

## POINT OF VIEW

# Overcoming obstacles to repurposing for neurodegenerative disease

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## Introduction

Repurposing, also called repositioning, reprofiling, or rediscovering, refers to the concept or process of taking a drug developed for one indication and applying it to another. Similar risk factors and biological pathways can underlie seemingly unrelated diseases,<sup>1</sup> opening the door for novel hypothesis-driven and data-driven repurposing strategies.<sup>2,3</sup> In addition, increasing challenges associated with developing new chemical entities (NCEs) drive interest in repurposing among the research community. This is especially the case for chronic neurodegenerative dis-

## Abstract

Repurposing Food and Drug Administration (FDA)-approved drugs for a new indication may offer an accelerated pathway for new treatments to patients but is also fraught with significant commercial, regulatory, and reimbursement challenges. The Alzheimer's Drug Discovery Foundation (ADDF) and the Michael J. Fox Foundation for Parkinson's Research (MJFF) convened an advisory panel in October 2013 to understand stakeholder perspectives related to repurposing FDA-approved drugs for neurodegenerative diseases. Here, we present opportunities on how philanthropy, industry, and government can begin to address these challenges, promote policy changes, and develop targeted funding strategies to accelerate the potential of FDA-approved repurposed drugs.

eases. The *de novo* drug discovery and development path can take 13 years and cost close to 2 billion dollars.<sup>4</sup> While we need to accelerate the development of new drugs, the slow progressive nature of neurodegenerative diseases, the long duration of trials, the large number of patients required, the lack of comprehensive understanding of the neurobiology, and the limitations of the clinical trial enterprise make it incredibly costly and challenging. Here, we do not advocate focusing on repurposing at the expense of *de novo* drug development efforts, but as an additional parallel strategy to hopefully increase the number of treatments available to patients. Existing knowledge

of pharmacological effects and safety profiles of repurposed agents can expedite early phases of clinical development, shorten drug development timelines, and reduce failure rates due to pharmacokinetic and safety issues. Repurposed agents are more than twice as likely across all disease indications to make it to market compared to NCEs.<sup>5</sup>

Repurposing does, however, have its own unique drug development challenges as described in more detail below. Repurposing clinical trials still costs a significant amount of money, safety needs to be clearly demonstrated, efficacy established, and the lack of patent protection, and commercialization potential significantly limit industry interest. Repurposing is common practice in current pharmaceutical research and development, but is often limited to drugs still in the development process (often called repositioning) or to drugs where development efforts have ceased but patent life remains and a new indication is up for consideration (rescuing).<sup>6</sup> Because the drug discovery process is expensive and risky, pharmaceutical and biotechnology companies must have a clear path to economic return in order to justify the capital expense of investing in a new use for an existing and approved drug. Companies may rely on remaining patent life, new “use” patents, or data exclusivity to support the necessary financial returns. However, the economic return of repurposing approved drugs, particularly generics, can be insufficient due to limited patent life or current regulatory exclusivity provisions. In this context, promising repurposed drug treatments may never reach the patient because of the limited incentive to invest in the trials required to prove efficacy.

For the purposes of this paper we focus exclusively on the unique challenges of repurposing FDA-approved drugs for new indications where limited or no patent life remains and there is no obvious commercial incentive to proceed with development. Although this is written primarily in the context of the United States, the principles do apply more broadly to the international community.

## Challenges With Repurposing

### Continued need for expensive and risky trials

While repurposed drugs can bypass early stage development and initial safety testing, they require very expensive, high-risk clinical trials to establish efficacy. A single phase III clinical trial for Alzheimer’s disease (AD) can cost up to 300–400 million dollars. In addition, there are specific challenges for neurodegenerative disease indications that need to be addressed. Clinical trials must have a long duration due to the slow progressive nature of the disease, drugs (in most cases) must be proven to penetrate the brain, and safety must often be tested in elderly

populations, who frequently have comorbidities and may take medications that interact with the repurposed drug. Safety is a major concern for an elderly population with neurodegenerative disease who will likely need to take the drug chronically. Most repurposed drugs to date have been targeted to the cancer space, likely due to the increased tolerance to safety concerns in this indication.

### Limited or no patent protection or patent life

A company is required to submit a New Drug Application (NDA) and gain FDA approval to market a repurposed drug for a new indication. Unfortunately, by the time a new drug is approved for its first indication, there is typically less than 10 years on the original 20 year composition-of-matter patent remaining,<sup>7</sup> which is not enough time to generate the data needed to approve the drug for a second indication and make a profit. “Use” patents for the new indication are an option, but must meet “nonobvious” criteria, are often harder to defend, and therefore have less value.

