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REVIEW ARTICLE

New business models for antibiotic innovation

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Abstract

The increase in antibiotic resistance and the dearth of novel antibiotics have become a growing concern among policy-makers. A combination of financial, scientific, and regulatory challenges poses barriers to antibiotic innovation. However, each of these three challenges provides an opportunity to develop pathways for new business models to bring novel antibiotics to market. Pull-incentives that pay for the outputs of research and development (R&D) and push-incentives that pay for the inputs of R&D can be used to increase innovation for antibiotics. Financial incentives might be structured to promote delinkage of a company's return on investment from revenues of antibiotics. This delinkage strategy might not only increase innovation, but also reinforce rational use of antibiotics. Regulatory approval, however, should not and need not compromise safety and efficacy standards to bring antibiotics with novel mechanisms of action to market. Instead regulatory agencies could encourage development of companion diagnostics, test antibiotic combinations in parallel, and pool and make transparent clinical trial data to lower R&D costs. A tax on non-human use of antibiotics might also create a disincentive for non-therapeutic use of these drugs. Finally, the new business model for antibiotic innovation should apply the 3Rs strategy for encouraging collaborative approaches to R&D in innovating novel antibiotics: sharing resources, risks, and rewards.

Key words: *3Rs strategy, antibiotic innovation, antibiotic resistance, business models, delinkage*

Background

The public health challenge of antibiotic resistance has received growing recognition among policy-makers in recent years, and a key intervention strategy has focused on the faltering pipeline for novel antibiotics. Twenty new classes of antibiotics entered the market from 1940 through 1962. Since then, only two new classes of antibiotics, oxazolidinones (linezolid) and cyclic lipopeptides (daptomycin) have come on the market (1). More troubling is the foreseeable horizon of research and development (R&D) for novel antibiotics. An EMA–ECDC–ReAct study of the antibiotic pipeline identified 90 antibacterial agents in clinical development. Of the 15 drug candidates that could be administered systemically, 12 showed *in vitro* activity against antibiotic-resistant Gram-positive bacteria, while only 4 had demonstrated *in vitro* activity against antibiotic-resistant Gram-negative bacteria, and not one of these acted via a novel mechanism of action (2).

Barriers to antibiotic innovation

Several reasons—financial, scientific, and regulatory—have been put forward to explain the dearth of novel antibiotics.

Financial barriers

Many have observed that as compared with other therapeutic areas, the antibiotic market is less profitable. In 2009, antibiotics generated global sales of US$42 billion, representing 46% of sales of anti-infective agents (including antiviral drugs and vaccines) and 5% of the global pharmaceutical market. Over the past 5 years, antibiotics showed

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an average annual growth of 4% as compared with an average annual growth of 16.7% and of 16.4% for antiviral drugs and vaccines, respectively (3).

Pharmaceutical firms size up the opportunity costs of R&D investment by considering the risk-adjusted net present value (rNPV), that is, the return in future dollars after adjustment for the investment and any lost income (4). By comparison to other therapeutic categories, the rNPV of antibiotics is not high. The relative rNPV expressed as the number of millions of dollars for an antibiotic would be 100, compared with 160 for vaccines, 300 for an anticancer drug, 720 for a neurological drug, and 1,150 for a musculoskeletal drug (5). This difference stems, in part, from the nature of antibiotic treatment. Treating a bacterial infection requires days of therapy compared with potentially lifelong treatment for a chronic condition like hypertension or high cholesterol. Worse yet, there is an inherent tension between efforts to conserve the effectiveness of novel antibiotics and to generate revenues through increased marketing and sales.

At the same time, antibiotics have also been described as the third most profitable class of drugs for pharmaceutical companies after central nervous system and cardiovascular drugs. However, a single antibiotic drug faces significant competition from other antibacterial agents, thereby commanding a smaller market share and realizing less profit than drugs from other therapeutic classes. For example, the best-selling antibiotic made $2.01 billion in 2003, while a lipid-lowering agent sold by the same company made $9.23 billion (6). However, few antibiotics coming on the market in recent years have been classified as breakthrough treatments, and many are analogues of existing drugs. This has generated significant therapeutic competition that only exacerbates limited returns on novel antibiotics entering the market.

Not all antimicrobials though are created equal in rNPV. Hospital-acquired infections rank sixth among leading causes of death in the United States (7). Compared with treatments for community-acquired infections, the smaller hospital market for antibiotics garners premium pricing for injectable or parenteral antibiotic treatments. While newer antibiotics targeting MRSA are in the pipeline, multi-drug resistant, Gram-negative bacteria, however, present a greater challenge, adapting more readily with resistance genes to drug therapy. Yet R&D incentives seldom signal the public health priority that needs to be placed on certain antibiotic drug candidates over others. Instead, the indiscriminate application of incentives risks bringing more analogues of existing antibiotics to market, which may exacerbate therapeutic competition and further erode the net present value of novel antibiotics.

