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Towards New Business Models for R&D for Novel Antibiotics

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Towards new business models for R&D for novel antibiotics☆

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ABSTRACT

In the face of a growing global burden of resistance to existing antibiotics, a combination of scientific and economic challenges has posed significant barriers to the development of novel antibacterials over the past few decades. Yet the bottlenecks at each stage of the pharmaceutical value chain—from discovery to post-marketing—present opportunities to reengineer an innovation pipeline that has fallen short. The upstream hurdles to lead identification and optimization may be eased with greater multisectoral collaboration, a growing array of alternatives to high-throughput screening, and the application of open source approaches. Product development partnerships and South–South innovation platforms have shown promise in bolstering the R&D efforts to tackle neglected diseases. Strategies that delink product sales from the firms' return on investment can help ensure that the twin goals of innovation and access are met. To effect these changes, both public and private sector stakeholders must show greater commitment to an R&D agenda that will address this problem, not only for industrialized countries but also globally.

1. Introduction

Against a growing burden of drug resistance, the pipeline for novel antibacterials has faltered. The challenges trace to both science and economics and call for the need to consider new business models for bringing novel antibiotics to market.

While there have been some clinically important modifications to existing antibiotics, only two new classes of antibiotics have emerged in the past three decades—oxazolidinones (linezolid) and cyclic lipopeptides (daptomycin). Both drugs are for the treatment of Gram-positive bacterial infections. In the publicly disclosed pipelines of the top 15 pharmaceutical companies, which provided 93% of the new antibacterials from 1980 to 2003, there are only five antibacterials, comprising only 1.6% of the R&D pipeline for these companies. None of these five antibacterials appear to have a novel mechanism of action (Spellberg et al., 2004).

EMEA, ECDC and ReAct conducted a more comprehensive analysis of potential antibiotics, identified from searches of all drug company clinical R&D using two commercial databases and reviewed by an expert scientific committee. The study yielded 90 antibacterial agents with *in vitro* activity in a best-case scenario (based on actual data or assumed based on known class properties or mechanisms of action) against at least one organism in the panel of bacteria selected for their public health importance. This analysis reaffirmed the dismal outlook. Of four with activity against Gram-negative bacteria based on actual data, two acted on new or possibly new targets, and none via novel mechanisms of action (Aronsson et al., 2009).

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2. Bottlenecks in the R&D pipeline

The R&D pipeline for novel antibacterial drugs faces multiple bottlenecks (see Fig. 1):

- *Lead identification*: Upstream in the R&D pipeline, high-throughput screening for antibacterial drug candidates has had a significantly lower yield for antibacterial drug candidates compared to other therapeutic categories.
- *Medicinal chemistry*: The process of transforming these leads into drugs that can enter clinical trials is the stage at which much attrition also occurs.
- *Crossing the valley of death*: The probability of success during lead optimization relies on the size of the medicinal chemistry effort that can be mounted, and this relates to the available financial resources, as well as the opportunity costs, of undertaking this. "Crossing the valley of death" is the term given to the gulf in translational research from basic science to clinical application and the financial chasm in moving from pre-clinical to clinical testing.
- *Regulatory approval*: Recruiting and enrolling adequate numbers of patients in clinical trials can still be challenging and costly. On the other hand, no one wants to cut corners on safety, and antibiotics as a class of drugs already enjoy among the fastest clinical approval times and highest approval rates across therapeutic categories.
- *Reimbursement*: Reimbursement signals have traditionally been mixed—rational use is compromised when high prices place a needed antibiotic out of reach while conserving the use of novel antibiotics also caps the potential for revenue returns to the firm.

In this workshop session, discussions focused on the upstream challenges in the R&D pipeline for novel antibacterial drugs. The value of co-developing diagnostics and drugs was noted, particularly for patient enrollment in clinical trials, but diagnostics development was covered in another workshop.

2.1. Lead identification and optimization

High-throughput screening (HTS) is designed to screen single enzyme targets identified through recent advances, predominantly in genomics. The yield from high-throughput screening has been disappointingly low for antibacterial drug discovery.

