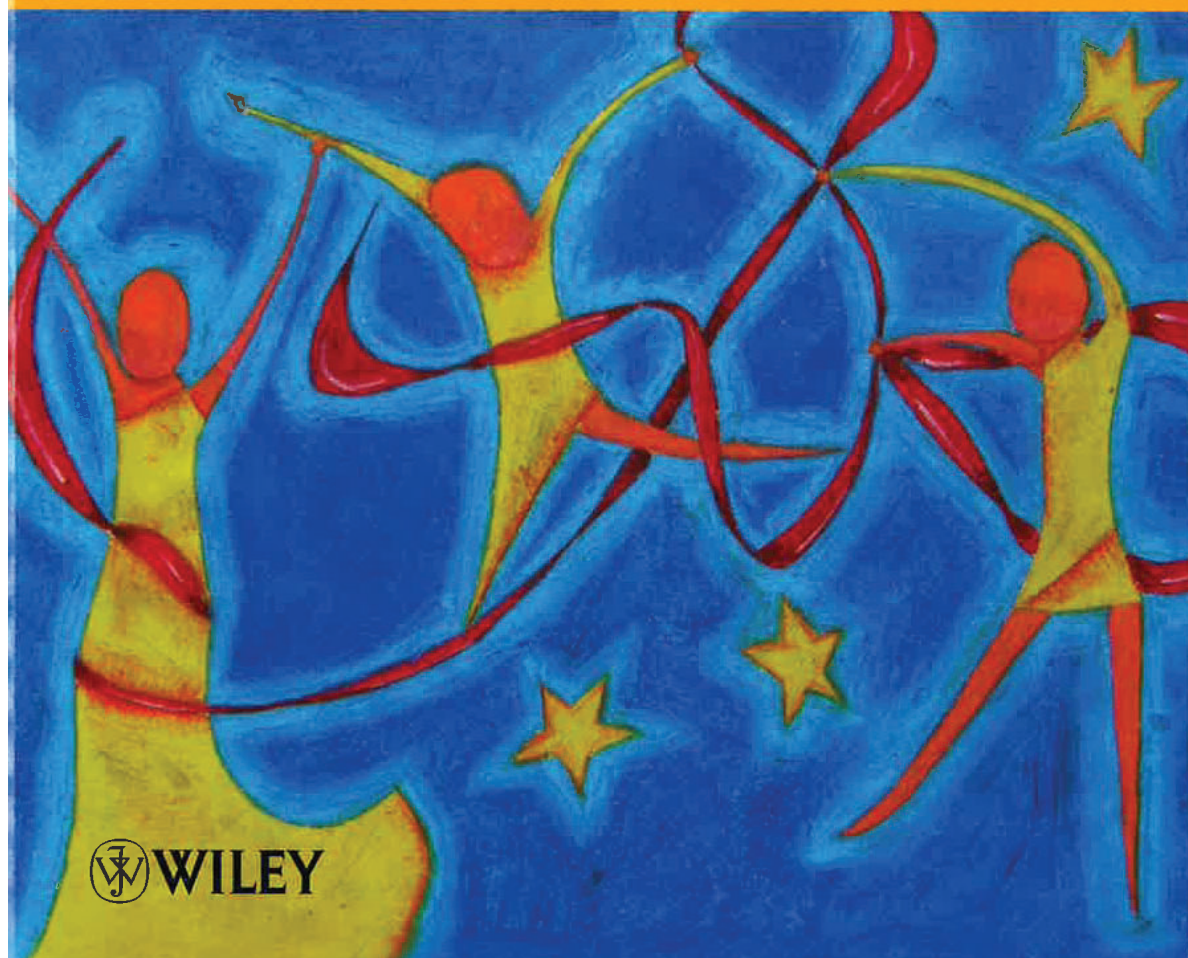


Drug Repositioning

*Bringing New Life to Shelved Assets
and Existing Drugs*

*Edited by
Michael J. Barratt and Donald E. Frail*



 WILEY

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.

Art of Possibility: Transforming Professional and Personal Life by Rosamund Stone Zander and Benjamin Zander. Harvard Business Press Books, 2000.

Cover image by Rachel Frail

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Donald E. Frail is currently Vice President, Science, in the New Opportunities iMED at AstraZeneca, a research unit focused on identifying developing new medicines through external partnerships and drug repositioning. Prior to this, Don founded and led the Indications Discovery Unit at Pfizer, a dedicated research unit focused on drug repositioning, and was an architect of the groundbreaking partnership between Washington University School of Medicine and the Indications Discovery Unit. He has also held positions as Site Head for Pfizer's St. Louis Laboratories, Head of Biology for the St. Louis Laboratories, Head of Central Nervous Systems Research at Pharmacia, and positions at Women's Health at Wyeth and Neuroscience at Abbott. He has been involved in bringing more than 20 potential new medicines into the clinic across multiple indications. He obtained his PhD in Biochemistry from McGill University and completed a postdoctoral fellowship at Washington University School of Medicine.

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Introduction

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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

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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 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.

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Clinical and Operational Considerations in Repositioning Marketed Drugs and Drug Candidates

DAMIAN O'CONNELL, DAVID J. SEQUEIRA, and MARIA L. MILLER

3.1. INTRODUCTION

One of the most attractive aspects of drug repositioning is the reduced time to clinically test the hypothesis compared with a *de novo* drug discovery program. In many cases, shorter routes to the clinic are possible because *in vitro* and *in vivo* screening, chemical optimization, toxicology, bulk manufacturing, formulation development, and even early clinical development have already been completed and can therefore often be bypassed in a repositioning program. In this chapter we will aim to provide the reader with an appreciation of the clinical considerations and operational complexities that are unique to a repositioning program. In many cases, the clinical validation strategy is influenced both by the existing data and by the ability to take advantage of factors that could shave several years, along with substantial risk and cost, from the pathway to the market.

The reduced risk offered by an existing favorable safety and pharmacokinetic profile of a repositioning candidate can be offset if the asset has not established proof-of-mechanism (PoM, or alternatively referred to as proof of pharmacology) in the clinic. Furthermore, toxicology or pharmacokinetics (PK) that were collected for the candidate in the original indication might now be inadequate due to the changes in regulatory standards. However, pioneering efforts can pay off handsomely: for example, achieving first-in-class status can allow for a significant head start on the competition, as exemplified by the first-mover advantage of about 5 years that Pfizer's sildenafil (Viagra®) had on Lilly and ICOS's tadalafil (Cialis®) and GlaxoSmithKline and Bayer's

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ildenafil (Levitra®). Brand awareness built during the first years of sales played a key part in maintaining Viagra's® position in the market despite strong competition.

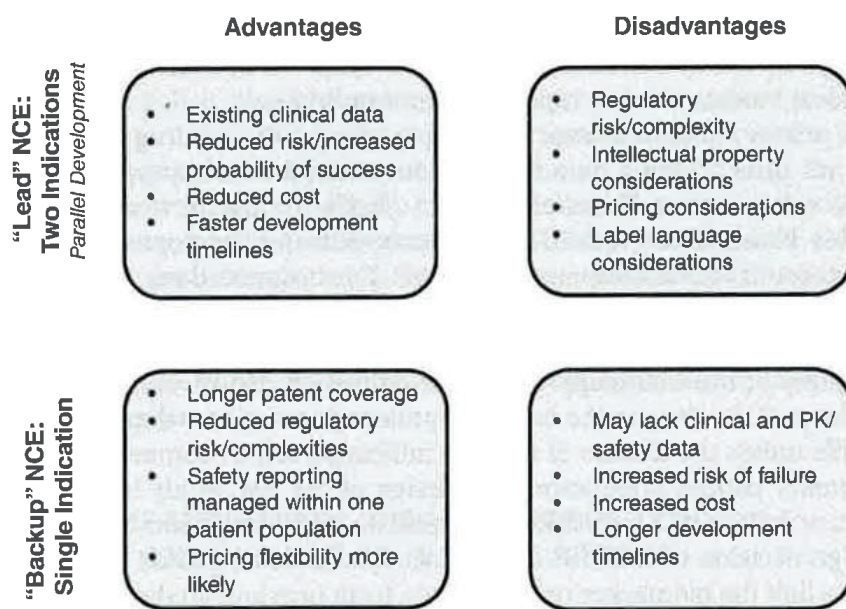
3.2. CHALLENGES AND OPPORTUNITIES IN ESTABLISHING A DRUG REPOSITIONING PORTFOLIO: MARKETING DRUG, LEAD CANDIDATE, OR BACKUP?

A portfolio of drug repositioning candidates can be comprised of marketed compounds and/or new chemical/biological entities (NCE/NBE). The amount of development risk and resource needed for clinical validation will vary depending on how far the candidate has progressed in its primary indication. If the candidate is a marketed drug, the extent of any remaining patent coverage and the potential for generic or off-label competition from drugs of the same mechanistic class will be key considerations. On the other hand, if the repositioning candidate is an NCE/NBE with recently granted patent protection, then the stage of development and amount of clinical and preclinical toxicological data will be the primary drivers. Another consideration when repositioning an NCE is that the lead candidate may have a clinical data package, whereas a "backup" candidate of the same class might only have preclinical data. Thus, the additional risk and time needed to establish clinical validation will be a factor for the latter.

Figure 3.1 captures the advantages and disadvantages of drug repositioning when there is a choice between selecting an NCE that is progressing in its primary indication versus a "backup" candidate of the same class that is less advanced. The development of a single NCE in two indications will increase the probability of the NCE reaching the market and maximizing return on investment. However, there are other factors requiring careful consideration. If the severity of the disease and co-morbidities across both patient populations are considerably different, there is a risk that nonrelevant label warnings will be "carried over" into the healthier patient indication label (e.g., risk for black box warning). Also pricing flexibility will be limited due to the potential for off-label use despite branding efforts, as discussed in Chapter 2. The commercial impact of these factors could be huge and therefore play a key role in the selection of a "backup" NCE for the second indication, despite the efficiency advantages that result from parallel development of the alternate indications with the "lead" candidate.

3.2.1. Proof-of-Concept (PoC) Trial Design

As previously mentioned, the repositioning of a drug candidate can provide many benefits that will vary depending on the stage of development at the time of repositioning. Many candidates will have extensive or complete Phase I clinical data packages while others may have Phase II or even Phase III data. Marketed compounds will have abundant clinical and safety data from



NCE—New Chemical Entity

FIGURE 3.1. Advantages and disadvantages of using a "lead" NCE versus a "backup" NCE when repositioning an active development candidate or marketed drug.

numerous Phase III and Phase IV clinical programs. This can be both a positive and a negative depending on the history of the clinical program and the overall value of the drug to the company if it is currently on the market. Additionally, how close the drug is to its patent expiry will impact the potential return on investment for a new indication.

The principal value of a legacy Phase I program for developers of a candidate in a new indication comes from the pharmacokinetic and pharmacodynamic (PK/PD) data package generated in these prior studies. Critical dosing information will be available along with exposure limits and general safety of the compound in healthy subjects. The existing data can be used to develop appropriate PK/PD models to assist with dose range projections for the new indication or aid in development of additional preclinical work if warranted. However, dosing and PK/PD for the new indication should be determined empirically, as they may differ from the first indication. If the data package has areas requiring clarification or missing information, additional Phase I clinical evaluations should be performed as appropriate to support the development plan. For example, these may include drug–drug interaction (DDI) studies, bioavailability/bioequivalence studies for new formulations, studies in a special population such as the elderly, and/or other safety studies that would apply specifically to the second indication (e.g., tolerability for local administration). If there are biomarker data, or other specialized methodology such as imaging studies that are beneficial to the proposed new indication, then

these would be key items that would be incorporated to further develop the program, especially if such biomarkers are validated and translate back to the preclinical models used to reposition the candidate.

The primary goal of a team attempting to reposition a drug candidate is to utilize all prior Phase I data in order to proceed into appropriate Phase II clinical validation or Proof-of-Concept (PoC) for the new indication. Any available Phase II or Phase III data can benefit the development program if it can assist in the development of a PoC. For instance, data on the duration of dosing beyond typical Phase I dosing periods (i.e., 14 days) could assist with defining appropriate clinical monitoring should there be questions on longer term safety of the candidate in the new indication. However, specific data on the effects of the drug in the intended patient population will probably not be available unless the disease of the new indication shares common aspects with the primary patient population. The design of the PoC study is critical to the success or failure of a repositioned candidate. Trial design, dose selection, and go-no-go decision criteria for the PoC study should be guided by a concerted effort to link the biomarker response data from previous studies with available clinical outcome data (i.e., internal and external sources) for comparators into an integrated PK/PD model.

If the PoC design is sound, as assessed for example by peer review or an appropriate scientific advisory committee, the PK/PD is well understood, and the results are compelling once completed, then the candidate can often proceed directly into Phase III testing. This can lead to more rapid commercialization for the candidate; however, it must be noted that additional complementary data may also be required for gaining approval depending on the indication under evaluation (e.g., acute vs. chronic disease). There are some scenarios where Phase IIb or Phase IIb/III adaptive design studies will be needed. For example, such studies will be required to support an alternative route of administration or when there is a large uncertainty in the estimates of efficacious dose.

When designing a PoC study it is important that repositioning teams bring in relevant therapeutic expertise and, wherever possible, retain access to the primary indication team's knowledge of the asset to assist in the development of the candidate for its new indication. Within big pharmaceutical companies, where this latter scenario is most likely to apply, this is a consideration that should not be underestimated due to the organizational challenges often faced when working across multiple therapeutic areas. Very often the expertise in the new therapeutic area **may not reside** inside the company or division repositioning the candidate, especially if the approach used to generate the repositioning hypothesis was unbiased (e.g., broad phenotypic screening or computational mining). Use of an academic research organization (ARO) is one way to access the requisite expertise since the research physicians are often well versed in both industry development and treatment of the patient population under study. For example, in the cardiovascular space, the Thrombolysis In Myocardial Infarction (TIMI) Study Group of Brigham and Women's

Hospital and Harvard Medical School is an excellent resource. Interactions with groups such as these can help to ensure the best possible PoC trial design is taken forward. It is also important to ensure that both the statistical and regulatory support available to the repositioning team is well versed in trial designs for the specific therapeutic area/indication in question (e.g., oncology, neuroscience, and infectious disease). The amount of resource required to perform a PoC can vary depending on the size of the intended PoC trial and nature of the repositioning trial sponsor. Large companies will probably be able to attain most of the required resource internally, whereas small companies or biotechs will often need to rely on outsourcing. However, even large companies are increasingly taking advantage of opportunities to outsource or partner in this space.

3.3. PROOF-OF-MECHANISM (PoM) FOR REPOSITIONED COMPOUNDS AND THE USE OF CLINICAL PROBES

The primary aim of drug repositioning studies is to characterize the pharmacodynamic effects of the candidate that could be used to treat other as yet untested condition(s). By using the appropriate study population (healthy volunteers vs. specific patient subgroup) and methodology, efficacy and safety/tolerant profiles can be determined in these new indications. Use of these drugs as pharmacological probes can facilitate the discovery of new drug targets. Doing so with a readily available internal candidate or a marketed/licensed drug that has a well-characterized safety profile, albeit perhaps in different populations, enables safe testing in new indications, minimizing the risk to patients or healthy volunteers.

If a drug repositioning study is conducted with a well-characterized compound (e.g., marketed/licensed drug or a drug candidate that is in Phase IIb/III clinical testing) with pharmacokinetic and safety profiles appropriate for the new indication, this can serve as a PoM study. PoM is a key concept that underpins the conduct of indications discovery studies. It entails demonstration that the drug binds and modulates its intended target at a safe dose (acceptable therapeutic index) in humans. The required degree of target modulation (enzyme inhibition, receptor occupancy, etc.) should be defined prior to the PoM study based on preclinical data or clinical data from compounds with a similar mechanism. PoM is usually demonstrated in Phase I in healthy volunteers using a target or mechanism biomarker or in a Phase Ib/IIa study in a target population (e.g., antigen challenge study in asthma patients, fluorodeoxyglucose [FDG] positron emission tomography [PET] signal in cancer patients, etc.) if target or mechanism biomarkers are not feasible in healthy subjects. A clear demonstration of PoM reduces the risk that an unprecedented or novel mechanism is unsafe in humans and helps define the effective dose range to evaluate in Phase II to fully test the drug target. PoM also increases the chance of program success and means additional indications for which

there exists strong confidence in rationale (CIR) can also be tested with greater likelihood of clinical success.

The following is an example of such a study. Phosphodiesterase 5 (PDE5) is a widely expressed enzyme. There is evidence that PDE5 inhibition can be useful in treating a number of conditions, including a range of cardiovascular diseases. Sildenafil, a PDE5 inhibitor approved for use in male erectile dysfunction, has been tested in studies in both systemic and pulmonary arterial hypertension (PAH). Results from these relatively small clinical target validation (CTV)/PoM studies in the appropriate patient populations suggested acceptable efficacy/target modulation at well-tolerated doses. The potential for its use in these additional indications was subsequently evaluated in larger confirmatory patient trials, which ultimately led to sildenafil being approved for PAH under the trade name REVATIO®.