There are strategies that allow developers of repurposed drugs to secure new intellectual property and differentiate the repurposed product from the one(s) already marketed. One can develop a novel formulation, a new dose that is not currently approved, a novel combination with another drug, or a combination with a proprietary companion diagnostic or service. However, the novel formulation or enhancement must provide true medical or economic benefit for the reasons described below.

An example of what can happen if IP barriers can be surmounted is the multiple sclerosis (MS) drug, BG-12, marketed as Tecfidera developed by Biogen Idec (Cambridge, MA, USA), also called dimethyl fumarate or DMF. DMF was originally synthesized 50 years ago, and a version registered in Germany 20 years ago for psoriasis.<sup>8</sup> Biogen Idec was able to develop a proprietary version and utilize “use” patents to commercially develop DMF for MS. DMF now has the potential to be the most widely used drug in this space despite the fact that it is an old, well-known compound with limited patent protection. The widely used Alzheimer’s drug, memantine, is another example. Memantine was originally developed in 1968 as a derivative of an anti-influenza agent before it was serendipitously found to have beneficial effects in dementia and developed for that indication also through “use” patents.<sup>9</sup> Similar opportunities may exist for other repurposed agents.

### Commercialization and reimbursement challenges

Even if the FDA approves a new formulation or combination product, commercial returns depend on payers

providing coverage and reimbursement when a therapy is prescribed to a patient. Payers are unlikely to cover a new formulation, altered dose, route of administration, and/or combination therapy over existing approved drugs without demonstration of clear clinical benefit at a reasonable cost. As with all pharmaceuticals today, but especially with repurposed drugs where the commercialization pathway is particularly risky, a product is unlikely to be developed without the potential of payer reimbursement at a level that will incentivize an investment to demonstrate the drug's efficacy for a new indication. As a result, FDA assessments of "safety and efficacy" become effectively linked to payers' criteria for the repurposed drug use to be "reasonable and necessary." Repurposing strategies must keep both hurdles in mind from the inception of the clinical development process.

While the FDA offers a period of 3 years exclusivity for a new use of a previously marketed drug for a new indication, this period is often too short to recoup investment and it does not prevent physicians from prescribing the existing drug "off-label" if dosages suitable for the new indication are already marketed or can safely be compounded from the marketed product. If generic versions are available, the challenges are even greater, since payers can promote a "generic switch" even if branded drugs have a new indication. Although such generic prescribing lowers costs for the patient and payer, it discourages companies from investing in clinical trials to prove drug efficacy because this approach limits pricing flexibility and the potential return from their risk investment.

In addition, demonstrating the value of new treatments is of growing importance in the United States and globally. Payers, whether they are patients, private insurers, or governments want significant clinical benefit or an overall reduction in medical costs for the patient (i.e., "cost effectiveness"). This is required in some health systems. As an example, the National Institute for Health and Care Excellence (NICE) determines which drugs are covered under the National Health Service in England and it requires a mathematical calculation to determine the potential cost effectiveness and benefits to patients. If the threshold is not met, governmental reimbursement is not recommended. In the United States, private insurers factor total cost of care and value of the drug into their decision as to which drugs will be included in their plans for reimbursement.

While the cost of the development path is lower with a repurposed drug, in the current pharmaceutical R&D context repurposing projects have very little chance to enter into the portfolios of established pharmaceutical companies. The price supported for a repurposed drug is no different than an entirely new drug and is ultimately based on its uniqueness/nonsubstitutability and its clinical

and economic benefits. Thus, the value of repurposing from an industry perspective for currently marketed, branded, or generic drugs will often be marginal due to limited patent life. At the same time, most pharmaceutical companies are faced with more phase II clinical opportunities across a wide range of disease indications than their research and development (R&D) budgets can sustain. As a result, any new clinical stage R&D project inherently must displace another project that is in the portfolio, and repurposing projects with limited return on investment will likely be deprioritized. For approved drugs with potential benefit for neurodegenerative diseases, alternate development pathways are needed. Foundations and government may need to take the initiative either by advocating for policy changes to incentivize company investment or by directly funding repurposed drug development.

## **Models for Foundations and Government to Accelerate Repurposing**

### **Nonprofit funding for repurposing clinical trials**

As described above, unless there is a viable commercial strategy, pharmaceutical companies are highly unlikely to fund clinical trials for repurposing of approved drugs. This creates an opportunity where foundations and government can take the initiative. While funding a repurposed agent through to an FDA approval for a new indication is an intractable financial commitment for most individual foundations, foundations and/or government can directly fund smaller proof-of-concept clinical trials of repurposed agents. Positive results from such trials may encourage larger investment from government and industry to fund larger, multicenter trials.