Seventy screens conducted by GlaxoSmithKline (GSK) from 1995 to 2001 (67 HTS, three whole-cell) produced five lead compounds, representing a mere 7% success rate. GSK's experience is corroborated by Pfizer's 6.5% success rate in producing lead compounds (personal communication Paul Miller, Pfizer). Even with top-drawer medicinal chemistry resources, lead optimization also proved significantly more challenging for antibacterial R&D than other therapeutic areas. Combining the probability of success of HTS with the success metrics for all the subsequent steps in antibiotic development, it is estimated that it could take 2066 HTS to yield one antibiotic with a novel mechanism of action whereas an average of just 24 screens yielded one drug launch across other therapeutic areas. This is clearly an untenable strategy and illustrates the need for new approaches which some companies are now exploring.

This HTS strategy has not proven particularly well suited for antibiotic discovery (Mullin, 2004; Baltz, 2006). HTS campaigns ordinarily yield multiple leads with target activity. Most antibacterial targets though are enzymes, not receptors, and therefore, hard to inhibit. Though complying with the Lipinski Rule of Five, druggable leads in compound libraries are biased towards mammalian targets which may explain their lack of antibacterial activity (Bleicher et al., 2003). After resources have been expended on drug optimization efforts, safety issues and permeability, explored later in the drug development process, often thwart many of these promising leads (Fernandes, 2006).

In addition to the shortcomings of HTS, the range of compounds explored in these efforts has been limited. Combinatorial chemistry, often used in tandem with HTS, is incapable of generating the molecular complexity and diversity found in the natural products from which many antibiotics have been derived (e.g., vancomycin, daptomycin, cephalosporin C, erythromycin, and rifampicin) (Baltz, 2006). The synthetic compound collections held by firms and most proprietary compound vendors do not represent the range of compound types that might be explored to yield new classes of antibiotics.

Thus interventions at several points in the R&D pipeline might improve the yield of novel antibacterial drugs. First, new approaches to lead generation may help. While compound collections have improved, one cannot rely on conventional high-throughput screening of synthetic compounds. Similarly, improving the probability of transitioning from clinical trial phase 1 to phase 2, through higher quality drug candidates, would also yield greater likelihood of success; however, creating such candidates will likely result in longer timelines and require greater resources.

2.2. Anticipated returns on investment

Investment in antibacterial drug discovery and translational research may also be hampered by relatively less favorable returns. The antibiotics market is less profitable than other, faster-growing therapeutic areas. Antibiotics generated sales of US$42 billion in 2009 globally, representing 46% of sales of anti-infective agents (which also include antiviral drugs and vaccines) and 5% of the global pharmaceutical market. Antibiotics showed an average annual growth of 4% over the past 5 years, compared with a growth of 16.7% and of 16.4% for antiviral drugs and vaccines, respectively (Hamad, 2010). By comparison, global pharmaceutical sales for 2009 are estimated at US$750 billion (Business Wire, 2009).

The metric used to prioritize investments in industry is the risk-adjusted net present value (rNPV): the return in future dollars after adjustment for the investment and any lost income, usually expressed as the number of millions of dollars (Stewart et al., 2001). DiMasi, Vernon and Grabowski estimate (in 2000 US$) the worldwide sales revenue over the product life cycle for a new antibiotic approved in the US during 1990–1994 to be, on average, US$2379 million. This compares to an average of US$4177 million for CNS drugs and US$3668 million for cardiovascular drugs (2004).

Several features inherent to antibiotics contribute to relatively low net present values. Treating an infection may require a short course compared to the lifelong treatment of chronic conditions, and resistance itself limits an antibacterial's lifespan. There is also significant therapeutic competition in a relatively saturated market. Efforts to conserve antibiotics through rational use guidelines also curb the opportunity to expand markets. This tension between conserving antibiotics and generating revenues through increased marketing and sales reflects a major misalignment of economic incentives.