When a marketed drug is used “off-label” in a drug repositioning study, the sponsor may have no intention of developing it for the new indication, but use the data from such a clinical pharmacology study to guide the discovery of another compound with the appropriate efficacy, safety, pharmacokinetic profile along with patent protection that would enable the development of a “best-in-class” drug. When using another marketed drug, a sponsor can use publicly available data such as the Summary of Product Characteristics or the European Public Assessment Reports (EPAR) for preclinical and clinical safety data to ensure that the drug can be used safely as a pharmacological tool. Subject safety should be the paramount consideration and the “off label” use of licensed drugs should be carefully considered to ensure that the program is conducted according to International Conference on Harmonization (ICH) principles.

3.4. IMPLICATIONS OF DRUG REPOSITIONING FOR CLINICAL PLANNING AND OPERATIONS

As already discussed, candidates for drug repositioning include both marketed compounds and NCE/NBEs. Each candidate presents unique operational challenges for the repositioning development plan before initiation of any clinical validation can proceed. One of the most frequent questions to arise once a drug candidate has been identified for repositioning is: “What do we need to do to get it into the clinic?” If the compound was originally developed “in-house,” then compilation of the various data components (e.g., clinical protocols and study reports, preclinical data, clinical databases, and regulatory documents) should be relatively straightforward. It should be noted, however, that internal constraints (sharing of clinical supplies, timing of Investigator’s Brochure updates, etc.) could exist if the compound is also involved in another development program, being co-developed, or is a marketed agent. On the other hand, if the compound was brought in from the outside, or had development activities spread across one or more companies, then bringing together

a cohesive package can be challenging. Teams must ensure that the original data package meets current regulatory standards if it is to be utilized to support the new indication. It is prudent for a repositioning team to include appropriate commercial and legal representation to ensure the best path forward for development as competitive landscape, intellectual property, and patent issues can make the development path complex.

The discussion below will focus on clinical and operational planning considerations when repositioning NCEs. There will be some differences, including regulatory pathway and manufacturing complexity, which will need to be considered for NBEs.

3.4.1. NCE/NBE

In order to test an NCE/NBE in a new indication, the sponsor will need to have access or ability to cross-reference all preclinical and clinical safety data and chemical, manufacturing, and controls (CMC) information. From an operational perspective, the drug supply plan will play a key role on the development timeline and budget. Drug substance and drug product manufacturing may be rate-limiting for the start of supportive toxicology or clinical studies. Critical information for estimating total drug supply requirements includes having the outline of the clinical protocol(s) with projected number of patients, route of administration, proposed doses, dosing period, and study design (i.e., placebo control and/or use of a blind comparator, parallel vs. cross-over design) including an estimate of the number of sites and countries, which will all be required to draft the overall plan. If the route of administration is different from that used in the existing toxicology package, then additional pre-clinical toxicology studies along with formulation development will be needed. For example, if an oral drug is being repositioned for a topical indication, a new formulation will need to be developed and new local tolerability preclinical studies will be required prior to human testing. If there is a strong rationale in support of abbreviated preclinical studies, then the sponsor should plan for a pre-investigational new drug (IND) with the U.S. Food and Drug Administration (FDA) meeting prior to triggering long and costly preclinical toxicology studies.

When a new formulation or drug product strength is required for the new indication, the repositioning team might need to trigger a bioavailability/bioequivalence study prior to the PoC study in patients. The need for these additional studies is determined by the formulation type or biopharmaceutical properties of the drug substance (permeability, solubility, etc.).

A repositioning program will also need to assess if the duration of the existing preclinical toxicology package will be adequate to support the proposed clinical dosing period. In general, the dosing period of the preclinical toxicology package needs to be of equal or larger duration than the proposed dosing period of the clinical study. If deemed insufficient, this could have a considerable impact on the development timeline and budget for the start of the new

study. A particularly costly scenario would be if a longer good laboratory practice (GLP) toxicology study is needed for the new indication and the compound is relatively safe. In this situation, not only would the duration of the study impact program timelines, but also large amounts of drug substance would be needed due to both the duration and the high doses required to obtain adequate understanding of margins. On the other hand, for anti-cancer Phase I oncology studies, treatment of patients can continue beyond the dosing period of the preclinical toxicological package as long as the patient is responding. Refer to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) S9 guidelines [1, 2] for different preclinical toxicology schedules based on examples of proposed oncology study designs and durations.

Once the drug supply needs are drafted, an assessment of the existing drug substance and drug product technology including inventory will need to be conducted. The best scenario will be that the supplies are available along with adequate storage stability and expiry dates. For compounds that are no longer in active development, that is, those that were previously discontinued, the inventory of available supplies will likely need requalification, depending on how long they have been in storage. When drug substance has been stored for longer periods than the assigned expiry date (based on previously collected stability data), it will need to be retested and subjected to further stability work to ensure acceptability prior to use in additional clinical studies. Drug substance expiry dates and usability are generally longer than the final drug product at early premarket stages, for example, due to higher risks for potential interactions with excipients in the latter. If drug substance is available, it may therefore be possible to use this existing material to manufacture a new drug product for clinical use. In addition, these supplies will need to have been stored under good manufacturing practice (GMP) conditions to maintain the chain of custody and GMP status. Analytical assays will also need to meet current regulatory standards. If not, assay development and validation work should be factored into the cost and timeline for the project.

In the case where no supplies are available or the stored material is deemed unsuitable for human studies, a new manufacturing campaign will be needed. Complexity of drug substance synthesis and quantities required will directly affect resources and time required for the manufacture of supplies. In order for a new lot to be released for clinical use, the levels of any impurities will need to be comparable to, or lower than those in the lot(s) used in the preclinical toxicology studies. For example, for a maximum NCE daily dose of ≤ 2 g/day, if a new impurity reaches a threshold of 0.10% or 1 mg/day intake (whichever is lower), the impurity will need to be qualified by conducting additional impurities/safety assessment studies per the FDA Q3A Guideline document [3]. In some cases, data might be available in the scientific literature (paper assessment) to support the qualification of the impurity without the need to conduct new *in vivo* qualification studies.

In parallel to the supply plan, the regulatory strategy to support the activities through PoC will need to be developed. A flow chart to assist with the investigational medicinal product dossier planning for new indications is shown in Figure 3.2. The project team should start building the dossier using the Common Technical Document (CTD) format and then edit specific sections (i.e., CMC) to satisfy different country requirements, if needed. However, if the paper format filed previously is acceptable to the regulatory authority, then any updates (i.e., justification for the new indication) can take place in paper version. In the meantime, plans to convert the paper version into a CTD format should take place in parallel with the ongoing clinical studies in the new indication to expedite future regulatory submissions.

In addition, key to the dossier preparation will be the status of the regulatory application for the original indication. For example, in the United States, if the sponsor has an existing open IND in another indication/division, the sponsor will be able to cross-reference sections from the open IND. For an inactivated IND, reactivation may occur with submission of new clinical study protocol, updated manufacturing information, and so on. The submission will be subject to a 30-day review clock. An IND enters in an inactive status when there has been no activity for a period of 2 years or more, or if all studies under the IND remain on clinical hold for 1 year or more. However, withdrawn (sponsor requests to end IND) and terminated (FDA orders sponsor to end all clinical activity) INDs cannot be cross-referenced and therefore a new IND submission will be required.

The operational aspects regarding drug safety, drug substance, drug product, and clinical supplies availability are summarized in Figure 3.3. The specific timelines to compile the dossier for submission will depend on the extent of any additional CMC and safety package requirements.

3.4.2. Approved Drugs

For an approved drug, using the same flow chart and considerations shown in Figures 3.2 and 3.3 will provide a good start in the planning process. From a regulatory perspective, if the drug is already approved, the sponsor is not required to own the data or have the right to reference from the original applicant. The application will include external published data and the FDA's previous findings of safety and effectiveness. In the United States, this may be done using the 505(b)(2) new drug application (NDA) application process (see Chapter 4 of this book).

With a good understanding of the compound's safety and pharmacokinetic properties, fewer clinical and/or toxicological studies will be required to support the IND application for the secondary indication. In the event of a positive PoC study, progressing the program using the 505(b)(2) NDA application process is likely to be completed faster and at a lower cost than a traditional 505(b)(1).

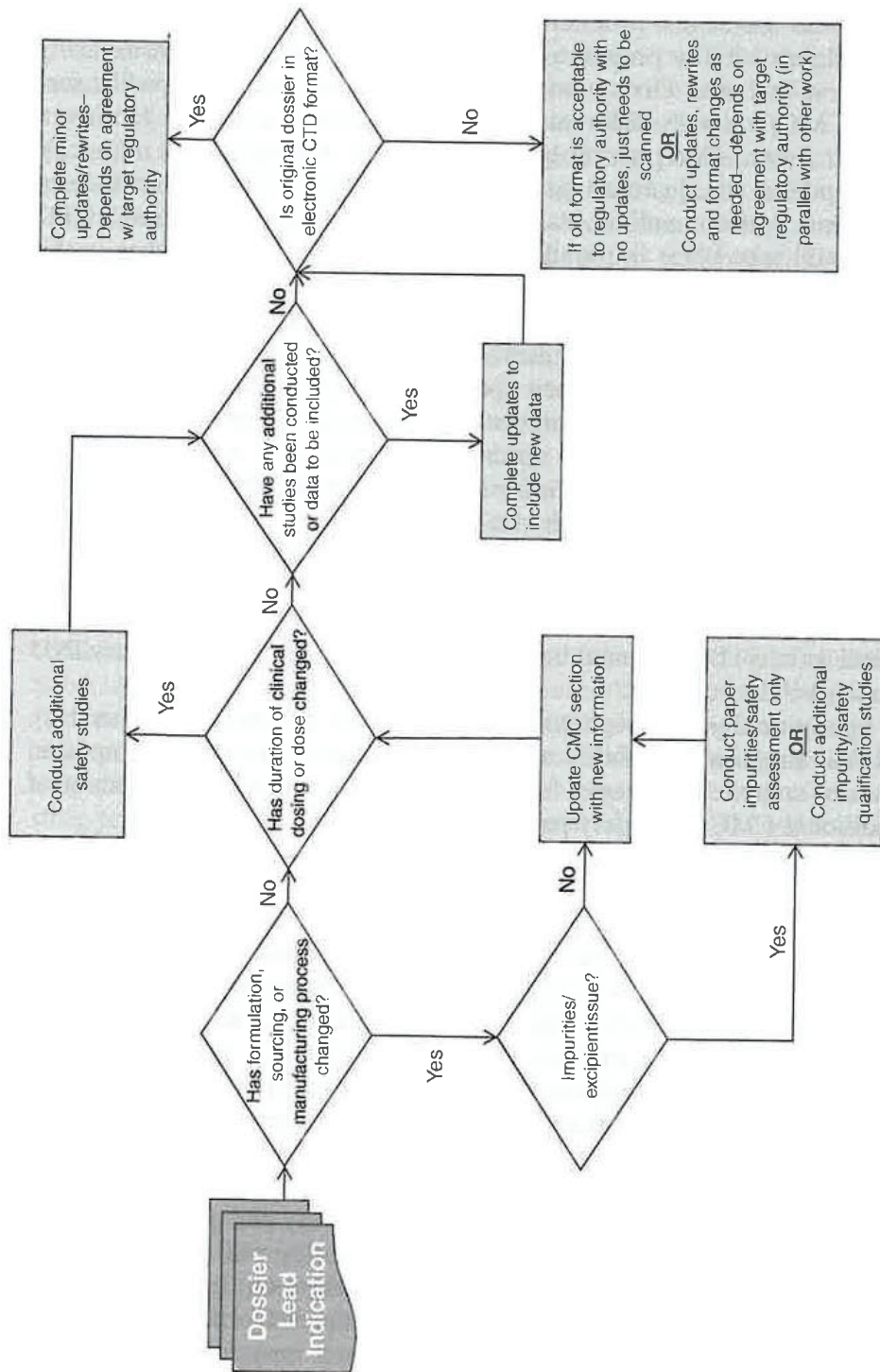


FIGURE 3.2. Dossier flow chart: Considerations when repositioning drug candidates.

CMC - Chemistry, Manufacturing and Controls
CTD - Common Technical Document

Prior Human Experience	Safety in New Population	Existing Regulatory Toxicology Coverage to Support Proof-of-Concept	Formulation and Supplies (Drug Substance and Product) in Hand
Both single and multiple Dose data exist with no safety issues out of the ordinary	No concerns highlighted for new population	Adequate coverage exists	Both formulation and supplies are available
Only single dose data exist with no safety issues out of the ordinary	Some potential concerns highlighted but just from limited preclinical data that can be easily monitored in a clinical setting	Additional <i>in vitro</i> regulatory toxicology studies will be needed prior to proof-of-concept	Both formulation and supplies are available but bioavailability data of formulation are not available
No prior human data with compound are available	Some potential concerns highlighted but from limited clinical data that can be easily monitored in a clinical setting	Additional <i>in vivo</i> regulatory toxicology studies will be needed prior to proof-of-concept	Drug substance reload needed and/or new formulation development will be needed to support clinical study
No impact on timeline and/or risk	Moderate impact on timeline and/or risk	High impact on timeline and/or risk	

FIGURE 3.3. Impact of availability of key data on clinical timelines/risk for repositioning drug candidates.

3.5. CONCLUSION

The repositioning of drugs to new indications can help companies increase the depth and value of their research portfolios, and importantly, provide opportunities to accelerate the delivery of new treatment options in areas of unmet medical need. Current trends of increased time-to-market approval, higher regulatory hurdles, and consolidation of industry research programs in recent years have created an environment where drug repositioning programs provide an attractive means to offset these challenges. Clinical validation of the candidate NCE, NBE, or marketed drug in a new indication is pivotal to this process. Development plans based upon existing preclinical and clinical data, CMC packages, and drug substrate provide significant leverage and give the repositioned candidate a head start to achieving PoM and/or PoC in the clinic. Overall, the risks and development costs associated with repositioning drug candidates are generally lower than those for NCEs being developed from “lead” status for a first indication. Importantly, however, as has been highlighted in this chapter and also that which preceded it, a repositioning team must be careful not to overlook critical operational, regulatory, and strategic considerations at the outset of the clinical program.

The complexity, cost, and risk in a development plan for a repositioning program is heavily dependent on the quality and completeness of data packages for toxicology, pharmacokinetics, and drug exposure/safety profiles available to the team. Moreover, investigators must be aware that requirements and standards for regulatory submission may have changed since studies for the primary indication were conducted. Perhaps more intuitively, the amount of drug substance available to support the development plan will also impact the reintroduction of the candidate, as will, among other factors, the potential need for formulation development, drug product manufacture, appropriate packaging, and availability of matched placebo controls for use in double-blinded patient studies. Thus, while in principle the progression of a repositioned candidate into the clinic can often be streamlined and more focused to answer any outstanding safety, regulatory, and subsequently efficacy questions, a significant amount of initial due diligence is required to fully understand the hurdles unique to that candidate before embarking on a development program. Time invested upfront to understand the current status of repositioning candidates and all relevant prior data, as well as to define what a new data package will require—and hence what needs to be in the plan—will pay dividends downstream by facilitating the selection of those opportunities that are most likely to achieve a definitive PoC outcome in a new indication in the most time- and cost-efficient manner.

ACKNOWLEDGMENTS

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Old Drugs Yield New Discoveries: Examples from the Prodrug, Chiral Switch, and Site-Selective Deuteration Strategies

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10.1. INTRODUCTION

Drug repositioning approaches are flexible, diverse, and dynamic. They can be customized to accommodate the goals and needs of the organizations implementing them. For example, repositioning can provide an approach [1] to capitalize on low risk opportunities by leveraging existing expertise on an in-house or in-licensed entity. In contrast, some biotechnology companies have developed repositioning approaches in the form of new technology platforms applied to generic, in-licensed, or *de novo* entities. Despite the varied applications of drug repositioning as well as the numerous technologies to implement them, a commonality among them is the goal to rapidly extract value from existing agents while improving the odds of successful development.

When applied to previously approved drugs and advanced clinical agents, repositioning approaches typically require less investment, shorter development time, and less risk for late stage clinical failure than typical pharmaceutical research and development (R&D) [2]. Through the examination of individual case studies, three repositioning strategies will be evaluated herein: (1) prodrugs: chemically modified analogs of approved agents which, upon administration, are metabolized *in vivo* into the parent drug molecule; (2) chiral switch: single enantiomer variants of previously approved chiral drug

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mixtures; and (3) site-selective deuteration: deuterium-labeled analogs of previously approved drugs.

10.2. PRODRUG APPROACH

10.2.1. Introduction

One of the most common methods employed for drug repositioning has been through the development of chemically modified analogs of approved agents which, upon administration, are metabolized *in vivo* into the parent drug molecule [3]. This prodrug strategy has been successfully applied to an array of previously approved agents across a wide range of therapeutic indications and chemical scaffolds. Prodrugs have demonstrated numerous clinically relevant enhanced properties including, but not limited to, increased bioavailability, improved PK profiles, more convenient dosing regimens, dramatic changes in tissue distribution, and decreased adverse events.

