**FOCUS**

**REPURPOSING**

**Drugs in Search of Diseases**

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Drug repurposing is in vogue, but stakeholders must address seminal challenges before this approach provides a reliable source of new medicines.

We know the molecular basis of ~5000 human diseases but have treatments for only ~250 of these diseases. Indeed, the development of safe and effective medicines is intricate, expensive, and time consuming. With attrition, a single new molecular entity (NME) costs more than $2 billion and can take 14 years to develop (1). During this process, more than 90% of NMEs fail because of safety concerns or lack of efficacy (1). Biomedical researchers desperately need alternative strategies to augment the traditional approaches to drug discovery and development.

One alternative strategy is drug repurposing—the therapeutic use of a drug or drug candidate for a disease other than that for which it was originally developed (2). This approach to drug discovery takes advantage of physiological processes shared across target organs, systems, or diseases and the likelihood that a drug’s mechanism of action might be applicable to other disorders. A successful example is sildenafil, which augments nitric oxide signaling. This blockbuster drug was approved for erectile dysfunction and then later for pulmonary arterial hypertension (3). Another is thalidomide, which was originally developed as a sedative during pregnancy but later was withdrawn because, tragically, it caused birth defects. Thalidomide was subsequently resurrected as an effective treatment for multiple myeloma and skin lesions in leprosy (4).

Repurposing of sildenafil and thalidomide followed from serendipitous observations, but a systematic approach could be more fruitful. To this end, partnerships between for-profit pharmaceutical companies and not-for-profit academic and government-funded research institutions have been formed. These partnerships are a step forward, but because the pharmaceutical industry will be the main source of repurposed drugs, any impediments to Pharma’s active (and enthusiastic) participation must be anticipated and removed. These impediments will be outlined in this article.

**PARTNERSHIP PILOTS**

As part of its mandate to accelerate drug development from “bench to bedside,” the U.S. National Center for Advancing Translational Sciences (NCATS) launched a program to facilitate collaborative efforts between industry and academia to explore new indications for small-molecule drugs or biologics that have completed phase I or II testing (5). So far, eight companies (6) have collectively agreed to make 58 compounds available for the program. For successful applicants—mainly researchers from academia or small companies who also complete preliminary preclinical feasibility studies—the U.S. National Institutes of Health will provide 2 to 3 years of funding for proof-of-concept clinical trials. In this partnership, the industry partner retains the composition of matter patent and has the first option to license new intellectual property (IP) that arises from the research.

In the United Kingdom, AstraZeneca and the Medical Research Council (MRC) launched a collaborative program in 2012 that allows the academic community to compete for access to 22 “de-prioritized” compounds in order to conduct preclinical and clinical testing for new indications (7). The MRC has committed £10 million in total research funding to investigators who submit the best scientific repurposing proposals. AstraZeneca retains IP rights related to a given compound’s composition of matter, whereas licensing of any methods-of-use IP arising from the research is negotiable according to the collaborative agreement.

The World Intellectual Property Organization (WIPO) Re:Search consortium was formed by WIPO in collaboration with BIO Ventures for Global Health in 2011 in order to accelerate development of treatments for the neglected tropical diseases tuberculosis and malaria (www.wipo.int/research/en/about). Participation in this voluntary program, which is open to all public and private research entities, involves providers who contribute compounds, enabling technologies, know-how, and other information to a publicly available database that can be accessed by users who leverage these resources to research and develop treatments. Providers also agree to grant users royalty-free licenses to IP for the sole purpose of addressing public health needs in the least-developed countries. The consortium has recruited more than 50 entities as members from around the world, has signed 13 research agreements, and has more than 30 other agreements in various stages of negotiation. As a philanthropic organization, WIPO Re:Search is particularly well suited to encourage public-private repurposing collaborations. From an industry perspective, successfully repurposed drugs arising from

**Shedding new light on old drugs.** Repurposing may illuminate a path to new medicines.
PHARMA RECKONS REPURPOSING

Drug repurposing bypasses the need for initial target discovery, lead optimization, preclinical development, and early clinical safety testing, which could reduce the time and out-of-pocket costs of development by ~50% (1). It also takes advantage of target-directed drug candidates that failed in clinical development programs. The attrition rates for phase II and phase III of clinical development have been estimated recently at 80% (8) and 50% (9), respectively; thus, only ~10% of compounds that enter phase II successfully complete phase III clinical testing, providing a large and growing reservoir of agents eligible for repurposing. Because the vast majority of failed drug candidates have already undergone preclinical safety assessment and some clinical development, the availability of safety and pharmacokinetic data means that development for alternative indications can begin at the proof-of-concept stage (phase IIA). This represents a tremendous opportunity for the pharmaceutical industry to take advantage of the enormous—otherwise sunk—costs already invested in a given compound and to capitalize on advances in our understanding of disease biology made after the compound’s original discovery. Repurposed drugs may also be eligible for faster regulatory review, and for currently marketed drugs, manufacturing scale-up costs may be obviated.

From a scientific perspective, making compounds (and associated data) available to all members of the biomedical ecosystem, such as academic investigators and disease-focused foundations, will undoubtedly increase the variety of scientific perspectives brought to bear and very likely raise the odds of finding a therapeutic indication. As a result, drug repurposing can augment the armamentarium of compounds with defined mechanisms of action that are available for clinical testing.