2.3. Regulatory issues

A 1995 study shows that antimicrobial agents have had a higher success rate of U.S. FDA drug approval and a shorter approval time than most other therapeutic classes (DiMasi, 1995). More recently, the picture may be more mixed. Compared to other therapeutic classes, anti-infectives as a class still fare well in the attrition rates from phase I through market approval (50%) and also register among the fastest clinical development times (87 months) of any therapeutic class (Evans et al., 2009). However, four new

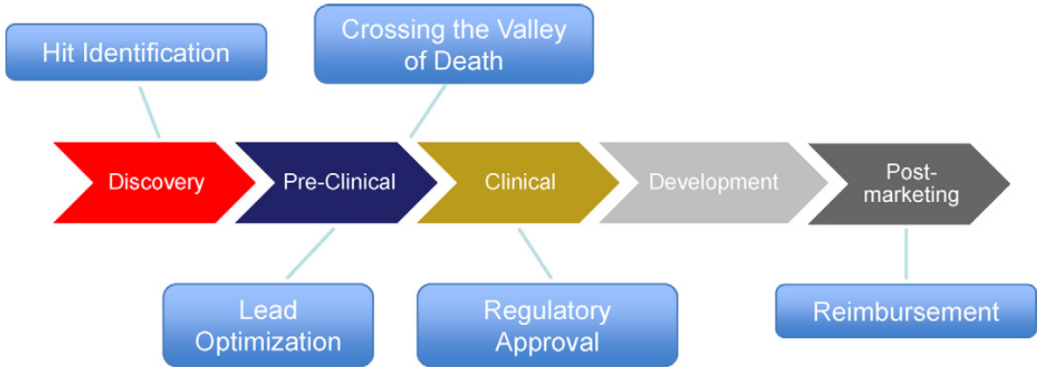

Fig. 1. Defining the bottlenecks in the value chain of pharmaceutical R&D.

MRSA drugs were submitted for registration, and unfortunately, only one progressed to launch, suggesting additional challenges and complexities for the successful registration of new antibiotics.

While antibiotics have enjoyed among the fastest clinical approval periods and highest regulatory success rates, clinical trials for novel antibiotics face several challenges. Guidance for clinical trial requirements has been in flux, leading firms to perceive this process as unpredictably costly. The FDA recently issued draft guidance calling for scientific justification of margins in non-inferiority trials for treatments of acute bacterial skin and skin structure infections (Center for Drug Evaluation and Research, 2010). This guidance may result in tighter margins. The FDA has also required superiority trials for antibiotics used to treat self-resolving non-lethal infections.

Some experts suggest that superiority trials place too high a threshold for regulatory approval. Tight margins on non-inferiority trials may also pose challenges because many antibiotics work well. The FDA has acknowledged that it may be difficult to show that an experimental drug works better than a current one (Tsouderos, 2010). It is critical that new antibiotics show clinical efficacy against infections caused by multi-resistant organisms, and without rapid diagnostics, firms must amass large sample populations in order to capture a sufficient number of patients infected with these drug-resistant pathogens.

Yet efforts to speed drug approval for antibiotics through non-inferiority trials and priority review mechanisms need to ensure that safety is not compromised (Outterson et al., 2010a; Powers, 2007). The U.S. Government Accountability Office found that a quarter of FDA new drug applications (NDAs) from 2002 to 2009 were based on some evidence from non-inferiority trials, and though the number of such NDAs decreased over the period, a majority of these applications received FDA approval. Half of these were for antimicrobial drugs, including tigecycline over which safety warnings were recently issued (U.S. FDA, 2010). Certain biases can creep into non-inferiority trial designs, from poorly defined or unreliable outcome criteria to missing data, and these biases tend to increase false-positive results. Also, more than a third of drugs awarded accelerated approval by FDA since 1992 never had studies done proving efficacy (Harris, 2010). Between 1980 and 2009, over forty percent of systemic antibiotics receiving FDA approval were subsequently withdrawn from the US market. This represents a significantly greater number of discontinuations compared to other therapeutic classes (Outterson et al., 2010b).