In addition to improving the pharmaceutical profile of the existing agent, the prodrug approach also provides additional intellectual property advantages. The prodrug variants are considered new chemical entities (NCEs) by the U.S. Patent Office and thus are granted appropriate protection. Furthermore, as described by the Hatch–Waxman amendments, the U.S. Food and Drug Administration (FDA) indicates that drugs for which no active ingredient (including any ester or salt of the active ingredient) has been previously approved are granted 5-year market exclusivity. Therefore, prodrugs of previously approved agents are viewed by the FDA as new molecular entities (NMEs) imparting the same extent of exclusivity as traditionally developed new therapeutic agents [4]. The atypical antipsychotic paliperidone palmitate (Figure 10.1e), however, represents an interesting exception to this rule. The FDA states that simple carboxylate ester derivatives of previously approved drugs do not earn the designation of NME. As such, the palmitate ester of paliperidone was classified as a new formulation and granted a shorter period of exclusivity [4c]. Furthermore, the FDA requires suitable evidence for safety and tolerability for the approval of all new drug applications (NDAs). This can be presented as new data received from Phase I clinical trials or by way of previously documented safety data. Companies developing prodrugs of their own parent agents may leverage internal safety data of the active metabolite for a traditional 505b(1) path to market. Alternatively, as described in detail in Chapter 4, other companies can proceed via a 505b(2) path, referring to the safety and tolerability data produced by the parent drug developer or other institution [5]. Either course can present a significantly accelerated path to market by circumventing the need for completely independent safety and tolerability studies.

A classic example of a prodrug with enhanced properties over its active metabolite is the naturally occurring amino acid levodopa (L-Dopa) [6].

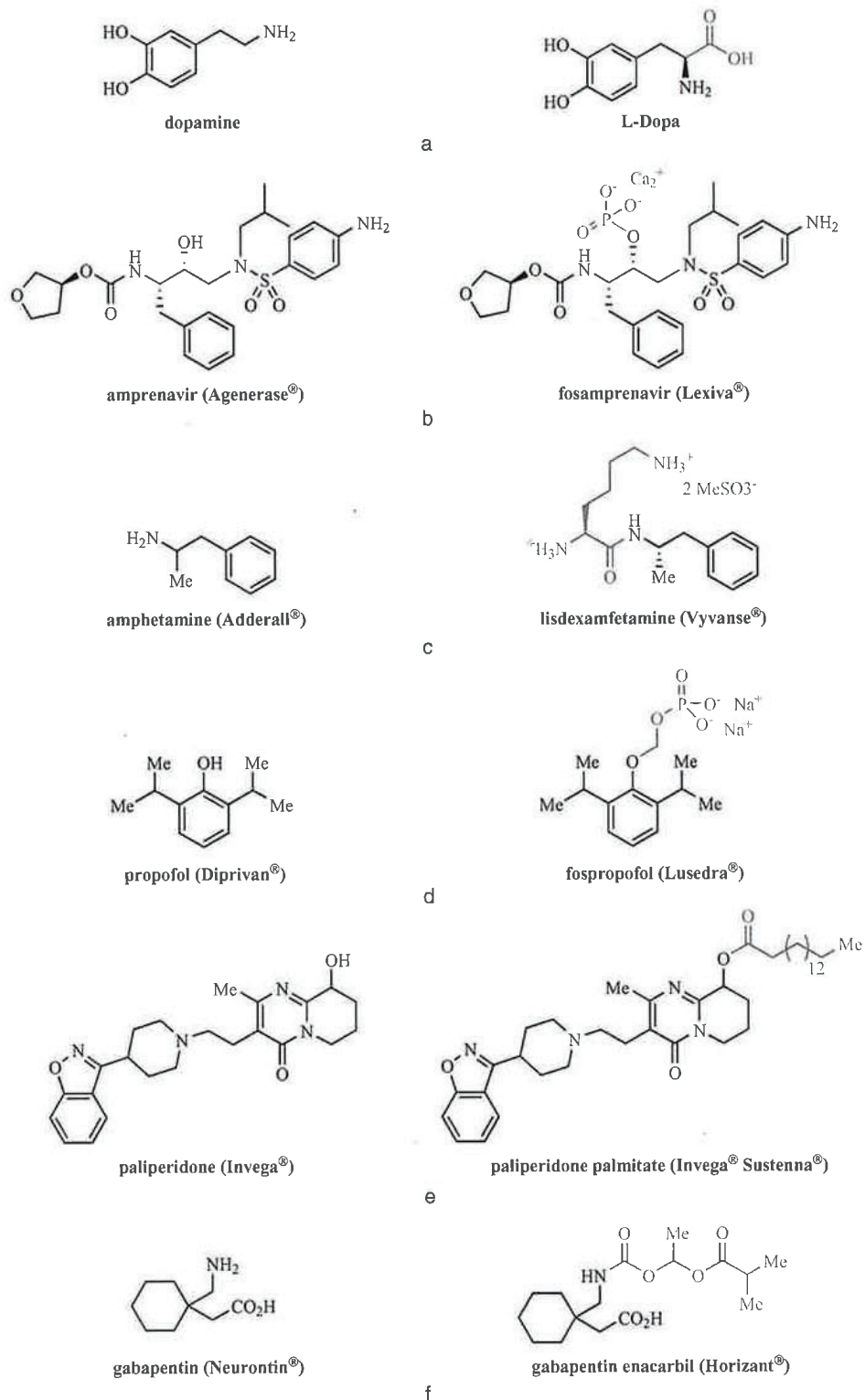


FIGURE 10.1. Prodrug case studies: (a) dopamine/L-Dopa, (b) amprenavir/fosamprenavir, (c) amphetamine/lisdexamfetamine, (d) propofol/fospropofol, (e) paliperidone/paliperidone palmitate, (f) gabapentin/gabapentin enacarbil.

This agent, approved in 1970 for the treatment of Parkinson's disease, efficiently crosses the blood-brain barrier, where it is converted to dopamine via DOPA decarboxylase, thereby increasing dopamine concentrations in the brain (Figure 10.1a). Dopamine, unlike L-Dopa, does not effectively cross the blood-brain barrier and cannot be used orally to significantly elevate dopamine levels in the brain. This natural prodrug success story has led to the development of numerous innovative examples of prodrugs with remarkable physical and biological properties. The remainder of this section will focus on recent examples of FDA-approved prodrugs exhibiting a range of advantages over their previously approved counterparts (Figure 10.1).

10.2.2. Fosamprenavir (Lexiva®)

Since the mid 1990s, the FDA has approved 10 HIV-1 protease inhibitors (PIs) for the treatment of HIV infection [7]. From the launch of saquinavir in 1997 to the acceptance of darunavir in 2006, significant evolutionary progress has been achieved in the discovery of new PIs with improved physical, pharmacokinetic (PK), and pharmacodynamic (PD) properties [8]. At the time of its approval, amprenavir (Agenerase®, developed by Vertex Pharmaceuticals and licensed to GlaxoSmithKline [GSK]) offered many advantages over previously approved PIs including increased antiviral activity, as well as improved, albeit low, aqueous solubility (0.04 mg/mL) [3, 9]. Unfortunately, in order to attain the gastrointestinal tract solubility necessary for adequate absorption, a formulation with an exceedingly high excipient-to-drug ratio was required [10]. As such, the FDA approved dosing schedule for Agenerase® imparted a significantly high pill burden: either 8×150 mg capsules dosed twice daily or 4×150 mg capsules dosed twice daily in combination with the boosting agent ritonavir [11]. The drawbacks of such a dosing regimen go beyond mere inconvenience and directly impact patient compliance and tolerability, potentially leading to a more rapid emergence of drug resistance [12]. In an effort to improve the dosage form of active amprenavir, researchers at Vertex Pharmaceuticals, in collaboration with GSK, investigated several potential prodrug candidates ultimately leading to the approval of fosamprenavir (Lexiva®) in 2003 (Figure 10.1b).

As is the case with many prodrug strategies, fosamprenavir was developed mainly to improve the aqueous solubility of the parent drug [3]. With that ultimate goal in mind, multiple potential amprenavir prodrugs were prepared and their conversion to amprenavir in Wistar rats was evaluated [13]. Five compounds were identified as potential candidates and, following further PK studies in dogs, the phosphate ester prodrug fosamprenavir was selected. Due to their highly ionic character and relative ease of hydrolysis, phosphate ester derivatives are commonly investigated as a means of increasing the aqueous solubility of therapeutic agents [3]. As is the case with the majority of phosphate ester prodrugs, endogenous alkaline phosphatases located within the

intestinal epithelium efficiently hydrolyze fosamprenavir, releasing the active drug and leaving minimal intact prodrug in the systemic circulation. In fact, within 15 minutes of oral administration, detectable plasma levels of amprenavir are attained with peak concentrations (C_{\max}) achieved at 1.5–2.5 hours [14]. In a Phase II trial of antiretroviral therapy in naïve HIV-1 patients, equimolar doses of fosamprenavir and amprenavir were shown to exhibit equivalent plasma amprenavir exposure. Interestingly, however, the cohort dosed with fosamprenavir presented significantly reduced C_{\max} levels, as well as elevated trough levels. Furthermore, a dramatically improved aqueous solubility of 54 mg/mL at pH 3.3 [10] provided a marked enhancement in GI tract solubility [14]. These factors ultimately led to the development of a solid tablet formulation of fosamprenavir containing 700 mg of active ingredient resulting in a much more convenient dosing regimen: either two tablets dosed twice daily or two tablets dosed once daily in combination with the boosting agent ritonavir [15].

Shortly after its approval in 2003, Lexiva® began to replace Agenerase® as GSK shifted resources toward this superior therapeutic agent [16]. The benefits to both patient and drug proprietor are clearly evident in the repositioning strategy described in this example (Table 10.1). The launch of Lexiva® provided patients with a much more convenient dosing form, improving both adherence and tolerability likely leading to a slower onset of drug resistance. Likewise, by discontinuing Agenerase®, GSK was able to extend their patent life by 3 years with Lexiva® [17]. In 2008, Lexiva® reached peak global sales of \$296 million declining in recent years due to the approval of new HIV-1 PIs such as darunavir (Prezista®), which offer enhanced activity and improved resistance profiles [18].

TABLE 10.1. Comparison of Agenerase® and Its Prodrug Successor Lexiva®

	Agenerase®	Lexiva®
Prodrug functionality	—	Phosphate ester
API	Amprenavir	Fosamprenavir
FDA approval ^a	1999	2003
Originator	Vertex	Vertex/GSK
Expected patent expiration ^b	Discontinued	2017
Peak global sales (year) ^c	\$79 million (2000)	\$296 million (2008)
Therapeutic class	HIV-1 protease inhibitors	
Key advantages		
• Aqueous solubility	0.04 mg/mL	54 mg/mL
• Approved unboosted dosing	8 capsules bid	2 tablets bid
• Approved boosted dosing ^d	4 capsules bid	2 tablets qd

^a Drugs@FDA.

^b Based on FDA Orange Book data for longest possible coverage.

^c Sales figures obtained from Thomson Reuters IntegritySM database.

^d Ritonavir (Norvir®, 100 mg) dosed concomitantly.

10.2.3. Lisdexamfetamine (Vyvanse®)

According to the National Resource Center on ADHD, "Attention-deficit/hyperactivity disorder (ADHD) is a condition affecting children and adults that is characterized by problems with attention, impulsivity, and overactivity." It affects between 5% and 8% of school age children, and between 2% and 4% of adults. ADHD is the current diagnostic label for a condition that has been recognized and studied for over a century [19]. Although there is no known cure for ADHD, symptoms of the disorder can, in many cases, be effectively controlled with a combination of medication, psychotherapy, and education. The two most widely recognized medications for the treatment of ADHD include the psychostimulants methylphenidate (MPH) (Ritalin®) and amphetamine (Adderall®, Figure 10.1c). Administration of these agents results in increased levels of dopamine and norepinephrine, addressing the hypothesis that the root cause of this disorder involves dysregulation of these two neurotransmitters [20]. A significant drawback of both Ritalin® and Adderall® is their potential for misuse and abuse. Reports of their misuse have been attributed to the grinding of various formulations and either oral or intranasal administration resulting in a sensation of euphoria [21]. Furthermore, both, MPH and amphetamine are classified as schedule II controlled substances by the U.S. Drug Enforcement Administration (DEA). Therefore, midday doses must be administered by a school nurse, potentially causing additional social stigma for these already atypical children [21].

To address the issues associated with amphetamine treatment, New River Pharmaceuticals set out to develop an inactive prodrug analog that would result in prolonged exposure to dextroamphetamine (*d*-amphetamine). A series of amino acid-linked analogs of *d*-amphetamine were prepared and evaluated, ultimately leading to the identification of the L-lysine conjugate lisdexamfetamine (Vyvanse®) shown in Figure 10.1c [22]. Results from non-clinical *in vitro* and *in vivo* studies indicate that lisdexamfetamine is readily absorbed through the small intestine and subsequently converted to active *d*-amphetamine in the blood [23]. Interestingly, while both rat and human whole blood samples were shown to effectively convert lisdexamfetamine to *d*-amphetamine, white blood cells and plasma were deemed ineffective. Enzymes located on red blood cells are therefore most likely responsible for the hydrolysis of lisdexamfetamine ultimately leading to an observed delayed exposure of *d*-amphetamine [23]. In fact, in a study of 12 healthy adult stimulant abusers, prodrug administration resulted in a significantly lower exposure to *d*-amphetamine over the first 4 hours (AUC_{0-4h}) compared with dosing *d*-amphetamine sulfate directly (165.3–231.1 ng/mL vs. 245.5–316.8 ng/mL) [21]. Similarly, lisdexamfetamine administration exhibited a dramatically increased T_{max} over *d*-amphetamine sulfate (3.78–4.25 hours vs. 1.88–2.74 hours) [21]. Furthermore, in an effort to assess the relative abuse potential for lisdexamfetamine versus *d*-amphetamine, intranasal administration of the two agents was compared in rats. Results from this study indicate that a 95% reduction

in AUC_{last} , a 96% reduction in C_{max} , and a 12-fold increase in T_{max} are attained upon intranasal dosing of the prodrug [24]. From this study it was determined that misuse of lisdexamfetamine via intranasal administration would result in minimal exposure to *d*-amphetamine, providing a dramatically reduced abuse potential.

In 2005, New River Pharmaceuticals entered into a collaborative agreement with Shire for the commercialization of Vyvanse®, which was subsequently launched in 2007 for the treatment of ADHD in adults and children ages 6–17 [25]. Shire was originally expected to attain patent protection for amphetamine through 2018 via the development of an extended-release formulation (Adderall XR®). This approach proved less successful than anticipated as generic forms ultimately became available in the United States as early as 2009 [26]. The release of the prodrug derivative of amphetamine (Vyvanse®), however, provided Shire with an improved amphetamine alternative with a patent life extending out to 2023 [27]. Although still classified as a schedule II controlled substance by the DEA, this prolonged release analog of amphetamine not only showed dramatic evidence for reduced abuse potential, but it also negated the requirement for midday dosing [21]. For these reasons, global sales of Vyvanse® have continued to grow since its release, amassing over \$500 million in sales in 2009 alone [28] (Table 10.2).

10.2.4. Fospropofol (Lusedra®)

Many conventional surgical procedures require the use of general anesthesia as a means of attaining unconsciousness, as well as relaxation of both the skeletal muscles and reflex actions of the body. While highly effective and typically safe, the use of general anesthesia is avoided if possible due to the

TABLE 10.2. Comparison of Adderall® and Its Prodrug Successor Vyvanse®

	Adderall®	Vyvanse®
Prodrug functionality	–	Lysine amide
API	Dexamphetamine (mixture)	Lisdexamfetamine
FDA approval ^a	1996	2007
Originator	Shire	Shire
Expected patent expiration ^b	Generic	2023
Peak global sales (year) ^c	\$1.1 billion (2008)	>\$500 million (2009)
Therapeutic class	Dopamine and norepinephrine regulators	
Key advantages		
• Abuse potential ^d	1032 ng·mL/h	56 ng·mL/h
• Approved dosing	qd-bid	qd

^a Drugs@FDA.

^b Based on FDA Orange Book data for longest possible coverage.

^c Sales figures obtained from Thomson Reuters IntegritySM database.

^d As inferred by reduced intranasal exposure in rats [24].

potential for significant adverse events and prolonged recovery time. Fortunately, with the advent of new and improved medical techniques and devices, more and more conventional surgical procedures are being replaced with minimally invasive methods, escalating the use of mild procedural sedation methods [29]. The administration of therapeutic agents for the attainment of procedural sedation is common practice among a variety of diagnostic routines as well as outpatient surgical procedures. These sedative drugs typically result in less overall discomfort, faster recovery time, and fewer side effects as compared with those used for general anesthesia [29]. In order to be considered an ideal agent for procedural sedation (moderate sedation), a drug must meet certain accepted criteria including: (1) a predictable PK/PD profile; (2) the ability to attain amnesia, analgesia, and anxiolysis; (3) rapid onset of action and ultimately a prompt recovery of both physical and cognitive function [30]. Although classical agents for sedation used in endoscopic procedures include both benzodiazepines and opioids, these drugs are not ideal agents due to their delayed onset, unpredictable PK/PD due to interpatient metabolic variability, as well as hangover effects [30a].

