

# Executive Summary

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Drug repurposing (an approach to drug development that is also known as drug repositioning, reprofiling, or retasking) has become a matter of intense interest during the past few years. In brief, it is a strategy that calls for reinvestigating drug candidates that have not succeeded in advanced clinical trials, for reasons other than safety, for potential new therapeutic applications.

In the more conservative approach, termed “on-target repurposing,” the drug’s known pharmacological mechanism is applied to a new therapeutic indication, which in clinical terms might be quite far removed from the original one but is known to have the same pharmacological underpinning. About 80% of drug repurposing efforts that are currently ongoing (or have already resulted in a successful relaunch) have followed this route, which must not be confused with simple line extensions, *e.g.*, a cancer drug obtaining additional approvals for other types of cancer. The classic example is sildenafil, which was unsuccessful in its development as a new drug for common hypertension but became immensely successful as a drug for male erectile impotence; it then established itself as a drug to treat pulmonary arterial hypertension, a life-threatening chronic disease. One can hardly imagine two applications that are more different from each other medically, yet they share phosphodiesterase 5, an enzyme which sildenafil inhibits, as a common critical element in their respective symptomatic pathways. Even more innovative is “off-target repurposing,” which looks at known molecules without prerogatives, looking for pharmacological mechanisms that have not yet been described for a known molecule. This approach uses what has been termed “systematic serendipity.” In either case, having failed is not a criterion; the avenue is equally open to drugs that are being marketed or have once been on the market.

Some industry observers have decried repurposing as “drug recycling” and labeled it as another defensive marketing move by the pharmaceutical industry to squeeze out yet more return from its existing resources in a time when truly novel therapeutic approaches have become increasingly rare and new chemical entity approvals are dwindling. However, others have hailed it as a matter of economic and medical common sense not to shelve a drug candidate forever because it failed efficacy endpoints in Phase II or III trials. The motto should probably be what Gregory A. Petsko, D.Phil., a Gyula and Katica Tauber Professor of Biochemistry & Chemistry at Brandeis University, wrote in a May 2010 piece in *BMC Biology*:

“Give me your tired, your poor, your Phase II failures... What if those drugs were not tried on the right disease? (...) What if the cure for Alzheimer’s disease is sitting on some drug company’s shelf, as a potential cancer drug that failed in Phase II? (...) People diagnosed with psoriasis are at greater risk of developing heart disease; in fact, in patients with severe psoriasis who are younger than 50 years old, the risk is comparable to that seen in diabetes. How many Phase II-failed psoriasis drugs have ever been tested in heart disease clinical trials? (...) So I REALLY want the Phase II failures. I want them for my own research and for your research. I want them because they could make a difference for a host of unmet medical needs.”

[Petsko GA. When failure should be the option. *BMC Biology*. 2010;8:61–3.]

Repurposing a drug or a failed advanced-stage candidate drug can have very different commercial implications. These will depend on where the drug comes from, how much accessible data exist, and how well the repurposer can exploit the new value chain created by a successfully repurposed drug. This will to a good part depend on what sort of intellectual property can be secured for the new use. Chapter 2 is dedicated to these issues, which can be tricky to argue: The repurposer fights an uphill battle against examiners who will scrutinize the prior art for any public facts that can be construed to have anticipated the new medical use of a known drug. Typically, methods-of-use patents (which usually is what a repurposer can hope for) are relatively weak when compared to composition-of-matter patents, which protect the active pharmaceutical ingredient itself; they are subject to off-label uses that effectively erode their market position. New court and patent office rules, as well as constantly improving data-mining technologies, make it much easier to find “obviousness” in the prior art—or even in a granted patent.

Tool sets combining state-of-the-art genomic, proteomic, animal model, and bioinformatics technologies are employed to identify repurposing opportunities. Together with expert knowledge in pharmacology, these technologies define repurposing business strategies. These more technology-oriented aspects are discussed in Chapter 3, followed by an outline of the regulatory environment for repurposing in Chapter 4. Here, we discuss the applicable legal framework and show that while repurposing can remove the initial 1–1.5 years of preclinical and Phase I development time (the latter only if no new formulation has to be developed and tested), the later stages of the regulatory review process for repurposed drugs are the same as with new chemical entities. While reviewers might be more comfortable with the safety aspects of the drug (provided that existing data are sufficiently recent to meet current regulatory standards), the proposed use of the drug in a different target population and with a correspondingly different set of efficacy criteria will in many cases make late-stage reviews and the preapproval process as lengthy as any other.

Chapter 5 discusses exemplary cases of drug repositioning and illustrates how the task can be approached, depending on the intended goal. Chapter 6 profiles selected key companies in the repurposing business and how they have fared during the past decade. This section focuses on companies that offer platform-based services to identify repurposing options, but it also discusses the internal repurposing efforts of three top-ten pharmaceutical companies—Pfizer, Novartis, and Eli Lilly—and how these programs tie into their overall development strategies. Not much to our surprise, we found that the structure of repurposing-platform companies, as well as the structures of deals they make with larger companies, is similar to that of drug

discovery platform companies, and they suffer from similar vulnerabilities. Their success has been mixed. Like most other service providers, their businesses suffered severely from the economic crisis of 2008–2009 and its aftermath. For Big Pharma, drug repurposing is usually not something that is broadly discussed; such programs are for the most part already integral to these companies' discovery efforts.

Chapter 7 adds financial aspects to the discussion. If repurposing is successful, extension of the drug's useful lifetime before patent expiry (resulting from the initial steps not being required) will be the greatest benefit for larger companies. For smaller companies, much of the benefit of repurposing will be indirect, resulting from the ability to attract venture capital funding more rapidly and offer investors a more dynamic development perspective that (in the ideal case) will more or less begin with initiation of Phase II proof-of-principle trials. For one-product startup companies, repurposing might be the single best rationale for entering the drug development business with a head start, saving up to \$5 million in direct, early-stage development costs.

In summary, we find that drug repurposing can take on many meanings in several dimensions. It spans the range from what (for a pharmacologist) might be blatantly obvious (at least in retrospect), to the cutting edge of innovation that completely reinvents a known molecule—exploiting a new mechanism, new dosing, and probably a different route of administration to address a disease or disorder that was not previously believed to offer any connection with the drug in question. Drug repurposing has also become a new business segment for the life science services industry. While it is easy for almost any existing contract research organization to directly monetize its existing services for the development of repurposed drugs, discovery of off-target repurposing opportunities is a matter of cutting-edge technology where high-content screening and multiplexed animal models are called for. For the decade ahead to 2020, we predict that such repurposing technology will see increasing integration as a standard process of resource utilization, de-risking, and acceleration of drug development.