3. Towards new business models for antibiotic R&D

The workshop discussed several potential pathways to solving some of the scientific and economic challenges that have contributed to the weak pipeline for antibacterial R&D. While R&D pipelines for treatments of neglected diseases falter for lack of paying patients in developing countries where these diseases are endemic, antibiotics have markets that span both North and South. Nonetheless there are development bottlenecks shared in common for both neglected tropical diseases and for antibiotics. Both share scientific challenges in sourcing compounds and optimizing drug leads as well as financial challenges with insufficient private sector incentives and pricing that may place products out of reach of those in need. While attentive to the differences, lessons in reengineering the value chain of R&D in one area might inform the other. Similarly, among bacterial diseases, the work of groups like the Global Alliance for TB Drug Development has heightened policymaker and funder interest in changing the picture where no new TB drug has been developed in 40 years.

3.1. Setting priorities through target product profiles

The target product profile (TPP) can help signal R&D priorities to funders and researchers. The FDA defines the TPP as a "summary of a drug development program" which provides a "format for discussions between a sponsor and the FDA that can be used throughout the drug development process" (Center for Drug Evaluation and Research, 2007). For the FDA, "beginning with the goal in mind" has helped the agency stay on the same page with firms.

Product development partnerships (PDP) for neglected diseases have adopted the TPP concept to focus priority on developing health technologies that respond to unmet needs in resource-limited settings. TPPs typically lay out a product's desired optimal and minimum-required characteristics, from route of administration to dosing schedule and price. These specifications may be modified as the R&D process yields new information. Specified from the outset, however, TPPs have the potential to align economic incentives to public health priorities, particularly where market-based incentives are wanting.

The Drugs for Neglected Diseases Initiative (DNDi), for example, makes use of TPPs for its portfolios on visceral leishmaniasis, human African trypanosomiasis, and Chagas disease to specify criteria that ensure usefulness and accessibility in resource-poor settings. Such guidance keeps the patients' needs foremost in mind in the R&D process. Overspecifying a target product profile, however, risks missing the unexpected breakthrough in innovation. Striking the right balance between setting parameters that define patient needs and not overspecifying the technological approach is key.

Still the TPP concept may be useful as a policy tool to convey basic criteria of need. The triad of such criteria might include evident public health need, a credible candidate technology, and available resources. The process for setting such priorities in an area like antibiotic resistance is complex. Metrics to demonstrate evident need may include a number of factors, from DALYs

(disability-adjusted life years) to the effect of infections on networks of patients and their families and communities. The process of acquiring such data poses its own challenges. With limited resources and capacity to conduct on-the-ground surveillance, ways to strategically collect local data to construct a global picture will need to be developed. The RAND group applied mathematical modeling to prioritize among potential new diagnostics for several infectious diseases by estimating the number of unnecessary treatments averted with the use of the diagnostic test (RAND Health, 2007). A credible candidate technology might signal low-hanging fruit and a timeline within practical reach. Feasibility might depend on the availability of the underlying platform technology, the commitment of major stakeholders, or available resources—financial and non-financial—already lined up. The commitment of stakeholders includes patients, and shaping the TPP to be patient-centered was considered key.

In assessing technology priorities, there are several ways to consider how to tackle antibiotic resistance. Should priorities for antibiotic resistance focus on syndromic categories (such as upper respiratory infection) or specific pathogens? The priorities for treatment might range from a cure to decreased symptomatology to a means for improving drug adherence. A prioritization strategy that lays out a business plan for bringing the technology to market also might make pricing and accessibility standards explicit from the beginning, perhaps guiding R&D decisions as in the case of DNDi.

3.2. Charting new directions for drug discovery

The workshop explored various approaches to reinvigorating the R&D pipeline for novel antibacterial drugs. These included moving beyond traditional, high-throughput screening to virtual high-throughput screening and structure-based discovery; looking at shelved compounds and existing drugs with new assays and mining sources such as the old journal literature for new leads; and expanding the search beyond small molecules to monoclonal antibodies and synthetic riboswitches, more diverse natural and synthetic compounds, and potentiator approaches such as efflux pump inhibitors. Yet fully exploring these approaches will require greater investment in antibacterial R&D and sizing up which directions to prioritize. The appetite to pursue these various leads will depend, in part, on the success of efforts to reengineer the value chain of antibacterial R&D, by raising the level of public sector commitments, effectively decreasing the costs of R&D, and providing adequate incentives for private firms and public research institutions.