In 1986, an injectable emulsified formulation of the sedative-hypnotic agent propofol (Diprivan®, Figure 10.1d) was first launched by Imperial Chemical Industries (now Astra Zeneca) in the United Kingdom [29]. This agent offered several advantages over benzodiazepine and opioid-induced sedation including rapid onset of action (<1 minute), predictable PK/PD profile, and an improved dose titration as well as a fast sedation recovery period. The mechanism of action of this drug is believed to be attributed to a wide range of pharmacological effects: propofol exhibits allosteric modulation of γ -aminobutyric acid (GABA) receptors in the brain [31], is involved in the endocannabinoid system [32], and serves as a sodium channel blocking agent [33]. In practice, moderate levels of sedation can be achieved with propofol either through a single bolus dose or via controlled infusion.

A significant drawback of propofol, however, relates to the sensitive dose-response relationship of this agent [34]. As such, small increases in the dose of propofol can result in dramatic changes in pharmacological effect, ultimately resulting in a higher potential for misjudged levels of sedation. With deeper levels of sedation come heightened cardiopulmonary risks and the possible need for distinctive methods of sedation recovery [29]. For these reasons, certain states have placed limitations on the personnel allowed to administer propofol [35]. Furthermore, approximately 30% of patients receiving a bolus administration of propofol report significant injection-site pain, likely due to the acidic properties of this compound [36]. The original lipid emulsion formulation of propofol did not include any preservative ingredients, leading to clusters of reported deaths associated with microbial contamination [37]. By pulling their initial formulation and relaunching a new formulation including the preservative agent ethylenediaminetetraacetic acid (EDTA), AstraZeneca maintained their propofol market while causing the FDA to require all future formulations of propofol to include preservative agents. On

one hand, this benefited AstraZeneca by hindering the production of generic versions of the original formulation. On the other hand, AstraZeneca was fairly specific in their claims for the use of EDTA as the preservative agent, opening the door for direct generic competition from formulations including other preservatives such as benzyl alcohol or sodium metabisulfite [37].

These disadvantages of propofol administration led researchers at ProQuest Pharmaceutical to investigate the development of prodrug analogs with the aim of improving solubility, prolonging single-dosed sedation, and alleviating injection-site pain. The methylene-bridged phosphate ester prodrug fospropofol disodium (Lusedra®) was ultimately identified and subsequently launched by Eisai in 2009 (Figure 10.1d) [29]. Upon intravenous administration, fospropofol is immediately exposed to the alkaline phosphatases responsible for the generation of the active metabolite [29]. This conversion, however, is not as rapid as one would expect from the metabolism rates of other phosphate ester prodrugs. In fact, the prodrug analog of propofol exhibits a slower onset of action ($T_{\max} = 3\text{--}7.2$ minutes for the prodrug vs. immediate T_{\max} for propofol), a reduction in maximum concentration (C_{\max}), and a slower elimination of active drug. This ultimately contributes to a prolonged sedation profile compared with that of the parent agent [38]. Further benefits of fospropofol over its parent counterpart include reduction in injection-site pain likely due to capping of the phenolic hydroxyl group, as well as resistance of the sterile aqueous formulation to microbial contamination [29].

One issue this prodrug strategy was unable to address, however, was the sensitive dose–response relationship attributed to potential oversedation. In fact, the interpatient variability regarding the bioavailability and conversion of this prodrug to active metabolite instills an elevated level of caution associated with its administration [29]. This disadvantage aside, fospropofol (Lusedra®) provides significant improvements over the parent agent including an enhanced PK/PD profile, prolonged duration of sedation, and the ability for sterile aqueous formulation (Table 10.3). These attributes have led to the widespread use of Lusedra® for monitored anesthesia care sedation in an array of diagnostic and outpatient surgical procedures [29]. In recent years, the halting of production of Diprivan® by AstraZeneca combined with recalls of generic propofol due to contamination has led to shortages of this widely used agent [39]. Through the development of the prodrug fospropofol, Eisai was able to gain entry into the propofol market with an exclusive agent expected to remain under patent protection until 2018 [40].

10.2.5. Paliperidone Palmitate (Invega® Sustenna®)

In 2006, the FDA approved the use of paliperidone (Invega®, Figure 10.1e) for both short-term and long-term maintenance treatment of schizophrenia [41]. As a member of the class of drugs known as atypical antipsychotics, paliperidone is believed to achieve its therapeutic effects via antagonism of dopamine (D₂) receptors, serotonin (5-HT_{2A}) receptors, α_1 , and α_2 adrenergic

TABLE 10.3. Comparison of Diprivan® and Its Prodrug Successor Lusedra®

	Diprivan®	Lusedra®
Prodrug functionality	–	Phosphate ester
API	Propofol	Fospropofol
FDA approval ^a	1989	2008
Originator	AstraZeneca	ProQuest
Expected patent expiration ^b	Generic	2018
Peak global sales (year) ^c	\$507 million (2000)	N/A
Therapeutic class	Allosteric modulators of GABA _A receptors	
Advantages		
• Injection-site pain	Reported	Not reported
• Formulation	Lipid emulsion	Aqueous solution

^a Drugs@FDA.^b Based on FDA Orange Book data for longest possible coverage.^c Sales figures obtained from Thomson Reuters IntegritySM database.

receptors as well as histamine receptors [41]. Although this extended-release oral formulation of paliperidone is dosed only once a day ($t_{1/2} = \sim 24$ hours) [42], a large degree of patient noncompliance is still reported. In fact, after two years of treatment only approximately 25% of patients can be classified as fully compliant due to several factors, including complex drug regimens, cognitive dysfunctions, and adverse effects [43]. To address this issue of noncompliance, Johnson and Johnson launched a palmitate ester prodrug of paliperidone in the United States in 2009 (Figure 10.1e).

Due to the poor water solubility associated with the prodrug, paliperidone palmitate (Invega® Sustenna®) was ultimately formulated as an aqueous suspension using proprietary NanoCrystal® technology developed by Elan Pharma International, Ltd [41]. Upon intramuscular (i.m.) injection of the suspension, the prodrug slowly dissolves and is subsequently hydrolyzed to the active metabolite ultimately entering the systemic circulation. Systemic exposure can be measured after 1 day and continues for up to 126 days [41]. The demonstrated 30-day half-life ($t_{1/2}$) for plasma paliperidone upon 50 mg eq. dosing of the prodrug supported the use of this agent as a long-term therapy option for patients suffering from schizophrenia. Furthermore, results from clinical studies comparing monthly administration of paliperidone palmitate with biweekly dosing of risperidone long acting injection (RLAI) demonstrated noninferiority of paliperidone palmitate [44]. As such, the current recommended prescribing procedure for Invega® Sustenna® involves an initial dose of 150 mg eq. followed by a second 100 mg eq. dose one week later. Maintenance therapy can then be achieved with monthly injections of 75 mg equivalents, modifying the dose from 25 to 150 mg eq. as needed [45]. The ability to achieve similar therapeutic benefits with monthly injections of the prodrug as opposed to daily oral administration of paliperidone will

TABLE 10.4. Comparison of Invega® and Its Prodrug Successor Invega® Sustenna®

	Invega®	Invega® Sustenna®
Prodrug functionality	–	Palmitate ester
API	Paliperidone	Paliperidone palmitate
FDA approval ^a	2006	2009
Originator	Ortho McNeil (Janssen/Johnson & Johnson)	Janssen(Johnson & Johnson)
Expected patent expiration ^b	2014	2017
Peak global sales (year) ^c	\$424M (2010)	N/A
Therapeutic class	Multiple receptor antagonists (D2, 5HT _{2A} , α1 + α2 adrenergic, and histamine)	
Key advantages		
• t _{1/2} (paliperidone)	~24 hours	~30 days
• Approved dosing	QD Tablet	Monthly injection

^a Drugs@FDA.^b Based on FDA Orange Book data for longest possible coverage.^c Sales figures obtained from Thomson Reuters IntegritySM database.

undoubtedly lead to improvements in patient compliance as well as overall market share for Johnson and Johnson (Table 10.4).

10.2.6. Gabapentin Enacarbil (Horizant®)

Gabapentin (Figure 10.1f), approved by the FDA in 1993 under the brand name Neurontin®, was originally developed for the treatment of epilepsy and has since been applied to a number of alternative indications, including neuropathic pain and hot flashes [46]. Structurally, gabapentin is an analog of the neurotransmitter GABA. However, the efficacy associated with gabapentin is believed to result from a different mechanism of action: arresting the formation of new synapses as well as imparting calcium trafficking effects via binding to voltage-dependent calcium channel subunits α2δ1 and α2δ2 [47]. A significant drawback of gabapentin relates to its PK profile. The zwitterionic nature of gabapentin at physiologic pH limits its diffusion into cellular membranes. As such, gabapentin exhibits a non-dose-proportional relationship due to saturation in the human intestine resulting in high interpatient variability, dose-limited PK, as well as sub-therapeutic exposures in some patients [48]. Furthermore, in order to maintain therapeutic levels, the recommended administration of gabapentin is 3–4 times daily due to its relatively short half-life (t_{1/2} = 5–7 hours) [48]. Such dosing regimens are commonly associated with higher rates of noncompliance. To address the issues of non-dose-proportionality, as well as dosing inconvenience, researchers at XenoPort, Inc. developed a prodrug analog of gabapentin designed specifically to take advantage of nutrient transporters located within the human intestine [48].

On April 6, 2011, XenoPort received approval for the use of gabapentin enacarbil (Horizant®) for the treatment of moderate to severe restless legs syndrome (RLS) (Figure 10.1f), a neurological disorder classified as an urge to move the legs in association with leg discomfort and unpleasant sensations [46]. Symptoms typically worsen during periods of rest and are partially or fully relieved by movement. Horizant® represents a nondopaminergic approved treatment option for these patients with potentially reduced dopamine-related adverse events. This monoanionic (at physiological pH) prodrug analog of gabapentin was specifically designed to be absorbed in the GI tract by serving as a substrate for the high capacity nutrient transporters MCT-1 (monocarboxylate transporter 1) and SMVT (sodium-dependent multivitamin transporter) [48]. Once absorbed, the prodrug is readily converted to gabapentin via nonspecific esterases, providing therapeutic exposure to the active metabolite. Due to these characteristics of gabapentin enacarbil, no evidence for intestinal saturation was observed providing a dose-proportional relationship lacking with the parent agent [46]. Furthermore, the improved bioavailability of the prodrug has permitted the formulation of gabapentin enacarbil as an extended release 600 mg tablet (Horizant®) exhibiting a significant increase in time to maximum exposure (T_{max} = 8.4 hours vs. 2.7 hours for gabapentin) [49]. As such, the FDA-approved dosing of Horizant® for the treatment of RLS is one tablet daily at 5 p.m. [50].

The repositioning strategy outlined in this case study provided XenoPort with a therapeutic agent approved by the FDA in an indication unique to the prodrug form of gabapentin (Table 10.5). This granted access to a new market with a significantly reduced risk of competition from generic gabapentin. With a patent life extending out to 2022, gabapentin enacarbil can be expected to gain approval in a number of indications associated with current gabapentin therapy.

TABLE 10.5. Comparison of Neurontin® and Its Prodrug Successor Horizant®

	Neurontin®	Horizant®
Prodrug functionality	–	Carbamate
API	Gabapentin	Gabapentin enacarbil
FDA approval ^a	1993	2011
Originator	Pfizer	Xenoport
Expected patent expiration ^b	Generic	2022
Peak global sales (year) ^c	\$2.7 billion (2004)	N/A
Therapeutic class	Arrestors of new synapse formation and modulators of calcium trafficking	
Key advantages		
• T_{max} (gabapentin)	2.7 hours	8.4 hours
• Dose response	Nonproportional	Proportional

^a Drugs@FDA.

^b Based on FDA Orange Book data for longest possible coverage.

^c Sales figures obtained from Thomson Reuters IntegritySM database.

10.2.7. Conclusions

As depicted in the above examples, the prodrug strategy to drug repositioning offers a unique approach to drug discovery with its own set of advantages and challenges. Often viewed as NMEs by the FDA, prodrug analogs have been developed by many companies as an effective way of resurrecting life into a parent agent with a looming patent expiration. Alternatively, this approach can be employed by rival pharmaceutical companies in an effort to improve upon the parent agent and directly compete or overtake market share. In some cases, prodrug analogs may exhibit significantly dissimilar physical properties, resulting in improvements in aqueous solubility, formulation, bio-availability, PK profiles, and even pill burden. Whether it be the discovery of a monthly injection treatment option to overcome patient noncompliance or the development of an agent engineered to take advantage of specific absorption mechanisms, prodrugs can provide unique opportunities to address a range of issues, resulting in substantial benefits to both the patient and the drug developer.

10.3. CHIRAL SWITCH APPROACH

10.3.1. Introduction

Interrogating biological space to elicit a therapeutic response is the central goal of drug discovery. Living systems are comprised of chiral environments developed from the systematic assembly of naturally containing chiral molecules. Amino acids, sugars, nucleosides, and nucleotides are all examples of these biomolecules utilized for processes that are stereospecific, preferring one stereoisomer over another. Early drug discovery efforts utilized either achiral small molecules or racemic mixtures of chiral molecules to produce a therapeutic response. Although successful as first-generation therapies, further understanding of the complexities of biological processes required more sophisticated approaches. Advances in chemical synthesis has allowed for a more thorough analysis of the influence of stereochemistry on biological processes. Single enantiomer small molecule drugs have since been shown to be a more powerful approach for tackling a variety of indications and needs.

Single enantiomer drugs may have a number of potential advantages over their racemic counterparts [51]. Lower doses of the single isomer may provide the same efficacy as the racemic mixture [52]. This requires that one enantiomer is the active eutomer and the other is the inactive or less active distomer. Alternatively each enantiomer may have activity but for different pharmacologies. The use of single enantiomer drugs in the latter scenario may also lead to a reduction in off-target effects. The metabolism and PK profile of each enantiomer may also differ. Thus dosing the desired eutomer may reduce the formation of reactive metabolites that may be toxic or limit efficacy of the drug. Utilizing only the eutomer may allow for an increase in tolerability over

larger doses and thus improve the therapeutic impact. Ultimately all of these advantages associated with single enantiomer drug development may reduce the amount of side effects and adverse events while improving efficacy and safety as compared to the racemate.

Regulatory agencies have also recognized the impact of stereochemistry in the safety and efficacy of new therapeutics [53]. For example, the current approval process for racemic mixtures involves evaluating each enantiomer separately for safety and efficacy along with the combination [54]. This requires the preparation of each isomer in quantities sufficient for animal toxicology studies. The advances in enantioselective chemical synthesis have rendered it plausible for the manufacturing cost of a single enantiomer drug to compete with that of preparing a racemic mixture.

Since 1990, the annual FDA approval of single enantiomers has surpassed that of racemates and achiral new molecular entities (NMEs). Further indication of the pharmaceutical industry's paradigm shift is the application of the chiral switch strategy on the existing pharmacopeia of racemic drug substances. The chiral switch approach involves developing single enantiomer components of marketed racemic drugs [55]. The FDA does not consider chiral switch compounds as NMEs (CHE1), which are defined as containing active ingredients never approved in the United States. Instead chiral switch drugs are categorized as derivatives of existing drugs (CHE2) or new formulations (CHE3) and benefit from 3 rather than 5 years of market exclusivity [55]. Unfortunately there are no set guidelines that would predict which category (CHE2 or CHE3) a new agent would be placed in and thus each is evaluated independently.

The patentability of the chiral switch strategy continues to be debated and evaluated by the USPTO and the European Patent Office (EPO) on a case-by-case basis. Many chiral switch filings are made under the selection invention designation. This type of invention is defined as one that selects a group of new members from a previously known class on the basis of superior properties [55]. Alternatively separate filings on the superior properties of each enantiomer are also being pursued. Although this area of patent law continues to evolve, both of these types of filings have been granted in the United States and ultimately have led to the successful launch of chiral switch drugs.

Several pharmaceutical companies have even used the chiral switch approach to direct their corporate strategy. They have benefited from the favorable regulatory and intellectual property environments surrounding this strategy as well as the demonstrable advantage of the single enantiomer over the racemate. Sepracor Pharmaceuticals (now Sunovion) has been a leader in advancing the chiral switch strategies. Their efforts have resulted in the successful approval and launch of desloratadine (Clarinx®), fexofenadine (Allegra-R®), levalbuterol (Xopenx®), and eszopiclone (Lunesta®). The following case studies (Figure 10.2) are provided as other successful examples of this approach to drug discovery.

