DRUG REPOSITIONING
About the Cover

Drug repositioning can be a daunting challenge, but one filled with possibility. There is a story in *The Art of Possibility* by Rosamund Stone Zander and Benjamin Zander of a man who comes upon a woman on a beach, surrounded by starfish that have washed ashore. She picks up individual starfish and throws them back into the water, in an almost “ritualistic dance.” The man approaches her: “There are stranded starfish as far as the eye can see. What difference can saving a few of them possibly make?” Smiling, she bends down and once more tosses a starfish out over the water, saying serenely, “It certainly makes a difference to this one.”

Like the woman, drug repositioning sifts through many compounds, particularly those “washed up,” failed compounds, to find the one that makes a difference to patients.


Cover image by Rachel Frail
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Drug repositioning, also commonly referred to as drug reprofiling or repurposing, has become an increasingly important part of the drug development process for many companies in recent years. The process of identifying new indications for existing drugs, discontinued, or “shelved” assets and candidates currently under development for other conditions—activities we refer to as “indications discovery”—is an attractive way to maximize return on prior and current preclinical and clinical investment in assets that were originally designed with different patient populations in mind. It is widely appreciated that the business impetus to recoup the vast investments in pharmaceutical research and development (R&D) is enormous. As discussed by Arrowsmith and Harrison in Chapter 1, output of new medical entities (NMEs) approved by the U.S. Food and Drug Administration (FDA) has remained steady at around 25 per year over the last decade, while pharmaceutical R&D expenditure has increased over 50% in the same time frame [1, 2]. Against this backdrop of escalating costs associated with increased development timelines and requirements, along with growing regulatory and reimbursement pressures, drug repositioning has emerged as a lower cost and potentially faster approach than *de novo* drug discovery and development. The objective of Part I of this book is to examine in detail the medical and commercial drivers underpinning the repositioning industry, and to highlight the key strategic, technical, operational, and regulatory considerations for drug repositioning programs.

Among the numerous case studies that are described throughout this book, perhaps the best known example of successful implementation of drug repositioning is that of the blockbuster and first approved treatment for erectile dysfunction (ED), Viagra® (sildenafil citrate). The story of the development of this drug, which was originally being developed by Pfizer for the treatment
of angina, offers a fascinating insight into how keen observation and good science can unlock the full potential of safe biotherapeutics that are either already marketed or, as was the case for sildenafil, under development for other indications [3]. This example serves to highlight some of the essential elements that underpin the rationale behind, and opportunities that exist in, drug repositioning.

At its core, drug repositioning takes advantage of three fundamental principles. First is the reality of biological redundancy, namely that “druggable” biological targets can contribute to the etiologies of seemingly unrelated conditions, due to common underlying pathology and/or shared biological signaling networks. In the mid-1980s, the biological target of Viagra®, an enzyme called phosphodiesterase 5 (PDE5), was being studied for its involvement in regulating nitric oxide (NO) signaling in smooth muscle cells associated with coronary blood vessels. NO activates the enzyme guanylate cyclase, which results in increased levels of cyclic guanosine monophosphate (cGMP), leading to smooth muscle relaxation, increased blood flow, and the associated hemodynamic effects characteristic of nitrates. cGMP PDE enzymes such as PDE5 inactivate cGMP by converting it into guanosine monophosphate (GMP), and attenuate NO signaling. With this underlying biology in mind, sildenafil was at the time being considered as an antiangina therapy. After initial clinical trials in angina indicated modest hemodynamic effects (i.e., efficacy) but dose-limiting adverse events including erections, attention turned to ED, where the role of NO/cGMP was emerging at the time; but the role of PDE5 in the corpus cavernosum of the penis had not previously been appreciated [3]. New biology was thus uncovered and the rest, as they say, is history.