3.2.1. Improving lead identification and medicinal chemistry

While firms have assembled large proprietary compound library collections for drug discovery purposes, these may not yet have been completely mined for novel antibacterial candidates, an area of interest and investment for relatively few firms.

Broader access to these compound collections may aid research efforts focused on finding new antibiotics. Equally important is the often confidential know-how—the biology and medicinal chemistry—behind such compounds in proprietary collections. Resource sharing, particularly of proprietary compound collections and preclinical data, has taken place in other areas of drug discovery. For example, GSK screened its corporate compound library of over 2 million molecules and released 13,500 compounds found to have activity inhibiting the malaria parasite, *Plasmodium falciparum* (Purlain, 2010).

The U.S. NIH Molecular Libraries Initiative hosts at its nine centers its Molecular Library Small Molecule Repository, against which researchers are free to submit assays for testing. Results of such screens, compound structure, and other preclinical data are made available through PubChem, an open access digital repository made available by NIH. Access to preclinical data associated with compounds can prove helpful in predicting downstream success, helping to direct efforts towards the most promising candidates.

While these collections are mainly comprised of small molecules synthesized for drug discovery primarily in other therapeutic categories, 34% of all small molecule new chemical entities approved between 1981 and mid 2006 are either natural products or semi-synthetic derivatives, and the majority of existing antibiotics are derived from natural products (Newman and Cragg, 2007). Compound collections for antibiotic research may need to expand from the contents of existing libraries to reflect better the complex properties of naturally occurring substances that have historically been developed into successful antibiotics (Wright, 2010).

The costly tasks of lead optimization and toxicity testing have also become shared endeavors, supported through both intramural and extramural services provided by programs like NIH's Therapeutics for Rare and Neglected Diseases Program (TRND) and Rapid Access to Interventional Development (RAID) Program. TRND assists with optimizing leads for first-in-man experiments under an Investigational New Drug Application while RAID provides access to NIH intramural or contracted services, from bulk supply and GMP manufacturing to formulation and pharmacokinetic and animal toxicology testing, for outside firms.

In the field of neglected diseases, public-sector R&D institutions such as product development partnerships have worked with experienced pharmaceutical industry chemists to support their medicinal chemistry efforts and frequently engage retired and active industry veterans on their Scientific Advisory Committees. Drawing on such expertise enables these institutions to make more strategic decisions early in the research process. Given the difficulty of lead optimization for novel antibiotics, this suggests another model that public-sector antibacterial discovery efforts might follow to leverage support from the private sector.

Drug discovery efforts have also recognized the shortcomings of HTS and begun looking to new methodological approaches for developing compounds better suited to become antibiotics. This has been the impetus behind the antibacterials unit of GlaxoSmithKline's Infectious Diseases Center for Excellence in Drug Discovery forging alliances with small firms that work on early-stage novel drug discovery projects. For example, GSK in 2007 partnered with Anacor Pharmaceuticals to support use of its boron chemistry platform to search for novel antibiotics. In 2010, the partnering firms announced the alliance had successfully delivered a novel mechanism antibiotic that has achieved clinical proof of concept (GlaxoSmithKline, 2010; Anacor, 2009). Using x-ray crystallography and nuclear magnetic resonance, fragment-based screening has enabled firms to engage in drug design by combining fragments that bind to the identified target (Jones, 2010). Virtual HTS, by which large libraries of compounds may be screened for the structural potential to bind to specific sites on target molecules, has enabled structure-based drug design (Simmons et al., 2010).

3.2.2. Testing drug combinations

The value of combination therapy in countering antibiotic resistance has received close attention in anti-TB treatment. It has been known for decades, since the introduction of the first anti-tuberculosis drug streptomycin, that the use of monotherapy in treating active TB very frequently generates resistance. Currently, many first- and second-line TB drugs have pharmacokinetic profiles poorly suited for use in combination. When co-administered, such drugs with differing half lives might leave gaps in antibiotic coverage from one or the other drug between doses, thereby opening the door to resistance during periods when, in effect,

only monotherapy is achieved. Therefore, optimized novel combinations are needed to advance TB treatment. The current TB drug development approach replaces one drug at a time, and as a consequence, takes decades to introduce a new regimen that consists of even three new agents. Traditional intellectual property barriers also may hamper cooperation to create combination therapies when the component drugs are patented by different firms.