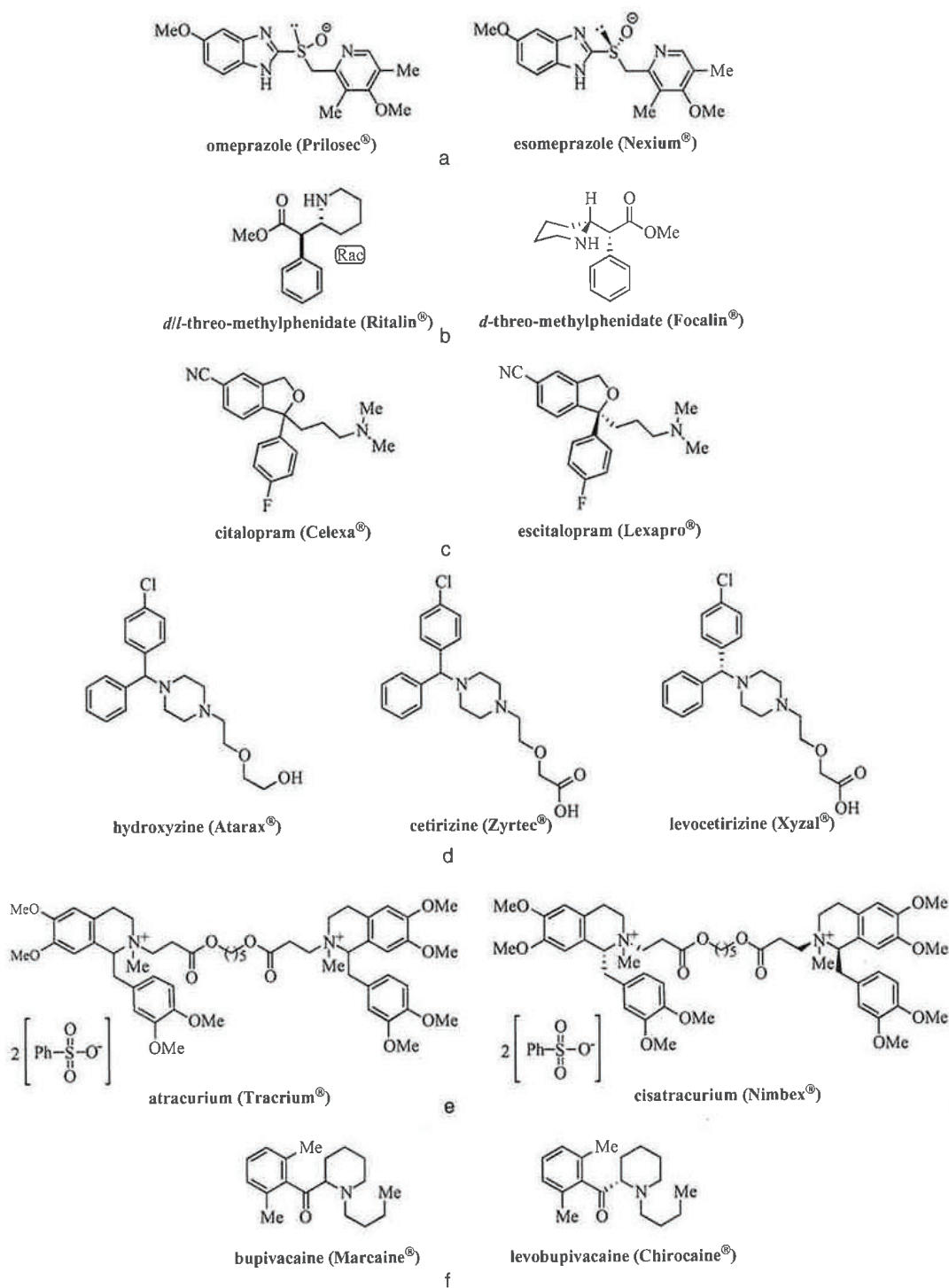


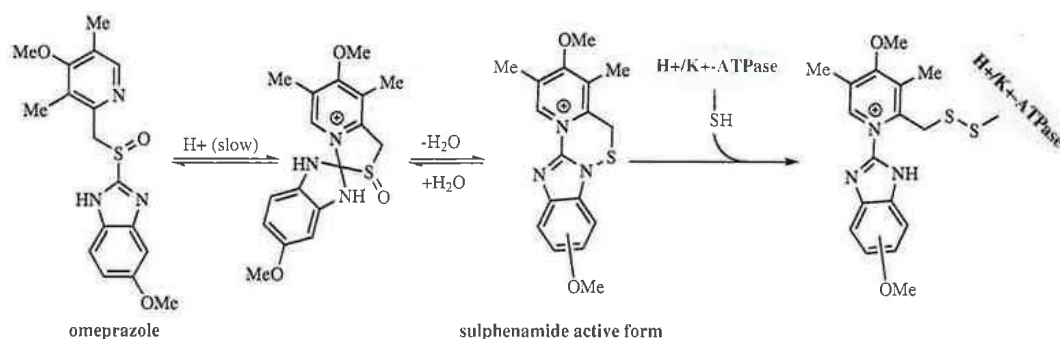
FIGURE 10.2. Chiral switch case studies: (a) benzimidazole proton pump inhibitors omeprazole and esomeprazole, (b) DAT reuptake inhibitors *d,l*-threo-methylphenidate and *d*-threo-methylphenidate, (c) selective serotonin reuptake inhibitors (SSRI) citalopram and escitalopram, (d) UCB's franchise of histamine H1 receptor antagonists, (e) rationally designed tetrahydroisoquinolinium NMBs, (f) topical analgesics.

10.3.2. Omeprazole (Prilosec®) to Esomeprazole (Nexium®)

Gastroesophageal reflux disease (GERD) affects 20–40% of the adult population globally. It is characterized by the frequent entry and subsequent clearing of gastric contents intermittently to the esophagus from the stomach [56]. In the body, a carefully calibrated system involving the lower esophageal sphincter (LES) and diaphragm allows for the forward passage of swallowed material and release of gas or air from the stomach (belch), while preventing undesired reflux of stomach acids into the esophagus. Disruption of this balance may result in esophagitis, swelling, inflammation, or irritation of the esophagus. Chronic exposure to stomach acids can lead to breaks or erosion in the lining of the esophagus. Approximately 40–60% of GERD patients present with this type of erosive esophagitis (EE), which may be diagnosed endoscopically [56].

The current first-line treatment for GERD symptoms is daily use of proton pump inhibitors (PPI). These agents irreversibly block the hydrogen/potassium adenosine triphosphate enzyme (H^+/K^+ ATPase) that is responsible for releasing hydrogen ions into the stomach. One of the most successful PPIs, omeprazole (Figure 10.2a), was launched by AstraZeneca in 1988 under the trade name Prilosec® and reached peak global sales (\$6.3 billion) by 2000 [57]. By targeting H^+/K^+ ATPase, omeprazole is able to intercept the final step in the generation of stomach acid and thus is an effective therapy regardless of how the gastric acid secretion is stimulated. The compound was sold as the racemate that is known to undergo a series of chemical modifications *in vivo* to produce an achiral sulphenamide (Scheme 10.1), the active form. This intermediate reacts with a cysteine residue (Cys 813) present in the H^+/K^+ ATPase machinery, irreversibly inhibiting the enzyme through the formation of a disulfide complex.

Despite its novel mode of action and clinical efficacy in targeting the proton pump machinery, omeprazole suffered from significant interpatient variability



Scheme 10.1. Omeprazole molecular mechanism of action.

[57] requiring larger or repeated doses. Human liver microsome studies (HLM) demonstrated that the CYP3A4 and CYP2C19 isozymes of the cytochrome P450 super family are responsible for omeprazole's metabolism [58]. The CYP2C19 enzyme is not equally distributed in all human populations as evident by its absence in 3% of Caucasian and 15–20% of Asian populations. Ultimately this genetic variation results in striations of therapeutic benefit of omeprazole within the population as mean plasma concentration (AUC) has been directly linked to its therapeutic benefit [59].

Investigations into the metabolism of omeprazole by CYP2C19 in extensive and poor metabolism patients (EM vs. PM) revealed a 7.5-fold increase in mean plasma concentration (AUC) of (*R*)-omeprazole in PM compared with EM [60]. This is in contrast to the AUC of (*S*)-omeprazole (esomeprazole), which had only a threefold increase for PM over EM. Similar disparities were seen in terms of the clearance. The (*R*)-omeprazole demonstrated a 10-fold difference in clearance between PM and EM groups while the (*S*)-omeprazole did not demonstrate any difference in clearance rates [60]. AstraZeneca recognized that capitalizing on this CYP450-derived stereochemical metabolism preference may lead to an improved PPI with respect to bioavailability. Esomeprazole reduced interpatient variability and helped standardize dose.

In an open-label, crossover study, 130 patients received either omeprazole or esomeprazole daily for 5 days [61]. Esomeprazole (40 mg) more effectively maintained intragastric pH > 4 in patients with symptoms of GERD over those taking once daily omeprazole (40 mg). Intragastric pH (24 hours) was monitored on days 1 and 5. In the esomeprazole treatment group, the patient's intragastric pH remained above 4 for 2 hours longer on day 1 than those in the omeprazole group and 1.5 hours longer on day 5. Significantly less inter-individual variation, with respect to the percentage of time with intragastric pH > 4, was observed in the esomeprazole group. These studies led AstraZeneca scientists to suggest that equal doses of racemate versus single isomer drug are not equivalent. The company subsequently set its standard dose for esomeprazole to 40 mg.

When evaluated in four different large multicenter double-blind randomized trials (6708 treatment patients total) esomeprazole (40 or 20 mg) was shown to have greater consistency of healing rates across all grades of baseline disease versus omeprazole (20 mg) [62]. Esomeprazole was also shown to reduce the incidence of GERD relapse as well as the time to recurrence (34 vs. 78 days) versus placebo in patients with healed esophagitis. The positive efficacy and safety clinical data led to the FDA approval of esomeprazole (Nexium®) in 2000 as a new PPI for GERD and EE. Since 2005, Nexium has consistently reported annual global sales over \$4.5 billion [63].

More recently esomeprazole and omeprazole were compared in a multicenter, double-blind, parallel-group trial for the healing of EE in 1148 patients with endoscopically confirmed EE [64]. Patients were given either esomeprazole (40 mg) or omeprazole (20 mg). Primary outcomes were

healing at 8 weeks and secondary outcomes included diary and investigator assessments of heartburn symptoms. Healing rates with the enantiopure drug were significantly higher than those with the racemate at both 4 weeks (61% vs. 48%) and 8 weeks (88% vs. 77%) in patients with moderate to severe EE at baseline.

Adverse events associated with nonsteroidal anti-inflammatory drugs (NSAIDs) and *Helicobacter pylori* infection are the two leading causes of peptic ulceration [65, 66]. Esomeprazole (40 mg, qd or bid) has been shown to be superior to omeprazole (20 mg, bid) when given in conjunction with amoxicillin (1000 mg, bid) and clarithromycin (500 mg, bid) as 7-day triple therapy for the eradication of *H. pylori* infection [67]. Patients positive for *H. pylori* infection with active duodenal ulcers also benefited from this single enantiomer treatment. In this population, an esomeprazole containing 7-day triple therapy followed by 3 weeks of placebo was shown to be as effective as omeprazole containing triple therapy followed by 3 weeks of daily omeprazole treatment [68]. The healing rates and infection eradication rates were comparable among the two treatment groups.

The omeprazole to esomeprazole chiral switch has been one of the most successful in the pharmaceutical industry (Table 10.6). Upon approval of esomeprazole (Nexium®, 40 mg), AstraZeneca priced the single enantiomer dose lower than omeprazole (Prilosec®, 20 mg), thus re-capturing the PPI market from its own product. This type of evergreening has led to consecutive years of multibillion dollar sales for each product for AstraZeneca. Although

TABLE 10.6. Comparison of Prilosec® and Its Chiral Switch Successor Nexium®

	Prilosec®	Nexium®
Stereochemistry	(<i>R/S</i>)	(<i>S</i>)
API	Omeprazole	Esomeprazole
FDA approval ^a	1989	2001
Originator	Astra Zeneca	AstraZeneca
Expected patent expiration ^b	Generic/OTC	2018
Peak global sales (year) ^c	\$6.3 billion (2000)	\$5.5 billion (2008)
Therapeutic class	Proton pump inhibitors (PPIs) for GERD	
Key advantages		
• PK data	Polymorph. metab. (CYP2C19)	> <i>t</i> _{1/2} and AUC than racemate.
• Clinical data	<ul style="list-style-type: none"> • Comparison study demonstrated (<i>S</i>)-enantiomer superior for maintaining gastric pH > 4 longer. • Triple therapy study for <i>H. pylori</i> treatment with (<i>S</i>)-enantiomer shortened treatment time over racemate 	

^a Drugs@FDA.

^b Based on FDA Orange Book data for longest possible coverage.

^c Sales figures obtained from Thomson Reuters IntegritySM database.

Nexium® demonstrated a measurable and significant improvement versus its racemic counterpart, the industry was vilified for taking advantage of the consumer [69].

10.3.3. *d,l*-threo-Methylphenidate HCl (Ritalin®) to *d*-threo-Methylphenidate HCl (Focalin®)

ADHD is the most commonly diagnosed and studied psychiatric disorder in children, affecting an estimated 3–5% of all children in America [70]. It is a neurobehavioral disorder that disrupts a person's ability to stay on a task and to exercise age-appropriate inhibition. Current research suggests that ADHD symptoms are caused by imbalances in neurotransmitter levels in the brain. As discussed earlier in this chapter, disruptions in dopamine signaling have been shown to be associated with ADHD symptoms [71]. The recommended treatment protocol involves a combination of behavioral modification at home and in the classroom along with oral medications such as methylphenidate (MPH) or dextroamphetamine.

MPH was first synthesized in 1944 [72] and the diastereomerically enriched racemate was evaluated as a stimulant [73] (Figure 10.2b). Two decades later it began to be evaluated for the treatment of ADHD in children. As understanding and acceptance of the disorder grew in the medical community, the prescription rates of MPH rose through the 1990s. Abuse and addiction have also been linked with the illicit use of MPH; therefore, it has been categorized as a Class II substance along with cocaine and amphetamines [74]. Similar to these drugs, MPH's primary target is the dopamine transporter (DAT) [75]. It is thought to increase brain levels of dopamine by blocking reuptake of the neurotransmitter and thus increasing its concentration at the presynaptic neuron. The net increase in dopamine levels is thought to alleviate the symptoms of ADHD although the exact therapeutic mechanism is still under investigation.

Recent advances in chemical synthesis [76] have allowed for the independent evaluation of each enantiomer of *threo*-methylphenidate [77]. Rodent and primate models with radiolabeled MPH have demonstrated that binding of *d-threo*-methylphenidate (*d*-MPH, Focalin®) to DATs was selective, saturable, and reversible, while binding of *l-threo*-methylphenidate (*l*-MPH) was unselective. The influence of each enantiomer on behavior has also been evaluated. Several studies suggest that efficacy resides solely with *d*-MPH. Seminal work by Ding and coworkers, through the use of positron emission tomography (PET) and microdialysis with radiolabeled agents, demonstrated a greater uptake in human and baboon basal ganglia of [¹¹C]-*d-threo*-methylphenidate when compared with [¹¹C]-*l-threo*-methylphenidate [78]. Localization in the basal ganglia is indicative of more selective binding to DATs. One hypothesis proposed to explain the difference in efficacy between enantiomers was that the absorption of *l*-MPH is poor due to presystemic metabolism. Ding and coworkers have demonstrated that radiolabeled *l*-MPH

TABLE 10.7. Comparison of Ritalin® and Its Chiral Switch Successor Focalin®

	Ritalin®	Focalin®
Stereochemistry	(<i>R,R/S,S</i>)	(<i>R,R</i>)
API	<i>d,l</i> -methylphenidate (MPH)	<i>d</i> -methylphenidate
FDA approval ^a	1955	2001
Originator	Ciba	Novartis
Expected patent expiration ^b	Generic	2019
Peak global sales (year) ^c	N/A	\$440 million (2009)
Therapeutic class	Attention deficit hyperactivity disorder (ADHD) agents	
Key advantages		
• Pharmacology	<ul style="list-style-type: none"> • Radiolabel studies in monkey and human brains demonstrate that <i>d</i>-MPH localizes in the areas of the brain associated with dopamine transport while <i>l</i>-MPH disperses randomly throughout the brain. • Metabolism and brain penetration is equal for each enantiomer 	
• Clinical data	<ul style="list-style-type: none"> • Single enantiomer therapy was more effective in improving the overall clinician's rating than racemate in comparison studies with ADHD children. 	

^a Drugs@FDA.^b Based on FDA Orange Book data for longest possible coverage.^c Sales figures obtained from Thomson Reuters IntegritySM database.

or its metabolites are absorbed and enter the brain after oral dosing in rats [79]. Clinical trials in children with ADHD have demonstrated that *d*-MPH and *d,l*-MPH have comparable efficacy, safety, and tolerability [80]. Furthermore, a comparison study between the racemate and *d*-MPH demonstrated that the single enantiomer was superior in clinical ratings of overall improvement [81] (Table 10.7).