A second key driver for drug repositioning, which is also highlighted by the Viagra® story, is that the pharmaceutical drug discovery process is typically therapy area–focused and sequential, meaning that a candidate is usually designed and developed single-mindedly for one disease, regardless of whether the drug target may have roles in other diseases in different therapy areas. Because of this focus—though less frequent now than in the past—consideration of alternative therapeutic applications for a candidate may not occur until it either succeeds in the primary indication (typically in Phase III or beyond), or fails. Even then, repositioning or “indications discovery” efforts are not guaranteed and certainly rarely systematic, due to potential stigma associated with a failed asset, or risk aversion in a successful primary project team that “owns” the candidate, or simply lack of cross-therapeutic expertise/ mindset. As described in Chapter 2 of the book, one consequence of this for a pharmaceutical company’s pipeline is that valuable patent life may be lost by delaying exploration of other opportunities, particularly if the candidate’s safety, pharmacokinetics (PK), and pharmacology have been adequately demonstrated—often several years previously—in Phase I studies. Thus, repositioning applies not only to previously shelved candidates or marketed drugs, but increasingly to candidates that are still under clinical development in a primary indication.
Among the key elements of any repurposing program are the unique clinical, regulatory, and logistical considerations of conducting patient studies with candidates in secondary indications. The purpose of Chapter 3 is to outline some of the requirements for generating a robust data package for a second indication, as well as to highlight some of the often underappreciated challenges of repositioning candidates to different patient populations, where the safety package, route of administration, site of action, and PK/pharmacodynamic (PD) requirements can all differ. Part I concludes with a review of some unique regulatory and market exclusivity opportunities that can be applied to repositioned candidates (Chapter 4).

Fortunately, for both companies and the patients they serve, the traditional, sequential approach to drug discovery is changing. Increasingly, companies are leveraging internal expertise and external collaborators in a more cross-therapeutic manner to assess the applicability of pipeline or shelved candidates (and in some cases, external opportunities) in alternative indications that may be in noncore areas, in a more systematic and intentional way. A key component of a systematic approach to repositioning is the application of bio- and chemoinformatics-based approaches to interrogate vast amounts of internal and published preclinical/clinical data (both on the drug candidates themselves and their cognate biological targets/pathways) to generate new hypotheses for experimental testing. Part II of this book—“Application of Technology Platforms to Uncover New Indications and Repurpose Existing Drugs”—addresses this aspect and outlines a number of computational strategies, tools, and databases that have been developed or successfully applied to repositioning studies. Authors in this section have been drawn from large pharmaceutical and biotechnology companies, as well as academia, in order to provide a wide spectrum of perspectives. Chapters in this section include descriptions and case studies using the numerous information sources that are publicly available to facilitate repositioning.

Also covered in Part II of the book is the topic of screening approaches for drug repositioning. As a complementary strategy to “hypothesis-driven” indications discovery, screening clinical candidates or marketed drugs in disease-relevant in vitro assays or animal models in an unbiased manner increases the probability of uncovering not only previously unknown connections between drug targets and diseases, but also the potential to reveal pharmacologically important “off-target” effects of a candidate. Off-target biology—the elicitation of useful pharmacology by a drug that was not intended or appreciated at the time of development—is a third and important driver for drug repositioning, particularly for older compounds that were less extensively profiled than present day candidates. For example, amantadine, originally developed for influenza through its ability to interfere with the viral M2 protein [4], was later found to have, among other activities, dopaminergic and noradrenergic effects and was subsequently repurposed for Parkinson’s disease [5]. Another well-known example is thalidomide. Originally prescribed as a sedative, it was found to have antiemetic effects leading to its use by pregnant
women in the late 1950s and early 1960s with tragic teratogenic consequences for the developing fetus [6]. Despite these tragic beginnings, thalidomide has since been found to have a number of pharmacologically beneficial effects including antitumor necrosis factor (TNF) and antiangiogenic activities and has been approved for use in erythema nodosum leprosum (ENL) and multiple myeloma [7].

From the perspective of drug repositioning, phenotypic, disease-relevant *in vitro* screening assays, or animal models are unbiased with respect to “on-target” or “off-target” effects; any activity that modulates the endpoint being measured will be detected, regardless of cause. Although often more complex to prosecute and automate than conventional target-based biochemical assays used in the drug discovery process, such models provide the significant benefit of enabling an investigator to probe all the possible activities of a candidate, or cohort of candidates, across a wide therapeutic spectrum of disease models. Examples of cell-based screening approaches, including searching for novel synergistic combinations of marketed drugs, are described in the Chapter 8 by Lee, while the application of “multiplexed” *in vivo* screening platforms to identify new indications clinical candidates is described in Chapter 9 by Saporito et al.