Several groups today are funding such pilot trials with the hopes of catalyzing larger interest in repurposed candidates. Cures Within Reach is a foundation exclusively focused on supporting repurposing studies. The ADDF, MJFF, Alzheimer's Society (UK), Cure Parkinson's Trust, the Multiple Myeloma Research Foundation and others have funded repurposing trials and have recently announced funding opportunities for repurposed drugs. Many academic centers are also leading repurposing efforts in collaboration with government initiatives. Through the "Learning Collaborative," the Leukemia Lymphoma Society is working with the National Center for Advancing Translational Sciences (NCATS) at the National Institutes of Health (NIH) and the University of Kansas on repurposing Auranofin for chronic lymphocytic leukemia. Thalidomide, infamous for causing severe birth defects when used for morning sickness in the

1950s, is now a widely prescribed and valuable treatment for leprosy and multiple myeloma thanks in part to the research findings from the academic community that resulted in Celgene seeking FDA approval for the new indications.<sup>10</sup> Methotrexate is another example of an approved drug which found a new life as a treatment for rheumatoid arthritis and is currently improving the quality of life for hundreds of thousands of patients.<sup>11</sup>

Federal funding or public–private partnerships, including interactions with academic institutions, could support clinical trials that lead to approval of generic repurposed agents. In the AD arena, the Alzheimer’s Disease Cooperative Study (ADCS) can conduct regulatory quality trials and this organization or a similar one could plan and implement a phase III program for a repurposed agent. If results from this trial are positive and the drug continues to demonstrate adequate safety, distribution by generic companies could follow. “Marketing” would occur through publication of the results in the scientific literature and through scientific conference presentations.

### **Build consortiums/collaborations between nonprofits, industry, and government entities**

A nonprofit drug development entity or consortium driven by foundations and government could directly fund trials to the point of FDA approval. When efficacy is shown, the company that owns the drug could apply for FDA-approval or the consortium could potentially sponsor the FDA approval on its own. At least two well-controlled clinical studies are required for FDA approval for an indication, unless there is robust finding in a single well-controlled study and confirmatory evidence are sufficient to establish effectiveness. For diseases like AD and Parkinson’s disease (PD) which have very large costs of care, the potential healthcare cost savings to the government from development of effective treatments may justify investment in such collaborative ventures.

In addition to cooperation between foundations and government, increased collaboration between regulators and other groups may accelerate repurposing. A collaboration between industry, academia, FDA, and the NIH to develop a path to make data available on failed or abandoned drugs would accelerate repurposing by helping to identify (or exclude) new repurposing opportunities. This collaborative framework could build on the NCATS program for “Discovery of New Therapeutic Uses for Existing Molecules.”<sup>12</sup> The goal of the program is to make available to the research community molecules that already have undergone significant research and development by the pharmaceutical industry but have been abandoned for reasons other than toxicity. While this effort has initially

focused on abandoned molecules rather than FDA-approved drugs, the structure could be a model for future collaborative efforts.

Opportunities already exist for foundations to work with the FDA to refine guidance on regulatory pathways for approval of repurposed drugs. The availability of new pathways for the FDA to rely on biomarkers as surrogates for outcomes in clinical trials provides a potential path to shorter, less expensive, and more efficient repurposing clinical trials where biomarkers can be the main endpoint.

Payers may also be important collaborators to accelerate repurposing. If a repurposed generic drug is shown to be efficacious for neurodegenerative disease, it may lower overall payer costs significantly as there will be an effective low-cost treatment available where previously there were none. Since payers are saving money, payers could share these savings with the drug developer to incentivize new indication development and registration. For public payers, the important drivers of change are legislation and public perception, in addition to costs and quality of care. Private payers often follow the coverage decisions made by the public bodies. The macroeconomic problem with linking these savings to the investment required to fund repurposing, as well to reimbursement, is that many of the indirect or informal costs to society of the major neurodegenerative diseases (e.g., caretaker burden, nursing home costs) are borne neither by those who fund R&D nor by the healthcare (medical cost) payer. Therefore, one major objective of policy innovation must be to explore approaches that allow those who will derive value from repurposing to invest directly into repurposing projects; for example, the creation of social finance bonds to fund development that could be sold to pension funds and individuals who are either in current or potentially in future caretaker roles. Foundations can also help to incentivize payers by lobbying for coverage, giving voice to patients, and helping to build consensus and collaboration across distinct groups.