10.3.4. Citalopram (Celexa®) to Escitalopram (Lexapro®)

Clinical depression is the leading cause of disability as measured by the World Health Organization's Years Living with Disability metric (YLD) and the fourth leading contributor to the global burden of disease [82]. Depression affects approximately 121 million people globally but fewer than 25% of those affected have access to treatments [82]. Symptoms of depression include chronic depressed mood, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, low energy, and poor concentration. Long-range studies have demonstrated that depression is a chronic disease with significant levels of remission [83].

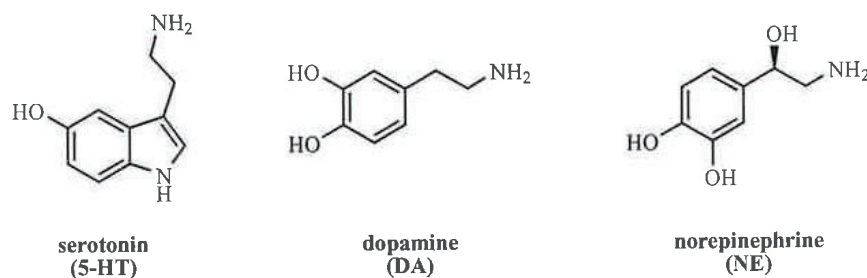


FIGURE 10.3. Endogenous neurotransmitters: serotonin, dopamine, norepinephrine.

The central amine theory of depression suggests that deficiencies in neurotransmitters such as dopamine, serotonin and norepinephrine (Figure 10.3) are responsible for the observed symptoms [84]. A tremendous amount of work has revealed that many biochemical and genetic pathways are involved in connecting neurotransmitter levels with disease pathology [85]. Chronic antidepressant use is thought to up-regulate the cAMP signaling cascade and eventually the expression of the CREB transcription factor [86]. Prolonged execution of these events may ultimately lead to a change in the evolution of neuronal pathways.

Antidepressant therapies have evolved from broad-spectrum agents such as tricyclic antidepressants (TCA) and monoamine oxidase inhibitors (MAOI) to targeted therapies such as selective serotonin reuptake inhibitors (SSRI) and most recently dual action serotonin–norepinephrine reuptake inhibitors (SNRI) [87]. The latter two categories of therapies are considered first-line due to their improved efficacy and safety profiles. In general SSRI and SNRI therapies are accompanied by fewer side effects and are more tolerable. The goal of all of these therapies is to increase the population of neurotransmitters at the synapse. Many of these approaches rely on binding the neurotransmitter's transporter, which leads to a conformational change that prevents the neurotransmitter from passing through the synapse and thus preventing reuptake so prolonging their biological effects.

Citalopram (Figure 10.2c) is a selective and potent SSRI launched by Lundbeck in 1989 under the brand name Cipramil® in Denmark [88]. Following successful launches throughout Europe and Canada, it was introduced by Forrest Labs to the United States in 1998 under the brand name Celexa®. Subsequently, an orally disintegrating tablet developed by Valeant has also been approved in the United States. Along with major depressive disorder (MDD) it has also been approved for anxiety in Europe and is being evaluated in clinical trials (Phase II/III) for bipolar disorder, Huntington's disease, and alcoholism in the United States. Its mode of action is in line with other SSRI therapies displaying nanomolar potency for human serotonin receptors and transporters [88].

Evaluation of each enantiomer of citalopram revealed that escitalopram (Lexapro®, [S]-enantiomer) had improved potency and specificity over the

racemate. *In vitro* binding experiments demonstrated that escitalopram ($IC_{50} = 2.1$ nM) was 100-fold more potent than (*R*)-citalopram ($IC_{50} = 275$ nM) for the inhibition of serotonin reuptake in rat brain synaptosomes [88]. Other studies have also shown that (*R*)-citalopram antagonizes the effects of escitalopram, although the precise mechanism for this has not been elucidated. This antagonism by (*R*)-citalopram may result from differential actions of the two enantiomers at a low-affinity allosteric binding site on the 5-HT reuptake transporter [89, 90]. This *in vitro* and *in vivo* animal data translated to a measureable clinical difference between citalopram and escitalopram [91].

Escitalopram was as effective as other SSRIs in treating MDD patients and more effective in comparison with those treated with SNRIs such as duloxetine and venlafaxine XR [87]. The racemate and single enantiomer have also been evaluated in comparison studies. In a 6-week multicenter prospective randomized double-blind study of 322 patients (mean age, 35 years) escitalopram (10 mg) proved to be superior over citalopram (10 mg or 20 mg) [92]. Clinical metrics of depression (MADRS, CGI-S, CGI-I) were used to demonstrate the statistically significant improvement of the escitalopram (10 mg) arm over the two citalopram arms (10 mg or 20 mg). Severely depressed patients saw the greatest improvement. In 2001, Lundbeck launched escitalopram as Cipralex® in Denmark and eventually in Europe. Forest Labs obtained FDA approval in 2002 to market it as Lexapro® in the United States (Table 10.8).

10.3.5. Cetirizine (Zyrtec®) to Levocetirizine (Xyzal®)

Seasonal hay fever or allergic rhinitis, an allergic inflammation of the nasal airways and symptoms include itching, sneezing, and nasal congestion, affects as many as 30–60 million people in the United States alone [93]. Rhinitis sufferers may also experience swelling of the eyes as well as middle ear effusions. Rhinitis is thought to be triggered by the body's response to the presence of allergens such as pollen or dust that catalyzes a series of pro-inflammatory events culminating in the release of inflammatory mediators such as histamine and tryptase [93]. These in turn stimulate the production of other mediators as well as trigger processes that lead to the observed symptoms of congestion [93].

A general goal of rhinitis therapies is to reduce or prevent the inflammatory events that lead to symptoms. In lieu of removing all potential allergens, antagonist approaches have provided a method of managing symptoms in the presence of suboptimal conditions. These approaches attempt to intercept the actions of the endogenous signaling molecules participating in the inflammatory cascade [94]. Histamine is responsible for increasing vascular permeability, which allows fluid release from capillaries to tissues and ultimately congestion, runny nose and water eyes. First-generation antihistamine drugs were plagued with sedative side effects [94]. This was later revealed to be the

TABLE 10.8. Comparison of Celexa® and Its Chiral Switch Successor Lexapro®

	Celexa®	Lexapro®
Stereochemistry	(<i>R/S</i>)	(<i>S</i>)
API	Citalopram	Escitalopram
FDA approval ^a	1998	2002
Originator	Lundbeck/Forest	Lundbeck/Forest
Expected patent expiration ^b	Generic	2023
Peak global sales (year) ^c	\$1.5 billion (2003)	\$1 billion (2010)/\$2.2 billion (2010)
Therapeutic class	Antidepressants (SSRI)	
Key advantages	<ul style="list-style-type: none"> • Escitalopram is 100-fold more potent than (<i>R</i>)-citalopram. • (<i>R</i>)-citalopram antagonizes the activity of escitalopram. Differential actions of the two enantiomers at a low affinity allosteric binding site on the 5-HT reuptake transporter is thought to be responsible. • Comparison studies demonstrated that escitalopram was more effective in improving all clinical metrics than citalopram in adult MDD patients. • Adverse event incident rate was lower with escitalopram. 	
• Pharmacology		
• Clinical data		

^a Drugs@FDA.^b Based on FDA Orange Book data for longest possible coverage.^c Sales figures obtained from Thomson Reuters IntegritySM database.

result of the penetration of these agents through the blood–brain barrier and subsequent interference with brain chemistry.

Cetirizine (Zyrtec®) (Figure 10.2d) is now an over-the-counter (OTC) remedy for seasonal and persistent allergic rhinitis available in the United States. It was first launched as a prescription medication for this indication by UCB Pharmaceuticals in 1987. Cetirizine is derived from another UCB product, hydroxyzine, one of the original first-generation antihistamines [95]. Hydroxyzine was launched in 1956 by UCB in Europe and marketed in the United States by Pfizer. Whereas hydroxyzine itself results in significant sedative effects due to its central nervous system (CNS) penetration, its major human metabolite, levocetirizine, transits the blood–brain barrier poorly. As such, when cetirizine is dosed directly, the side effects related to sedation are not observed [95].

Further expanding the antihistamine franchise, UCB investigated the activity of each enantiomer of cetirizine separately and determined that (*R*)-cetirizine, levocetirizine, was the eutomer (active enantiomer) [95]. Studies using human H₁ receptors transfected into hamster ovary cells demonstrated

that levocetirizine had a 30-fold higher receptor affinity than dextrocetirizine (the less potent */S*-enantiomer, or “distomer”, of cetirizine) [95]. **Levocetirizine distribution** is confined to the plasma as indicated by a low volume of distribution ($V_d = 0.3\text{--}0.41$ L/kg) [95]. Volume of distribution (V_d) relates drug concentration in blood or plasma to overall drug in the body. Levocetirizine’s low V_d contrasts with other approved antihistamines such as loratadine and ebastine [95]. Low values for this metric suggest that organs and systems not involved in the desired therapeutic effect are not exposed to the drug, which may improve the tolerability of the agent.

The observed preclinical potency, selectivity, and toxicity yielded measurable clinical benefits as evidenced by the comparison studies of levocetirizine, cetirizine, and dextrocetirizine [96]. Both cetirizine and levocetirizine were superior to dextrocetirizine; however, only levocetirizine demonstrated a faster onset and a greater postdose effect [97]. A large (28K patients) randomized double-blind crossover comparison study evaluated the impact of cetirizine, levocetirizine, and dextrocetirizine on the histamine-induced skin allergy in healthy adults [97]. Inhibition of histamine-induced wheal and flare, inflammation within the skin, was used as a primary read-out. Levocetirizine (2.5 mg) had comparable antihistamine activity as cetirizine (5.0 mg) and was superior to dextrocetirizine, which had no activity. Plasma concentrations of levocetirizine (AUC) were greater than cetirizine (Table 10.9). Encouraged by these results, UCB filed for and was granted FDA approval in 2007 for levocetirizine, marketed as Xyzal®.

TABLE 10.9. Comparison of Zyrtec® and Its Chiral Switch Successor Xyzal®

	Zyrtec®	Xyzal®
Stereochemistry	(<i>R/S</i>)	(<i>R</i>)
API	Cetirizine	Levocetirizine
FDA approval ^a	1986	2007
Originator	UCB	UCB
Expected patent expiration ^b	Generic/OTC	2013
Peak global sales (year) ^c	\$117 million (2009)	N/A
Therapeutic class	Antihistamines	
Key advantages		
• Pharmacology	<ul style="list-style-type: none"> Levocetirizine is a competitive agonist of histamine H₁ receptor. Binding studies have demonstrated a twofold greater affinity of levocetirizine compared to cetirizine. 	
• Clinical data	<ul style="list-style-type: none"> Levocetirizine has a faster onset and a more sustained efficacy as evident by clinical studies. 	

^a Drugs@FDA.

^b Based on FDA Orange Book data for longest possible coverage.

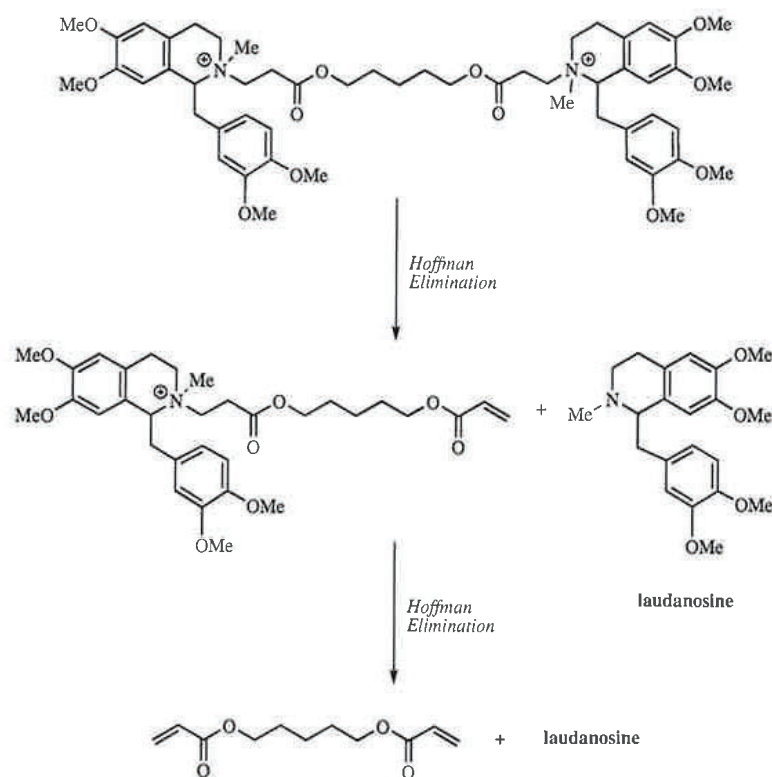
^c Sales figures obtained from Thomson Reuters IntegritySM database.

10.3.6. Atracurium (Tracrium®) to Cisatracurium (Nimbex®)

The introduction of neuromuscular blocking agents (NMB) represented a significant advance in **anesthetic sciences** and has had an immediate impact on the success of **surgical practices**. NMBs relax skeletal muscle, allowing for intubation and access to body cavities [98]. Recently these agents have also found applications in outpatient and **pediatric applications**. NMBs are divided by their mode of action: depolarizing or **nondepolarizing**. Nondepolarizing agents are competitive antagonists of nicotinic acetylcholine receptors (**nAChR**) at the **neuromuscular junction**. Inhibition of these receptors **prevents polarization of the cell membrane**, resulting in relaxation of muscle. **Examples of this class include mivacurium, pancuronium, and cisatracurium**. The majority of the clinical NMBs are members of this class. Depolarizing NMBs are agonists of nAChR that cause contractions known as fasciculation and have longer receptor residency causing persistent depolarization and desensitization [99]. Due to a greater side effect profile, few agents with this mode of action have been developed. Succinylcholine is the only depolarizing NMB agent used clinically.

Atracurium besylate (Figure 10.2e) was the first rationally designed non-steroidal NMB. It undergoes chemodegradation to inactive forms *in vivo* [100]. It was first prepared in the academic labs of the Strathclyde University [101] and later licensed to The Wellcome Foundation, which developed and launched the drug as a mixture of 10 stereoisomers (Tracrium) in the United Kingdom [102]. The design of **atracurium** was based on the importance of *bis-quaternary* structure for **neuromuscular blocking efficacy**. Degradation of **atracurium** occurs via nonenzymatic Hoffman elimination under mildly alkaline conditions at physiological pH and temperature (Scheme 10.2). The degradation products are not antagonists for nAChR and thus the **programmed decomposition** leads to a measurable and reliable off-rate of the **NMB agent**. The half-life of the agent is thus expectedly short, 17–20 minutes, which allows the anesthesiologist to plan dosing around the expected surgery time.

Atracurium was quickly superseded by cisatracurium when the active isomer of the mixture was discovered as the (1*R*, 2*R*, 1'*R*, 2'*R*)-*cis-cis* configuration (Table 10.10) [103]. This isomer makes up only 15% of the original mixture and thus dosing it as a single stereoisomer was expected to improve both efficacy and safety. Common side effects associated with the **tetrahydroisoquinolinium** class of NMBs include **hypotension**, **reflex tachycardia**, and **cutaneous flushing** resulting from a **rapid release of histamine** after administration of the NMB agent. Supratherapeutic dosing of cisatracurium (8× ED₉₅), on the other hand, does not result in increased histamine production, resulting in a significantly improved adverse event profile [104]. Both the single isomer and the mixture have also been evaluated in **neurosurgical mechanically ventilated patients**. Cisatracurium was superior over the **mixture** as measured by reduced intracranial pressure, cerebral perfusion, and lower overall blood pressure [105]. Furthermore, lower dosing of cisatracurium



Scheme 10.2. Rationally designed *in vivo* chemodegradation of atracurium.

TABLE 10.10. Comparison of Tracrium® and Its Chiral Switch Successor Nimbex®

	Tracrium®	Nimbex®
Stereochemistry	Multiple	(<i>R</i> -cis, <i>R</i> -cis)
API	Atracurium	Cisatracurium
FDA approval ^a	1983	1995
Originator	The Wellcome Foundation	GSK
Expected patent expiration ^b	Generic	2012
Peak global sales (year) ^c	N/A	N/A
Therapeutic class	Depolarizing neuromuscular blocking agents (NMB)	
Key advantages		
• Pharmacology	<ul style="list-style-type: none"> Nicotinic acetylcholine receptor antagonist (nAChR) Rationally designed bis-quaternary warhead decomposes at a measurable and reproducible rate to allow for precise dosing. 	
• Clinical data	<ul style="list-style-type: none"> Single stereoisomer is threefold more potent than mixture with slower onset and reduced histamine releasing profile. Lower dosing allows for less exposure to reactive metabolite. 	

^a Drugs@FDA.

^b Based on FDA Orange Book data for longest possible coverage.

^c Sales figures obtained from Thomson Reuters IntegritySM database.

results in the reduction of the amount of laudanosine, a major metabolite related to increased seizure events in animals [104].