The existence of a global pipeline of new agents in clinical trial for TB coupled with the need for a new paradigm for rational selection and development of novel combination therapy for TB prompted the launch of the Critical Path to TB Drug Regimens initiative. In this partnership among the Bill & Melinda Gates Foundation, the Critical Path Institute, the Global Alliance for TB Drug Development, and various institutions and sponsor companies of potential new TB drugs, efforts to change the traditional R&D approach are underway. Drug combinations would be developed as a unit of therapy without having to change present regimens one drug at a time. With sufficient funding, this alternative development paradigm could shave years off the R&D time required for bringing novel anti-TB drug combinations to market.

3.3. Financing the crossing of the valley of death

Relatively lower anticipated returns on investment have deterred firms with a broad portfolio from investing in the search for novel antibiotics over other therapeutic categories. Of course, these opportunity costs are different for small firms without a broad portfolio of R&D options.

3.3.1. Push incentives

Push incentives that pay for R&D inputs can play a significant role. Notable support for R&D for novel antibiotics has come from both government and philanthropic sources. The US Department of Defense's Defense Threat Reduction Agency is supporting the search for novel antibiotics that align with its bioterrorism threat research (Purlain, 2010). The Wellcome Trust has developed a broad set of projects, primarily through its Seeding Drug Discovery initiative, and provided funding to a number of companies for antibacterial projects. For example, among the Seeding Drug Discovery awards, Prolysis Ltd. received financing to develop a new class of antibiotics to fight hospital-acquired staphylococcal infections, GSK was funded to develop new antibacterials to combat the rise of certain drug-resistant, hospital-acquired infections with a focus on Gram-negative bacteria, and Achaogen received funds for the continued preclinical studies of two antibacterials showing promise against multi-drug resistant *Enterobacteriaceae* and *Acinetobacter baumannii* and *Pseudomonas aeruginosa* (Wellcome Trust, 2007, 2009; GlaxoSmithKline, 2007). A further evolution of this model would be to provide funding for a portfolio of programs enabling risk to be spread among more than one project. For small start-up firms, public or philanthropic funding can be an important source of non-diluting cash investment.

3.3.2. Pull incentives

Provided that initial scientific hurdles can be surmounted, the prospect of pull incentives that pay for R&D outputs draws upstream, private capital investment. Incentives, such as tax deductions for R&D, presume the company has revenues to tax, and that may not be the situation of biotech start-ups. Several proposals have been put forth to increase reimbursement to firms for providing much needed antibiotics.

The value-based reimbursement model aims to reward development of novel antibiotics with public health value by using public funds to pay firms for their contribution (Kesselheim and Outterson, 2010). For example, under the proposed Health Impact Fund approach, participating firms would be required to provide a low price globally, pegged to the average cost of manufacturing, and to extend a royalty-free, open license for generic production after 10 years, but in exchange, would receive direct payment from the Health Impact Fund. The Health Impact Fund would offer pharmaceutical firms a share of a fixed fund each year for a period of 10 years following market approval. The payment would be proportional to the share of the health impact of the firm's registered product among all of the registered products. Under the Health Impact Fund proposal, participation would be voluntary, so firms could opt to exercise their monopoly pricing position instead. The fund would have to be sufficiently large, even when divided among participating companies, to provide an adequate financial incentive, particularly to manufacturers of important therapies now protected by patent or data exclusivity. Both valuation of the quality-adjusted life years saved by a specific product and securing long-term financing commitments from partner countries for the Health Impact Fund would be challenging. Others have argued for proposals that require open licensing and generic production as a condition of public financing, rather than after a period of 10 years.