The final chapter in Part II by Morgan et al. addresses a common strategy employed for drug repositioning or “drug salvaging,” namely the development of chemically modified analogs of approved agents which are either metabolized *in vivo* into the parent drug molecule (prodrugs), or may themselves be viewed essentially as NCEs, in the case of deuterium-labeled analogs. Also covered in this chapter is the “chiral switch” approach, namely single enantiomer variants of previously approved chiral drug mixtures. Collectively, such strategies have yielded numerous clinically relevant, enhanced drug properties including increased bioavailability, improved PK profiles, more convenient dosing regimens, dramatic changes in tissue distribution, and decreased adverse events. A number of case studies are provided to illustrate these concepts.

It is noteworthy that many of the strategies covered in Part II have been driven by specialist companies that have developed and validated technology platforms to provide unique and cost-effective screening/repurposing services to the pharmaceutical/biotechnology industry. In many cases, these same companies have utilized their own platforms together with strategic alliances with large pharmaceutical companies to build internal pipelines of repurposed drugs of their own.

In Part III of the book, we turn our attention to repositioning approaches being pursued outside the industry, but often in partnership with it; specifically some of the efforts being championed in academia and by not-for-profit organizations/foundations. One of the increasingly important contributions that academic investigators and foundations provide in the field of drug discovery in general—and repositioning in particular—is their advocacy for rare or neglected diseases (sometimes collectively termed orphan diseases), which are frequently overlooked by big pharmaceutical companies due to lack of
commercial return. In the United States, the Rare Disease Act of 2002 [8] defines rare disease strictly according to prevalence, specifically as “any disease or condition that affects less than 200,000 persons in the United States,” or about 1 in 1500 people. A similar definition exists in Europe [9]. Neglected diseases [10] generally refer to a group of tropical infections prevalent in developing countries of Africa, Asia, and south/central America but essentially nonexistent in developed nations (e.g., parasitic trypanosomal and helminth infections, bacterial infections such as cholera, and viral episodes such as dengue fever). Chapter 11, written by Curtis Chong, describes several examples of repositioned candidates for diseases of the developing world that have been identified through open source screening campaigns such as the Johns Hopkins Clinical Compound Screening Initiative. Chapter 12 provides case studies from several different patient advocacy groups/foundations to highlight the unique work these organizations perform, as well as the tremendous potential advantages afforded by repositioning for patients suffering from rare diseases whose existing treatment options are often extremely limited. The book concludes with an overview of some of the business thinking that is currently being applied to drug repositioning within the pharmaceutical and biotechnology sectors with an emphasis on partnerships between the various stakeholders that are engaged in this sector. Chapter 13 highlights the increasing use of strategic alliances and risk-sharing partnerships as approaches to increase the industry’s clinical development capacity and number of successful proof-of-concepts and recoup value on otherwise stalled assets. This chapter examines the various drivers for each party in such alliances and assesses the potential of current and future repositioning joint ventures between industry, academia, and not-for-profit organizations. Finally, Chapter 14 exemplifies some of the key considerations for drug repositioning partnerships through a case study on the Japanese biopharmaceutical company Sosei, which pioneered a unique business platform for reprofiling previously shelved drug candidates using a sophisticated shared risk partnership model.

The Appendix at the end of the book seeks to provide a compilation of valuable resources for the prospective repositioner, providing information on drug repositioning and reformulation companies, databases, relevant government resources and organizations, links to regulatory agency guidance, along with academic and nonprofit organization initiatives related to repositioning.

We hope that the book is as informative to the reader as it has been enlightening to compile.

REFERENCES


PART I

DRUG REPOSITIONING: BUSINESS CASE, STRATEGIES, AND OPERATIONAL CONSIDERATIONS