10.3.7. Bupivacaine (Marcaine®/Sensorcaine®) to Levobupivacaine (Chirocaine®)

Reducing the abuse potential of analgesics has been a standing goal in this therapeutic class. This has spurred the evolution of agents from the original cocaine (1884) to tetracaine (1941) to bupivacaine (1967) and most recently ropivacaine (1996). All of these compounds share the same pharmacophore and thus capitalize on similar modes of action.

Bupivacaine (Marcaine) (Figure 10.2f) has been used as a topical anesthetic for many years [106]. When administered intravenously, however, the agent causes cardiac toxicity. Bupivacaine is approved as a racemic mixture and studies on the individual enantiomers have demonstrated that the therapeutic activity and improved safety resides with the (*S*)-enantiomer, levobupivacaine (Chirocaine®) [106]. In an effort to study the enantiospecific cardiotoxicity, effects on the action potential of each enantiomer on guinea-pig papillary muscle were evaluated. Less of the (*R*)-bupivacaine was needed to elicit a reduced maximal rate in the action potential amplitude of the membrane. The time for the membrane potential to recover was also extended [107]. Further, *in vivo* rat studies examined the influence of agent stereochemistry on the cell firing rate (CFR) and subsequent cardiovascular system. Although similar in many cardiac metrics (i.e., blood pressure, heart rate), the (*R*)-bupivacaine-treated rats exhibited higher rates of severe bradycardia, hypotension, and eventual death compared with the levobupivacaine rats [108].

Along with the pharmacological differences, the two enantiomers also have unique PK profiles specifically with regard to metabolism, exposure, distribution, and elimination. In animal studies, (*R*)-bupivacaine was found to have a higher clearance than levobupivacaine [106]. This observation was correlated in healthy humans exhibiting higher mean total plasma clearance for the (*R*)-enantiomer. In a study of patients undergoing minor surgery, levobupivacaine had higher peak plasma concentrations than its enantiomer.

In smaller comparison trials, levobupivacaine was shown to be as efficacious as bupivacaine for major extradural anaesthesia for cesarean delivery [109], epidural analgesia during labor [110], and major orthopedic surgery [111]. In a more recent study [112], levobupivacaine (7.5 mg) was compared with bupivacaine as spinal anesthetics for transurethral surgery. Less motor block and shorter motor block duration were observed with the single enantiomer treatment. Longer sensory block duration and prolonged intervals until requested supplemental analgesia were also associated with the single enantiomer dose group. In a double-blind comparison study, patients undergoing lower abdominal procedures were provided levobupivacaine, 50% enriched (*S*)-bupivacaine, and bupivacaine [113]. The most common procedures in the study were hysterectomy (75%) followed by tubal ligation (15%). All patients were provided

TABLE 10.11. Comparison of Marcaine® and Its Chiral Switch Successor Chirocaine®

	Marcaine®	Chirocaine®
Stereochemistry	(<i>R/S</i>)	(<i>S</i>)
API	Bupivacaine	Levobupivacaine
FDA approval ^a	1978	1999
Originator	AstraZeneca/Sanofi	UCB Celltech
Expected patent expiration ^b	Generic	2009
Peak global sales (year) ^c	N/A	N/A
Therapeutic class	Local and regional anesthetics	
Key advantages		
• Pharmacology	<ul style="list-style-type: none"> • Animal and receptor binding studies have confirmed that the (<i>R</i>)-bupivacaine is more closely related to the cardiac toxicity observed in the racemate. 	
• Clinical data	<ul style="list-style-type: none"> • Less motor block and shorter motor block duration were observed with the single enantiomer over racemate. 	

^a Drugs@FDA.^b Based on FDA Orange Book data for longest possible coverage.^c Sales figures obtained from Thomson Reuters IntegritySM database.

epidural anesthesia 1 hour prior to surgery. Motor and sensory block profiles were evaluated in addition to monitoring of pulse, blood pressure, and heart rate. Motor block was evaluated according to the Bromage scale for 30 minutes prior to surgery and 30 minutes during surgery. No statistical differences were observed among patient groups with regard to cardiovascular parameters. Although similar levels of sensory block were observed in all patients, the levobupivacaine group did demonstrate the least amount of motor block compared with the two other patient groups (Table 10.11).

10.3.8. Conclusion

The preceding case studies are provided as examples of successful execution of the chiral switch strategy, which has been utilized across a variety of therapeutic classes and indications. The success of chiral switch drugs has been made possible by significant advances in enantioselective synthesis as well as through further understanding of the chiral nature of biological systems. Although the strategy has been scrutinized for merely being a tool for patent life cycle management, the clinical data suggest that there is often a demonstrable advantage of the single enantiomer over a racemic mixture. Although single enantiomer drugs have overtaken mixtures and achiral entities, the chiral switch approach may continue to provide new and improved therapeutics based on older, racemic agents.

10.4. SITE-SELECTIVE DEUTERATION APPROACH

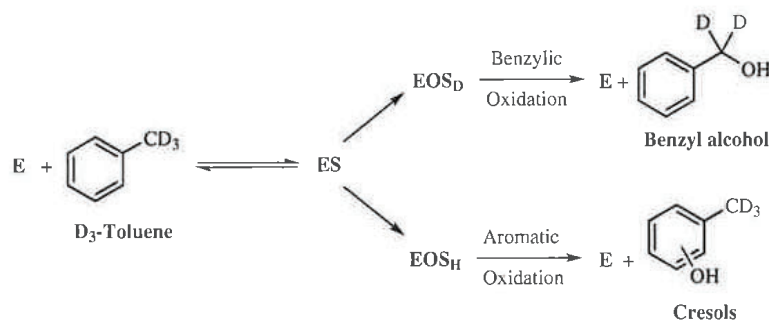
10.4.1. Introduction

Deuterated compounds have been widely used in nonclinical settings as metabolic or PK probes both *in vitro* and *in vivo* [114, 115]. Depending on the route of metabolism and the location of the deuterium, deuteration can be metabolically silent, allowing use as a PK tracer, or it can alter the compound's metabolism, enabling use as a mechanistic probe. In spite of the potential to alter a compound's metabolism, deuterium-containing compounds have rarely been clinically explored as new therapeutic agents, and no deuterated compound has advanced beyond Phase II clinical evaluation [116–118]. This section will provide a brief review of the use of site-selective deuteration as a strategy to alter the metabolic properties of clinically validated agents and will discuss past and current approaches to the development of deuterium-containing drugs. While not all of the case studies detailed below are formally repurposing efforts in terms of developing a deuterated drug for a new indication, the reader will appreciate that improvements to the PK profiles of existing agents may make them more amenable to repositioning strategies.

10.4.2. Primary Deuterium Isotope Effect

Deuterium is a naturally occurring, stable, nonradioactive isotope of hydrogen discovered in 1932 [119]. Hydrogen consists of one electron and one proton and has a mass of 1.008 atomic mass units (AMU), whereas deuterium also contains a neutron, which results in a mass of 2.014 AMU. Due to this mass difference, deuterium–carbon bonds have a lower vibrational frequency and therefore a lower zero-point energy than a corresponding hydrogen–carbon bond [120]. The lower zero-point energy results in a higher activation energy for C–D bond cleavage and a slower reaction rate (k). This reaction rate effect is known as the primary deuterium isotope effect (DIE) and is expressed as k_H/k_D , the ratio of the reaction rate of C–H versus C–D bond cleavage with a theoretical limit of about 9 at 37°C in the absence of tunneling effects [121, 122].

A very large number of studies have appeared in the literature over the years reporting DIEs for enzyme-catalyzed reactions. The DIE has the potential to affect the biological fate of many drugs metabolized by pathways involving hydrogen–carbon bond scission. k_H/k_D is the intrinsic deuterium isotope effect and is the full isotope effect observed in reactions where the C–H bond cleavage is rate limiting. However, the observed isotope effect, $(k_H/k_D)_{obs}$, for an enzymatic/metabolic reaction is often much smaller than the intrinsic isotope effect [123, 124]. This reduction, or masking of the isotope effect, results from the complexity of biological systems and the number of competing effects. For example, if the C–H bond breaking is only partially rate limiting, a reduced DIE will be observed. Likewise, if another enzymatic step is rate limiting (e.g., product release), then no isotope effect would be observed.



Scheme 10.3. Metabolic shunting for D₃-toluene. **E** represents free enzyme; **ES** is the enzyme–substrate (D₃-toluene) complex; **EOS_D** is the active oxygenating species for C–D bond oxidation to yield benzyl alcohol; **EOS_H** is the active oxygenating enzyme species for C–H (aromatic) oxidation to yield cresols.

Masking of the isotope effect also results from metabolic switching, which is a change from one site of metabolism to another on the molecule [121, 122, 125, 126]. When metabolic switching occurs, one can observe no change in the rate of substrate metabolism but will observe a change in the ratios of products formed [127]. There is at least one example in the literature in which an increased rate of metabolic turnover is attributed to metabolic switching [128]. In this study with D₃-toluene (Scheme 10.3), metabolic switching occurs away from benzylic oxidation, producing benzyl alcohol, to aromatic oxidation, producing cresols. The authors propose that the increase in turnover results from the more rapid product release for cresols than benzyl alcohol, thereby accelerating catalytic turnover. In spite of the ability of deuterium to alter metabolism patterns, the authors are not aware of any reports of deuteration resulting in the formation of unique metabolites that were not also observed for the all-hydrogen analog.

The complexity of biological systems and the number of competing effects in enzyme-catalyzed reactions that can mask the DIE have made the application of deuterium to drug discovery highly unpredictable and challenging [122]. The most important enzymes in drug metabolism are the cytochrome P450s (CYPs), which are responsible for the Phase I metabolism of a majority of drugs. The structures and mechanisms of CYPs have been reviewed in addition to the application of DIEs to the study of CYP-catalyzed reactions [121, 129].

In spite of the complexities surrounding the expression of a DIE, the incorporation of deuterium into pharmacologically active agents offers potential benefits such as improved exposure profiles and switching metabolic pathways away from the production of toxic metabolites [117, 130], thereby offering possible improvements in efficacy, tolerability, or safety. As noted in a recent review [131], there has been a resurgence of interest in the application of deuterium in medicinal chemistry as evidenced by the emergence of several new companies largely or solely focused on this technology.

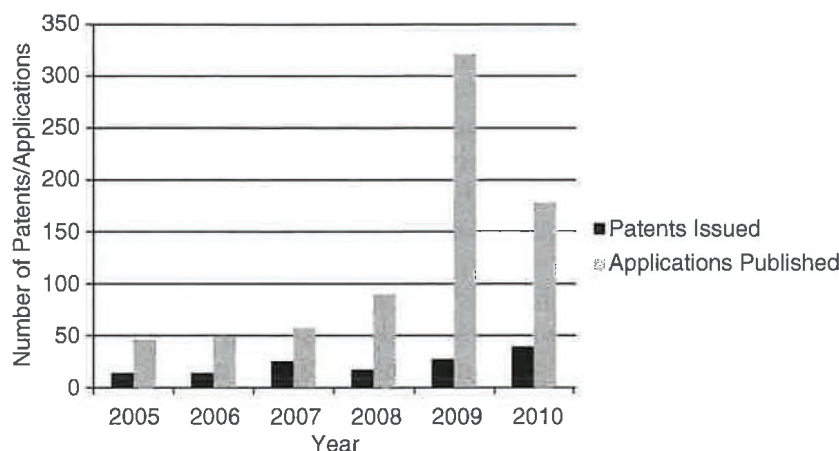


FIGURE 10.4. Issued patents and published applications containing “deuterium” or “deuterated” in the claims and “pharmaceutical” in any field for 2005–2010.

The increased level of interest in deuterated drugs by the pharmaceutical industry is also reflected by the number of published patent applications and issued patents over the last five years. A search of the USPTO database covering the years 2005 to 2010 for the terms “deuterium” or “deuterated” in the claims and “pharmaceutical” in all fields of published U.S. patent applications and issued U.S. patents resulted in 761 and 142 hits, respectively. For all years prior to 2005, the total hits were less than 80. Figure 10.4 shows the annual breakdown. There has been a large overall increase in published U.S. applications for 2008 through 2010 with a smaller but steady increase for issued patents over the same period, which shows the continuing patentability of deuterated drugs. The patentability of these new molecular entities is based on a showing of unexpected differences between the deuterated analogs and the prior art all-hydrogen compounds [132]. As more companies explore the potential of deuterated drugs and applications enter prosecution at the USPTO, it will be of great interest to see if the number of issued patents continues to grow.

10.4.3. Deuterium Effects upon Pharmacology, Metabolism, and Pharmacokinetics

When deuterium is substituted into molecules in place of hydrogen, in most respects the deuterated compound is quite similar to the all-hydrogen compound. Since the electron clouds of the atoms define the shape of a molecule, deuterated compounds have shapes and sizes that are very similar to their all-hydrogen analogs [133]. Small physical property changes have been detected in partially or fully deuterated compounds, including reduced hydrophobicity [134, 135], decreased acidity of carboxylic acids and phenols [136], and increased basicity of amines [137]. These differences tend to be quite

small and the authors are aware of only one report—deuterated analogs of sildenafil—in which deuteration of a reversibly binding drug appears to change its biochemical potency or selectivity to relevant pharmacological targets, which in this case are phosphodiesterases (PDEs) [138]. This paper by F. Schneider et al. reports that a deuterated analog of sildenafil exhibits a twofold enhancement in selectivity for PDE5 versus PDE6 and greater activity in an *in vitro* assay (relaxation of phenylephrine contracted rabbit corpus cavernosum strips). Binding isotope effects are well known and have been recently reviewed [139–141]. Although the effect of isotopic substitution on binding to receptors and enzymes has been previously considered negligible, these more recent data support that they are unpredictable, and can be insignificant, or contribute positively or negatively to measured DIEs.

The kinds of PK effects that may be achieved with deuteration, and that have been observed in certain cases, can be classified as illustrated in Figure 10.5. Panel 5 of Figure 10.5 illustrates the case where the major effect of deuteration, as shown by the theoretical solid line for the deuterated compound versus the theoretical dashed line for the all-hydrogen compound, is to reduce the rate of systemic clearance, which results in an increase of the biological half-life of the compound. Potential drug benefits could include a reduction in dosage and the ability to maintain similar systemic exposures with decreased peak levels (C_{\max}) and enhanced trough levels (C_{\min}). This could result in a lower incidence of C_{\max} -associated side effects and enhanced efficacy, depending on the particular drug's PK–PD relationship. D₁₅-atazanavir shown in Figure 10.7a is an example of this effect that will be discussed in greater detail as a case study. There are also two other examples in the recent literature

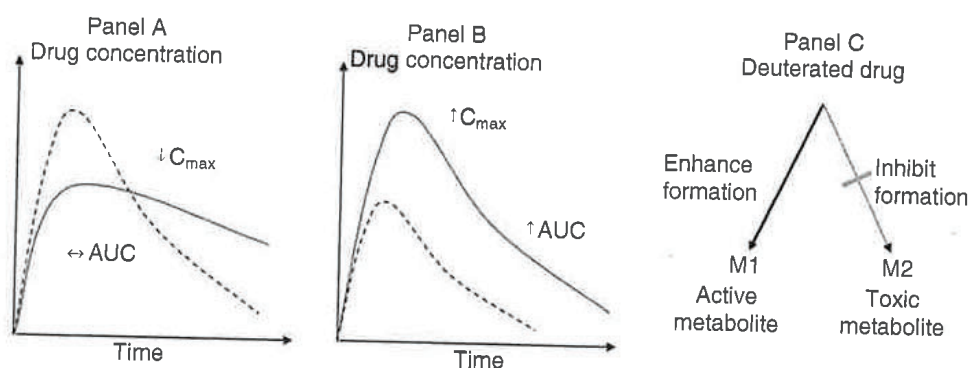


FIGURE 10.5. Panel A: Theoretical PK curves for reduced systemic clearance resulting in increased half-life for a deuterated compound (solid line) versus an all-hydrogen compound (dashed line). Panel B: Theoretical PK curves for decreased presystemic metabolism resulting in higher bioavailability of unmetabolized drug for a deuterated compound (solid line) versus an all-hydrogen compound (dashed line). Panel C: Deuterium mediated metabolic shunting resulting in reduced exposure to an undesired metabolite (M2) and increased exposure to a desired active metabolite (M1).