Conservation of valuable antibiotics through rational use and limited marketing is at odds with innovation traditionally financed through sales-based incentives. Conservation goals, while good for public health, undercut drug industry sales and therefore R&D incentives. Proposals have been put forth to compensate firms for capping their sales of novel antibiotics. The Strategic Antibiotic Reserve is a mechanism to pay companies to achieve conservation targets for their drugs (Kesselheim and Outterson, in press). Workshop participants discussed hurdles to the implementation of such a program. It would require global coordination and extended market exclusivity on all relevant drugs to ensure higher reimbursement levels. This coordination would also need to take into account resistance caused by different drugs which belong to the same functional resistance group. Health system incentives and prescribing norms contribute significantly to the way in which antibiotics are used, but the concept of a Strategic Antibiotic Reserve places significant responsibility on the shoulders of drug firms to ensure rational distribution of the limited drug supply.

Through his plenary address, Richard Bergström, Director-General of the trade association for the research-based pharmaceutical industry in Sweden, offered important guidance to this workshop's discussions on pull incentives. Speaking on behalf of industry, he argued that "Incentives that separate the financial return from the use of a product are the only way to change this behavior." Another approach receiving mention was prizes or patent buyouts that are not reliant on the volume of subsequent sales of the product.

3.4. Open innovation approaches

Beyond push and pull incentives, there is a need for new approaches to reinvigorate antibiotic research. R&D efforts for rare and neglected diseases might offer lessons in reengineering the value chain of pharmaceutical R&D. To highlight a few initiatives, these efforts have taken various forms: open access resource sharing, open source innovation, product development partnerships, and South–South innovation platforms.

3.4.1. Open access resource sharing and open source innovation

Some pharmaceutical firms have created avenues for publicly funded scientists to avail themselves of proprietary resources. GlaxoSmithKline's Open Lab initiative is designed to host up to 60 visiting scientists from academia or biotech, providing access to the corporate compound collection. The firm has also provided

seed funding through the Tres Cantos Open Lab Foundation to help support these efforts.

Beyond facilitating greater use of existing proprietary resources, open source infrastructure might be employed to establish new mechanisms for upstream R&D collaboration and resource-sharing. An example is the Open Source Drug Discovery Initiative for TB. An interesting project undertaken by OSDD has been the collective efforts to study the *Mycobacterium tuberculosis* genome in search of novel drug candidate targets. With over 4328 registered participants from 130 countries, the OSDD mustered numerous volunteer contributions needed to complete a remapping and annotation of the genome in just over 4 months. Academia, hospitals, and contract research organizations have signed on to help with *in silico* screening and *in vivo* target validation, identifying lead molecules, and carrying them through preclinical and clinical trials. As of September 2010, the OSDD identified 18 targets, conducted 19 virtual screens, and is currently optimizing two lead novel compounds as potential TB drugs. This initiative, led by India's Council on Scientific and Industrial Research, receives public funding and taps into a network of universities, companies, contract research organizations, and volunteers—all elements that may help make this experiment into open source innovation more feasible. Adding another dimension to its digital platform for scientific collaboration, the OSDD will launch an Open Access Small Molecule Repository comprised of acquisitions from existing libraries, dedicated synthesis efforts, and other contributions. Having disbursed US$12 million from the Indian government, OSDD releases these funds on condition that supported projects are posted on-line and subject to peer review and approval by the community. The open lab notebook of the OSDD facilitates sharing of research results in real time with the community. This type of inclusive, networked approach to R&D demonstrates that while its costs and challenges may be too great for just one firm to bear, platforms that draw on a multitude of collaborators may lower costs, diffuse risks, and recruit a broad array of resources.

Another type of upstream platform from which lessons might be drawn is the Structural Genomics Consortium, which aims to promote drug discovery by creating and placing protein structures in the public domain. Funders nominate protein targets to the "SGC Target List," which is comprised of 2400 proteins. Members of the consortium—over 250 collaborators in 19 countries—contribute to its research activities. While the list and nomination information remains confidential, targets are placed in the public domain upon completion. The SGC contributed 29.6% of the global output of novel human protein target structures in 2009. These research outputs are free from restrictions on use and not covered by intellectual property. Such a model maintains open access to the fruits of its collective labor, while protecting competitive advantage for firms that seek not to disclose the types of targets into which they are investigating. Initiatives like the Structural Genomics Consortium are helping to redefine the line between pre-competitive and competitive research by setting research consortia norms that encourage greater sharing throughout the value chain of R&D.

