of this approach would be to ensure that all parties contribute to fund antimicrobial development, while spreading out the cost so no party bears a disproportionate burden.

Next Steps

Overall, the discussion has brought many insightful ideas around antimicrobial economic incentives, and members were encouraged to submit follow-up thoughts on this issue. A meeting summary and presentation slides will be later disseminated to members to highlight important points proposed in the meeting.

As next step, the Duke-Margolis team will work with members to develop a more articulated proposal of incentivizing antimicrobial development. The Duke-Margolis Center will work closely with members of the Advisory Groupon specific incentive measures and publish white papers. Over the next few weeks, Duke-Margolis will schedule follow-up conference calls with different members to discuss a more detailed future plan.