### **Policy innovations to incentivize industry investment in repurposing drugs**

Historically, repurposing efforts have focused on treatments for the rare and pediatric diseases, but the value to society is equally compelling in the area of high-need cures, specifically neurodegenerative diseases where there are no disease-modifying treatments. Below we list a number of ideas for policy and legislative changes that could be implemented to incentivize companies to invest in repurposing.

- Extend the length of time for data exclusivity for small molecules when applying for a new indication. This

provision is currently under review in Congress as part of the MODDERN (Modernizing Our Drug and Diagnostics Evaluation and Regulatory Network) Cures Act.<sup>13</sup> The MODDERN Cures Act creates a new class of therapies defined as “dormant therapies,” which can be “rescued if the drug or new biological product meets an unmet medical need.” This legislation would provide a designated data exclusivity period in exchange for certain patent rights to encourage manufacturers to investigate dormant therapies.

- Develop a program to accelerate the development of repurposed agents so that robust data could support approval after phase II trials. These efforts could be linked to the reauthorization of the Prescription Drug User Fee (PDUFA) Act which will be under discussion in Congress shortly. Post-approval pharmacovigilance could be employed in phase IV to further demonstrate safety and efficacy in the specified indication.
- Advocate for priority review vouchers, similar to those available in the Rare Pediatric Disease Priority Voucher Program implemented in 2013, for repurposed agents targeted to high-need conditions including neurodegenerative diseases. This would allow for expedited FDA review.
- Consider staged approvals or adaptive licensing under a pilot or “safe harbor” program.<sup>14</sup> Drugs could be approved for certain populations of people based on defined risk. As further studies are conducted, the eligible patient populations can be increased as “stages” of approval are achieved. This model is currently gaining some momentum in the European Union.
- Lobby for changes in how payers view cost effectiveness, shift the conversation to total cost of care and value, and increase transparency among payers. For example, a delay in disease progression may not always be viewed as “effective” from the payer’s perspective despite analyses showing that it often reduces long-term costs particularly for age-related diseases. Patient-relevant outcomes should ultimately drive the definition of value. This change could be linked to the Patient Centered Outcomes Research Institute (PCORI) efforts.
- Examine different royalty structures. For example, a royalty structure could be implemented that would allow pharmaceutical companies to receive a royalty, from generic drug companies, for example, for sponsoring a phase III trial with a generic repurposed drug and getting FDA and payer approval. This model would help to secure value for an off-patent drug and would allow the company to get returns by bypassing the need for manufacturing (if the drug is generic) and marketing costs. This could also be linked to PDUFA reauthorization.
- Introduce legislation that provides a range of incentives within the government payment structure for access to repurposed drugs. The incentive could be structured in the form of a rebate from CMS, other federal payers such as the Veterans Health Administration, or private payers to the company that sponsored the trial of a repurposed drug for a new indication. This model provides an incentive for innovation and could reduce cost for payers by introducing new generic, inexpensive treatments for disease.
- Consider social finance bonds to support the development of repurposed drugs. This strategy could be funded up-front with bonds guaranteed by the government and paid back over time (effectively a royalty) on medications. For this model to become operative, negotiations with CMS would need to occur before initiating trials, the cost savings to the government would need to be mapped with sufficient specificity to support the bond repayment, and a government guarantee would need to be provided based on the savings rendered to CMS.
- Advocate for more government funding for repurposing initiatives, although it is critical that funding not be diverted from important basic research, new drug discovery and development, and other efforts. Public/private consortia, advocacy efforts like Research!America, and industry organization like PhRMA and BIO can all work together toward this goal.

Each of these policy ideas needs further attention and review. Nonprofit organizations like FasterCures, ADDE, MJFF, and others can help to begin the conversation with advocacy organizations, policy makers, government, and the public. It is critical to put the right incentives in place in order to accelerate interest in repurposing to make the best use of the innovative drugs already created.

## Conclusion

The more we learn about human disease, especially chronic diseases manifesting later in life, the more we learn to embrace its complexity. Through utilization of large data sets, electronic medical records, and bioinformatics, we can identify new unexpected opportunities for drug repurposing. However, those opportunities require funding to prove that the drug will be safe and effective in the target patient population. In the current climate, the funding is not there and repurposed drugs are unlikely to reach the patient because companies typically have insufficient financial incentive. Innovations in policy, risk sharing, and collaborations may change that reality. Foundations and government can drive the change by investing in the necessary proof-of-concept efficacy

studies and advocating for policy changes that will incentivize industry. Through the strategy options outlined above, we can create feasible commercial paths to test promising repurposed agents for neurodegenerative disease and accelerate the availability of drugs to the patients in need.

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