3.4.2. Product development partnerships

Partnerships forged to bring a specific health technology to market have overcome significant market barriers in the neglected disease space by leveraging strengths and resources from both the public and private sectors. The Drugs for Neglected Diseases Initiative has been a successful pioneer in holding to a specific product profile from discovery to market through collaboration at each stage along the value chain. Its once-daily, fixed-dose combination drug for malaria, ASAQ (artesunate–amodiaquine), for example, was developed in partnership with Sanofi Aventis and is available at cost in the public sector. A second antimalarial combination, ASMQ (artesunate–mefloquine), resulted from South–South collaboration between Brazil's Farmaguinhos and the Indian drug firm, Cipla. For each artemisinin-combination treatment, a host of other partners around the world have also been integral to the process. Clinical trial platforms were developed at the Universiti Sains Malaysia and the Institut de Recherche pour le Developpement in Senegal. In bringing ASAQ to market, DNDi worked with the Indian Council of Medical Research and with the Kenya Medical Research Institute, both of which helped to shape antimalarial policy development through their efforts (ASAQ, 2010). The patient-centered approach DNDi has taken in collaborating with Southern institutions serves as an exemplar that might be emulated in broadening the search for novel antibacterials.

3.4.3. South–South innovation platforms

Indeed, several institutions have taken steps to harness developing country R&D capacity through collaborative infrastructure. Such initiatives may be localized to a specific point on the value chain, such as the European and Developing Countries Clinical Trials Partnership, which facilitates Phase II and III clinical trials for drugs, vaccines and microbicides against HIV/AIDS, TB and malaria in sub-Saharan Africa (European and Developing Countries Clinical Trials Partnership, 2010). Firms have increasingly recognized the advantages of outsourcing clinical trials to Southern countries, where patient samples are readily available, overhead costs are lower, and capacity to uphold clinical research standards is growing (Thiers et al., 2008). But such platforms may also go farther than providing inputs to the existing, industry-dominated R&D value chain.

The African Network for Drugs and Diagnostics Innovation (ANDI) and its sister networks in Asia and the Americas seek to promote regional networks that are locally owned and led to drive innovation for urgently needed therapies. One study found that collaborations more commonly can be found between Northern and Southern institutions (Nwaka et al., 2010). By linking centers of excellence across Africa, ANDI may help build South–South partnerships where few have existed. Their unique strengths, such as access to an underexplored diversity of natural resources and to local patient populations, may propel R&D in novel directions.

4. Conclusions

Facing the global challenge of antibiotic resistance, clearly new business models for bringing novel antibiotics to market will be needed. The workshop discussions laid out key bottlenecks along the value chain of R&D, some scientific and others economic. Some scientific challenges may be surmounted with greater investment, but others will require commitment to new forms of collaboration. Such collaboration will need not only to expand stakeholders' access to compound libraries, but also diversify the compounds available in such repositories. Where there are common challenges, policymakers might draw upon the experience of how product development partnerships for neglected diseases have effectively mobilized public and private resources. This will require a strategy for leveraging public and philanthropic funding to overcome traditional hurdles to antibiotic innovation.

In addition, public sector interventions are needed across the value chain, from improving lead identification and medicinal chemistry to restructuring the reimbursement system. Engaging new and old partners, a platform for antibiotic innovation might benefit from a more open source environment for R&D and from greater South–South exchange. The public sector will also need to take some calculated bets in prioritizing some approaches over others. Without overspecifying the technology approach or compromising the spirit of creative innovation, target product profiles can help signal priorities and anchor public sector commitments to

create products that meet the twin goals of innovation and access. In so doing, some of the proposals put forward may have promise to reengineer the value chain of R&D, to alter the equation of net present value, and thereby, change the way pharmaceutical products are brought to market. The industry's call to delink profit from product sales is no longer business as usual, but an invitation for the scientific, public health and policy communities to consider new business models to meet one of the most pressing global health challenges of our time.

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