Notwithstanding their promise, public-private drug repurposing partnerships also face considerable challenges. The odds of success are directly related to the number and quality of available compounds and to the numbers of scientists from broad-ranging backgrounds who are motivated to explore potential alternative indications. Obtaining sufficient numbers of each will require an uncomplicated, cooperative business model that avoids unnecessary bureaucracy and provides incentives to all parties. The system for handling applications for collaboration will also need oversight to ensure that the arrangements between partners work effectively.

For drugs with a long history, regulatory standards may have changed since their initial preclinical and clinical testing, and so regulatory review processes may need to be reexamined so as to ensure there are no unnecessary obstacles to further clinical development or eventual approval. Although repurposing may be less expensive and time-consuming than de novo development of NMEs, there are still considerable costs, including those associated with subsequent phases of clinical testing and with maintenance of and access to preclinical and clinical data on potential repurposed compounds. Thus, reliable and sufficient sources of funding—public or private—are required to support pursuit of scientifically rigorous proposals. Given the current paucity of public funding and often limited, targeted support of private foundations, financial resources from the pharmaceutical industry will be needed for public-private repurposing initiatives to achieve their translational goals.

This reality suggests that the financial viability of repurposing initiatives may need to be revisited. For example, IP protection based on composition of matter—which lasts for 20 years from first submission for an NME—is likely to be near or past expiry for the majority of compounds contributed to such initiatives. For drugs with expired patent protection, generic competitors may already be on the market. Special provisions on reimbursement or pricing may need to be considered for repurposed generic drugs in order to provide sufficient incentive for funding the requisite clinical trials that lead to registration. Although methods-of-use patents may allow protection for some repurposed compounds, they generally do not provide sufficient exclusivity protection since the basic compound patent expires. Incentives are also limited by the duration of regulatory data exclusivity (RDE)—the period of time in which generic competitors are prevented from using data generated and paid for by the innovator company to gain regulatory approval. For small-molecule drugs in the United States, RDE is granted for 5 years from the time of marketing approval for a first indication and an additional 3 years for a second indication (10). The period of exclusivity in Europe is 10 years, with an added year for new indications. Given the substantial investments of time and money required to successfully bring an agent to market, it is not clear whether a sufficient amount of market exclusivity exists under current regulatory law in the United States or Europe to offset the risks and clinical development costs of repurposed compounds. Thus, success in recruiting industry to invest the substantial funds required to complete clinical development (including costs of clinical trials and manufacturing) will likely require incentives such as enhanced data exclusivity. One relatively simple approach to address this issue might be to extend regulatory data exclusivity for small molecules to match that already enjoyed by biologics; the Follow-on-Biologics legislation passed by the U.S. Congress in 2010 provides 12 years of data package exclusivity (DPE). If a valid patent exists, other approaches might include enhanced patent term protection (i.e., patent term extension) for repurposed drugs. This could take several forms depending on the drug and disease in question. Proposals for new IP and DPE strategies would need to be well received by all stakeholders, including corporate partners who require sufficient incentive to participate in repurposing initiatives and the public at-large who would benefit from the development of repurposed drugs.

UPPING THE ODDS OF SUCCESS

As with any publicly or privately funded program, the probability of success will be enhanced by ongoing assessments and adjustments. Metrics need to include both immediately measurable and shorter-term outputs, such as numbers of compounds made available for testing and numbers of collaborative research agreements signed annually. Evaluations of the shorter-term deliverables will allow for adjustments in repurposing programs to enhance the odds of success. Longer-term outcomes such as number of compounds moved into pivotal clinical registrational trials or approved by regulatory agencies will be useful for determining the translational success of these programs. Template agreements between industry and academic investigators will need to be reviewed periodically to determine whether they accelerate timelines and to provide the necessary framework for handling issues that arise from collaborations. It is important that qualitative goals also be set. In particular, for drugs that have previously had development stopped prior to registration, clear evidence for on- and off-target pharmacological mechanisms in humans will be needed to reduce the odds of failure in late-stage clinical trials.
The success of these repurposing efforts will be enhanced by the support of patient advocacy groups, which typically have strong ties with academic investigators and industry. Patient advocates are keenly aware of unmet medical needs and have powerful voices that can be enormously useful to engage and galvanize stakeholders, including policy-makers, on the policy changes required to maximize the value of drug repurposing for patients, payers, and the public as a whole. Support from patient advocacy groups, together with industry, will be instrumental to facilitate the collaboration of like-minded physician-scientists who will be needed to complete clinical development in a timely fashion.

Clearly, successful repurposing programs will offer benefits for virtually all stakeholders. For the public, any increase in the availability of safe and effective treatments for poorly treated diseases would have lasting positive impact on the quality and cost of health care. From an industry perspective, these initiatives present an opportunity to explore novel therapeutic indications for existing drugs with a favorable risk-benefit ratio and to reduce costs by shortening the research and development cycle time. Academic investigators will be offered access to a broad range of drugs with which to explore human disease biology and the opportunity to advance biomedicine. A bold approach to drug repurposing will almost certainly accelerate the approval of more effective drugs and biologics by making the most of the considerable resources already invested.

REFERENCES AND NOTES
6. The NCATS industry collaborators are Pfizer, AstraZeneca, Eli Lilly, AbbVie, Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, and Sanofi.
7. Medical Research Council, MRC/AstraZeneca: Mechanisms of Disease call for proposals; available at www.mrc.ac.uk/Fundingopportunities/Calls/MoD/MRC008389#content.

Competing interests: S.M.P. is the former Executive Vice President of Science and Technology and President of Lilly Research Laboratories at Eli Lilly and Company.

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