Scientific barriers

This greater challenge is not just financial, but scientific as well. High-throughput screening (HTS) designed to identify promising drug leads has yielded disappointing returns for antibacterial drug discovery. From 1995 to 2001, only 5 lead compounds were identified from 70 screens (67 HTS, 3 whole-cell) conducted by GlaxoSmithKline (GSK). This represents a mere 7% success rate (8). In a study by investigators from GSK, it was noted that most corporate compound collections closely conform with the Lipinski rule of five—properties that make a compound more easily druggable as an orally active drug in humans—but antibacterial drugs did not (9). The differing chemical properties of antibacterials have also been characterized (10). 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 (11). So the scientific bottleneck may, in part, reflect this mismatch between proprietary compound libraries and potential new families of antibacterial compounds.

Regulatory barriers

Regulatory barriers to antibiotic innovation are frequently blamed for the faltering pipeline. However, there are few examples of truly novel antibiotics being shelved because of such barriers. Moreover, as compared with most other therapeutic classes, antimicrobial agents have both a higher success rate of US FDA drug approval and a shorter approval time. Admittedly many of these may be 'me-too' drugs. For drug candidates in phase I clinical trials, nearly half of anti-infective agents make it through to market approval in contrast to 24% for anticancer agents (12). And among 17 therapeutic areas, the time in clinical development for anti-infectives (87 months) is among the shortest of all, considerably speedier than, say, anti-cancer agents (108 months) (13).

The FDA issued draft guidance calling for scientific justification of margins in non-inferiority trials for treatments of acute bacterial skin and skin structure infections (14). Experts though have warned that non-inferiority trial designs must not rely on poorly defined or unreliable outcome criteria and that such shortcuts should not replace superiority trials that would identify true breakthrough, novel classes of antibiotics. Of note, a recent study found that out of the 61 antibiotics approved as new medical entities

(NMEs) between 1980 and 2009, 43% were withdrawn as compared with a withdrawal rate of 13% among non-antibiotics (15). This 3-fold higher rate of drug withdrawals among antibiotics may, in part, reflect the high number of follow-on antibiotics approved.

It would be important not to repeat the mistakes in the approval pathway of Ketek® (telithromycin), a ketolide antibiotic touted to be a first-in-class antibiotic. This drug subsequently 'has been linked to dozens of cases of severe liver injury, been the subject of a series of increasingly urgent safety warnings, and sparked two Congressional investigations of the FDA's acceptance of fraudulent safety data and inappropriate trial methods when it reviewed the drug for approval' (16). The FDA subsequently concluded that non-inferiority trials, then considered acceptable for approving two of Ketek's three indications, were no longer deemed acceptable (17). Just last year, Public Citizen flagged concerns over the US FDA's approval of bedaquiline, hailed as a first-in-class drug to combat multidrug-resistant tuberculosis, to the agency's attention. Bedaquiline received accelerated approval on the basis of a single phase II clinical trial despite the mortality rate being five times higher in bedaquiline-treated subjects than in those treated with placebo (18).

Pathways for new business models

The contours of this financial, scientific, and regulatory context suggest the need for new business models to bring novel antibiotics to market. In describing the way forward, no single intervention will suffice, and the need for a hybrid approach is clear.

In recent years, policy-makers have applied a range of financial incentives to coax greater innovation from pharmaceutical firms. Pull-incentives that pay for the outputs of R&D have received greater attention than push-incentives that pay for the inputs of R&D. Pull incentives ensure return on investment through prizes or through higher drug prices protected by patents or extended data exclusivity (19). These incentives might be tied to requirements for effective stewardship and conservation of the novel antibiotic, or delinked from returns on investment. By delinkage, returns on investment might be divorced from volume-based sales of the product. These incentives could be targeted to truly novel classes of antibiotics, with demonstrable activity against multidrug-resistant pathogens. Failing to target such incentives appropriately, more analogues of existing antibiotics might come forward, thereby creating greater therapeutic competition and further lowering the NPV for any new antibiotic. The approach taken by the Generating Antibiotic Incentives Now (GAIN) Act that became part of the US Food and Drug Administration Safety and Innovation Act poses such risk. Extending monopoly protections on novel antibiotics, this law provided five more years of data exclusivity and priority review for qualified infectious disease products, broadly characterized as 'antibacterial or antifungal drug[s] for human use intended to treat serious or life-threatening infections, including those caused by an antibacterial or antifungal-resistant pathogen, including novel or emerging infectious pathogens' as well as those drugs treating a pathogen on an FDA-created list. These awards, however, are without assurances of true novelty or significant therapeutic advance, antibiotic stewardship, or delinkage. Premium pricing will not ration the antibiotic's use according to clinical need, especially across borders in low- and middle-income countries.

Beyond better targeting, financial incentives might encourage delinkage. Delinkage of a firm's return on investment from *revenues* on a product is key to realigning economic incentives for rational use of antibiotics. Revenues reflect both price and quantity. At the same time, delinkage of a firm's return on investment from the *price* of a product can help ensure close-to-marginal cost pricing. To conserve novel antibiotics for those most in need, attention must be paid to both price and quantity. Prizes could buy out the patents behind promising antibiotic drug leads and enable scale-up for access, but not excess. Push-mechanisms such as grants could also be applied similarly and, in exchange for such support, could be conditioned to ensure affordable access and controlled scale-up and distribution for rational use (20).

Financial incentives might also be structured to reduce the misuse of human antibiotics for non-therapeutic purposes, such as growth promotion, in animal husbandry and aquaculture. A tax might be placed, if not a ban, on non-human use of antibiotics that pose a risk of cross-species resistance. The magnitude of this tax could make it economically unattractive to use antibiotics for growth promotion.

Regulatory barriers would matter if there were evidence of novel antibiotics being slowed or aborted in the R&D pipeline, but there is little to support such a picture. Moreover, compromising drug safety for patients in favor of speedy shortcuts to approval may ultimately prove counter-productive. Serious adverse consequences from an antibiotic too hastily approved might end up chilling the speed of regulatory approval of other novel and safe antibiotics. More productively, drug regulatory agencies might look into how to encourage greater efficiency without lowering requirements for safety and efficacy of the drug. Developing a companion diagnostic for multiple

companies working on different drugs but targeting a common pathogen might not only improve the rational use of these novel antibiotics, but also lower the clinical trial recruitment costs of those involved in such clinical testing. Combinations of antibiotics might be tested in parallel rather than serially. The Critical Path to Tuberculosis (TB) Drug Regimens—a partnership founded by the TB Alliance, the Critical Path Institute, and the Bill & Melinda Gates Foundation—seeks to save 75% of the time required to develop a new TB drug regimen by taking this approach. Finally, allowing for the pooling of clinical trial data might also lower the costs of bringing a new drug to market. A pooled data set of controls against which novel antibiotics targeting the same pathogen might be more readily compared could lower costs and speed up such clinical trials. For Alzheimer's disease, the Coalition Against Major Diseases created an online repository, where control arm data from 6500 patients across 24 clinical studies of Alzheimer's disease and mild cognitive impairment are being shared. These studies came from multiple companies, and their working group created a standard for collecting, storing, and interchanging Alzheimer's clinical trial data, and seven of the participating companies remapped their existing clinical trial data into this new format for sharing (21).

New business models should help reengineer not just the financing, but also the way novel antibiotics are developed and brought to market. This will require applying the 3Rs for innovating novel antibiotics: sharing resources, risks, and rewards (22).

By sharing resources, the barrier to needed research inputs might be lowered. For example, enriching a public compound library, particularly with natural product sources, would provide an innovation platform for discovering new classes of antibiotics. Over a third of small molecule drugs over the past three decades have originated from natural products, and among antibiotics coming to market between 1982 and 2002, over three-quarters of the drugs derived from natural products (23).

By sharing risks, public financing can offset the need for private sector capital returns. This both lowers the opportunity costs of capital—which comprise nearly half of the US$800 million in R&D expenditures that a US pharmaceutical company requires to bring a new drug to market and can enable close-to-marginal cost pricing (24). The NIH's National Center for Advancing Translational Sciences accomplishes much of the same by providing, on a competitive basis, contracted services for precompetitive R&D needs, from toxicology to pharmacodynamics/pharmacokinetic studies, for reaching first-in-human trials. Support under the US Biomedical Advanced Research and Development Authority (BARDA) also shares risks in a public–private partnership.

By sharing rewards, fair returns to the public under such arrangements might be sought. Delinkage could remove the misalignment of economic incentives and policy tension for companies between rational use and return on investment from volume-based sales. Lessons might be harnessed from how the Green Light Committee and the Global Drug Facility have helped to ensure rational use of second-line TB drugs along with the challenges of scale-up. Under these procurement arrangements, these drugs are provided at concessionary prices on condition that plans for their appropriate use could be assured (25). With greater public financing of the pharmaceutical value chain, closer-to-marginal cost pricing might become feasible, and this would help place life-saving, novel antibiotics into the hands of those who need such treatment, not just those who can afford such treatment.

Putting the 3Rs together, India's Council on Scientific and Industrial Research has begun piloting the Open Source Drug Discovery (OSDD) initiative, beginning with TB drugs. Through an online collaboration platform, OSDD shares resources across a network of collaborators. Those joining this online community commit to a clickwrap license not to take from the research commons, nor to privatize the product of their work. With funding from the Indian government and a private foundation, OSDD shares the risks and rewards of these efforts. Many volunteer and receive micro-attribution for their work. It is anticipated that the druggable leads generated will receive support for publicly funded clinical trials, and the resulting inventions would come to market as a generic drug licensed for affordable access and not excess. If this bold experiment succeeds, open-source innovation may offer a new business model, one that could complement and catalyze the faltering, traditional R&D pipeline of bringing novel antibiotics to market.

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