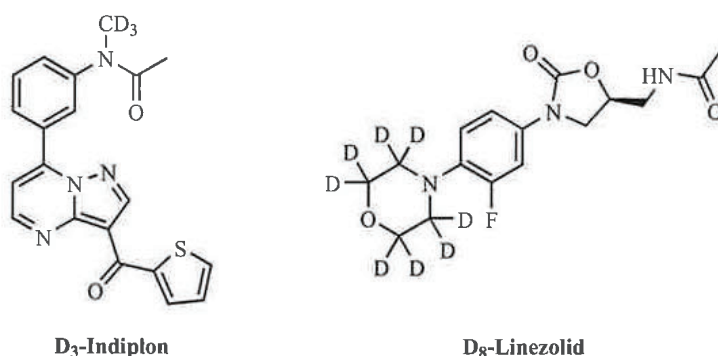


FIGURE 10.6. Structures of D₃-indiplon and D₈-linezolid.

shown in Figure 10.6, D₃-indiplon [142] and D₈-linezolid [143], in which deuterium substitution results in a longer half-life *in vivo*. Indiplon is a GABA_A receptor agonist that was in development for the treatment of insomnia. The D₃-indiplon compound showed an approximate twofold increase in half-life when orally dosed to rats. Linezolid (Zyvox®) is the only oxazolidinone antibiotic approved for the both intravenous (IV) and oral treatment of susceptible and resistant Gram-positive pathogens, particularly methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). The recommended dosage regimen for linezolid is 600 mg twice per day. The D₈-linezolid compound showed a 43% increase in half-life versus linezolid following IV dosing in primates. In both cases, the increase in half-life could have potential clinical value. D₃-indiplon may have a longer duration of action and improved sleep maintenance in humans, whereas D₈-linezolid may have prolonged exposure enabling a once-daily dosing regimen. These two examples are not presented as case studies since only preclinical data have been reported.

Figure 10.5, Panel B illustrates a largely presystemic (or first-pass) effect of deuteration. In this case, reduced rates of oxidative metabolism in the gut wall and/or liver results in a larger percentage of unmetabolized deuterated drug (shown by the solid line) versus the all-hydrogen drug (shown by the dashed line) reaching systemic circulation while the overall rate of systemic clearance remains unchanged. Deuterated drugs showing this effect may have reduced dosing requirements and produce lower metabolite loads. Since, in many instances, gastrointestinal irritation has been shown to be a dose-dependent rather than a plasma concentration-dependent phenomenon, this effect could allow for enhanced tolerability and/or the ability to achieve a higher maximum tolerated dose. Figure 10.5, Panel C illustrates metabolic shunting in which a drug is metabolized to form both active (M1) and toxic metabolite (M2) species. In such a case, deuteration could result in the reduced formation of M2, the toxic or reactive metabolite, as well as the increased formation of the desirable active metabolite M1.

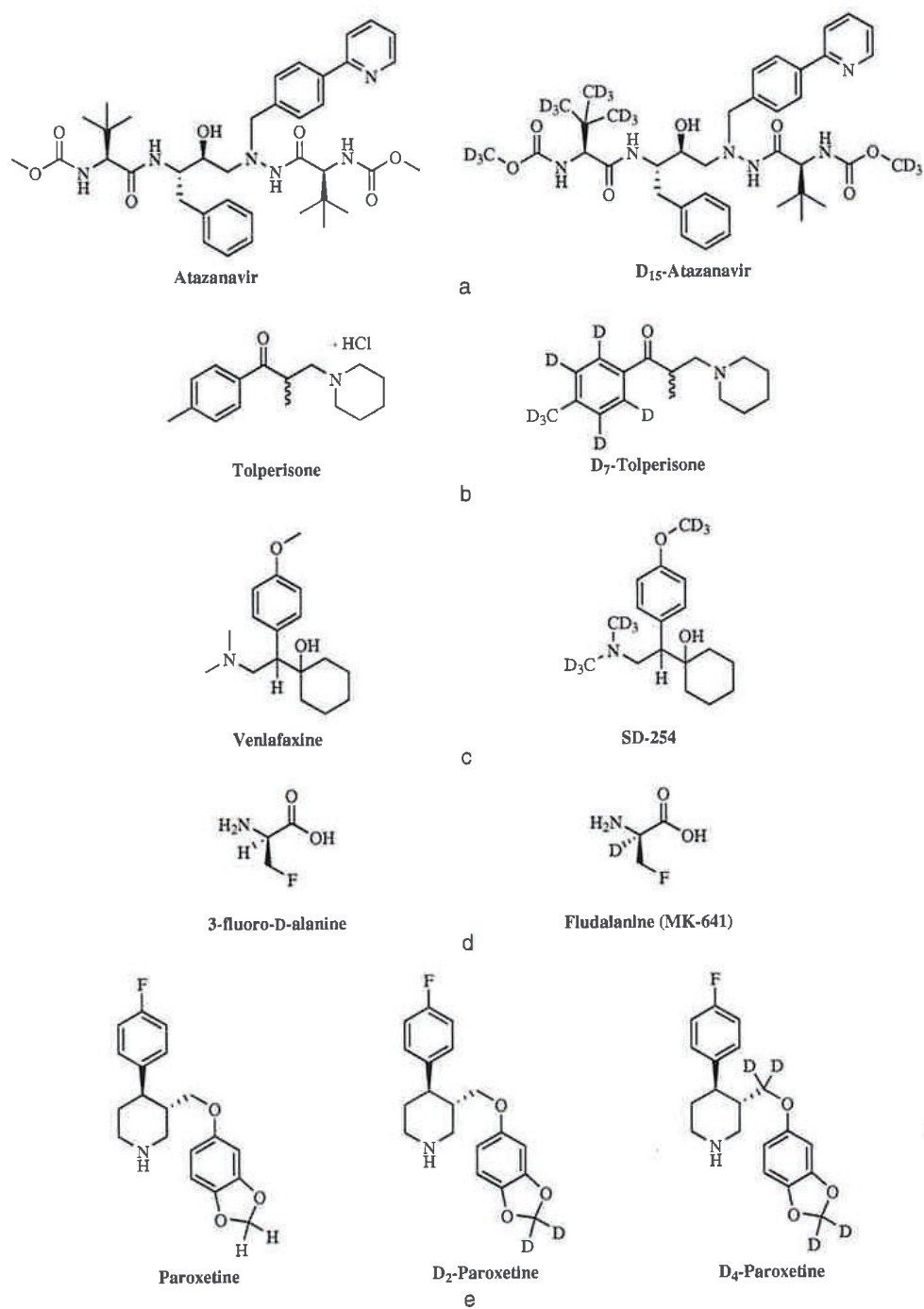


FIGURE 10.7. Structures of the site-selective deuterium modification case studies: (a) atazanavir, (b) tolperisone, (c) venlafaxine, (d) fludalanine, (e) paroxetine.

The case studies that follow are deuterated compounds exemplifying the PK effects represented in Figure 10.5. Each of these examples is a deuterated molecule that has been advanced to clinical studies in humans. However, only fludalanine progressed to clinical studies in patients; the other examples appear to have not advanced beyond Phase I studies in healthy volunteers. Deuterated atazanavir (Figure 10.7a) represents a deuterium effect to increase half-life as illustrated in Figure 10.5, Panel A. Deuterated tolperisone (Figure 10.7b) and deuterated venlafaxine (Figure 10.7c) show an increase in exposure resulting from decreased presystemic metabolism as represented in Figure 10.5, Panel B. The final two examples, fludalanine (Figure 10.7d) and deuterated paroxetine (Figure 10.7e), exhibit a deuterium effect, which produces metabolic switching away from an undesired metabolite to produce a safer or better tolerated drug (Figure 10.5, Panel C). The published data for each of these case studies will be reviewed.

10.4.4. CTP-518, Deuterated Atazanavir

Atazanavir (Reyataz®) (Figure 10.7a) is an HIV protease inhibitor (PI) launched in the United States in 2003 by Bristol-Myers Squibb and is labeled for the oral treatment of HIV-1 infection in combination with other antiretroviral agents [144]. The recommended dosage in HIV-1 positive treatment-naïve patients is either 300 mg with 100 mg ritonavir (Norvir®, a PK booster) once daily or 400 mg once daily if unable to tolerate ritonavir. For HIV-1 positive, treatment-experienced patients, the recommended dose is 300 mg with 100 mg ritonavir once daily.

Atazanavir is extensively metabolized in humans and *in vitro* studies suggest that metabolism is primarily via CYP3A4/CYP3A5 isozymes [145]. Ritonavir is an approved HIV-PI that is also a strong inhibitor of CYP3A isozymes; therefore, it can increase plasma concentrations of agents that are primarily metabolized by CYP3A [146]. Studies have shown that ritonavir increases the exposure (AUC), C_{max} , C_{min} , and half-life of atazanavir in a 300/100 once-daily regimen [145, 147]. A ritonavir-boosted atazanavir regimen is associated with greater virologic control due to greater exposure and higher C_{min} levels [148, 149]. Ritonavir, however, is associated with adverse events such as hyperlipidemia, hyperglycemia, and gastrointestinal intolerance [150]. Therefore, a once-daily, unboosted PI regimen for HIV-1 patients remains a significant unmet need.

CTP-518 is a deuterated version of the atazanavir (Figure 10.7a) that has entered Phase 1 clinical studies [131]. Selective deuteration is directed towards developing a drug that retains the anti-viral potency of atazanavir without the need for ritonavir or another PK boosting agent [151]. The structure of CTP-518 has not been published; however, D₁₅-atazanavir (Figure 10.7a) has been disclosed in a patent [152] with data showing increased human liver microsome (HLM) stability versus atazanavir. The half-life in HLM for D₁₅-atazanavir was increased 51% versus atazanavir. The increased stability in HLM translated

to an *in vivo* setting. Following an IV codose of D₁₅-atazanavir and atazanavir (1:1) in primates, an average 52% increase in half-life for D₁₅-atazanavir versus atazanavir was reported. Atazanavir and D₁₅-atazanavir exhibit similar HIV anti-viral activity in an *in vitro* viral assay. No clinical data for CTP-518 have been published; however, if deuterium substitution results in a longer half-life and more closely matches the exposure and C_{min} for boosted atazanavir, then viral replication could be effectively suppressed by unboosted CTP-518.

10.4.5. BDD-10103, Deuterated Tolperisone

Tolperisone-HCl (Figure 10.7b), was introduced into Hungary in 1959 by Gedeon Richter and is used for the treatment of various spastic paralyses [153]. Tolperisone possesses several desirable characteristics including a low adverse event profile, a lack of sedation and no interaction with alcohol as well as no potential for tolerance and addiction. However, tolperisone still has several pharmacological limitations, the most notable of which is a high first-pass effect in various species that requires high daily doses [154]. The metabolism of tolperisone is highly dependent on the genetic background of the patients and thus subject to considerable inter-individual PK variation. The major metabolic path for tolperisone is hydroxylation of the aryl methyl, predominantly via CYP2D6 with some contribution from CYP2C19 [155]. CYP2D6 is a genetically polymorphic enzyme and this polymorphism can be used to separate subjects into phenotypes: poor and extensive metabolizers, which results in significant individual differences in the ability to metabolize certain drugs [156]. A clinical study in 15 healthy male Korean volunteers reported highly variable pharmacokinetics upon oral dosing of tolperisone [157]. The volunteers were given a single oral 450 mg dose of tolperisone HCL (3 × 150 mg Mydocalm® tablets) and plasma drug levels were monitored over an 8 hours period. The AUC values ranged from 125.9 to 1241.3 ng/mL-h and the C_{max} values ranged from 64.2 to 784.9 ng/mL. These data emphasize the large inter-individual PK variability of tolperisone.

BDD-10103 is a deuterated analog of tolperisone that emerged from Bero-lina innovative Research and Development Services (BiRDS) Pharma GmbH using their Atomic Substitution Technology platform. The compound reportedly addresses current drawbacks of tolperisone while maintaining its advantageous features. The structure of BDD-10103 has yet to be reported and the intellectual property rights to the compound have recently been transferred to D4Pharma [158]. The company reports [159] that various animal models have shown oral doses of BDD-10103 to be more efficacious than the corresponding doses of tolperisone both in selected preclinical rodent and non-rodent animal models; BDD-10103 and tolperisone inhibited the monosynaptic ventral root reflex roughly to the same extent. BDD-10103 reportedly showed superiority in the tremorine test in mice after oral administration. Metabolic degradation of BDD-10103 and tolperisone was assessed in hepatic liver microsomes. The results suggested that a longer elimination half-life could be

expected for BDD-10103 in humans than that reported for tolperisone. However, the corporate website reports that in a single dose (300 mg) study of BDD-10103 in man, an increase in bioavailability was observed but no mention of an increase in half-life [159]. Although the structure of BDD-10103 has not been disclosed, D₇-tolperisone has been disclosed [160] and is reported to show a 10-fold decrease in aryl methyl hydroxylation versus tolperisone by both CYP2D6 and CYP2C19. If deuterium substitution suppresses both the first-pass metabolism by CYP2D6 and interpatient variability resulting from CYP2D6 polymorphism, then BDD-10103 could be clinically superior to tolperisone. The company reports that pharmaceutical development includes the evaluation of an improved oral formulation to enhance the bioavailability of BDD-10103 in the human body, but the current clinical status of BDD-10103 is unclear.

10.4.6. SD-254, Deuterated Venlafaxine

Venlafaxine (Effexor®, Effexor XR®) is a centrally acting serotonin-norepinephrine reuptake inhibitor (SNRI) launched in the US in 1994 by Wyeth Pharmaceuticals for the treatment of MDD, generalized anxiety disorder, social anxiety disorder and panic disorder with or without agoraphobia [161]. Venlafaxine (Figure 10.7c) has also been studied clinically for the treatment of hot flashes [162, 163] and neuropathic pain [164, 165]. Venlafaxine is orally absorbed and extensively metabolized in the liver by CYP2D6 to produce its major active metabolite O-desmethylvenlafaxine (ODV) [166, 167]. ODV or desvenlafaxine (Pristiq®) was launched in the US in 2008 for the treatment of MDD [168]. Since venlafaxine is metabolized by CYP2D6, plasma levels are higher in poor metabolizers than extensive metabolizers. However, since the metabolite, ODV, is also active and the total exposure for venlafaxine plus ODV are similar in poor and extensive metabolizers, there is no recommended dose adjustment for venlafaxine in these two groups [161].

SD-254 (Figure 10.7c) is a selectively deuterated analog of venlafaxine that has advanced into clinical development. Limited clinical data are available; however, the compound has been dosed in a Phase I healthy volunteer study to evaluate the effect of deuteration on drug behavior [169]. As illustrated in Figure 10.8, site-selective deuteration of venlafaxine resulted in enhanced exposure of SD-254 while reducing the levels of the major metabolite (ODV, or O-desmethyl venlafaxine). The left panel of Figure 10.8 shows the blood plasma levels for SD-254 versus venlafaxine, represented as their time versus concentration PK profiles. The right panel shows the time versus concentration PK profile observed in healthy volunteers for the deuterated versus all-hydrogen versions of the major metabolite, ODV. The data in Figure 10.8 show that when human subjects are dosed with the SD-254, they experience higher blood concentrations of the parent drug relative to venlafaxine. The SD-254 treated subjects also exhibit lower plasma concentrations of the major

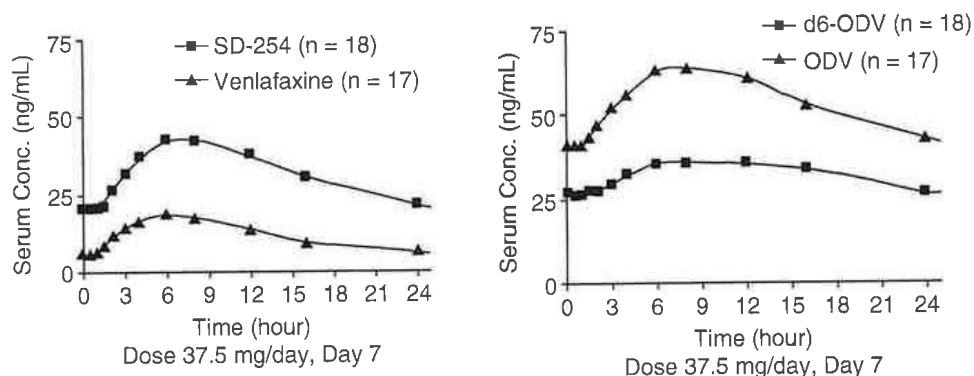
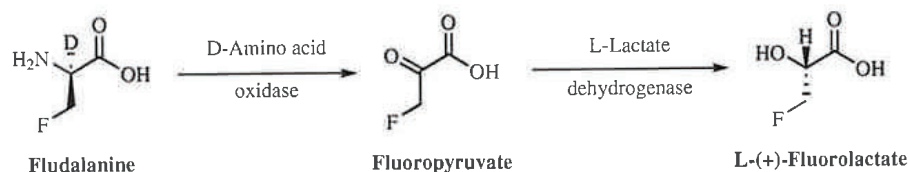


FIGURE 10.8. Left Panel: Time versus concentration PK profiles of deuterated venlafaxine (SD-254) and venlafaxine in healthy volunteers after 7 days of dosing. Right Panel: Time versus concentration PK profiles of the metabolites: d6-O-desmethyl venlafaxine and O-desmethyl venlafaxine (ODV) in healthy volunteers after 7 days of dosing. Reproduced from [169] with permission, Auspex Pharmaceuticals.

metabolite (ODV). Development in neuropathic pain is reportedly planned for SD-254 [131, 151].

10.4.7. Fludalanine (MK-641)

Fludalanine (Figure 10.7d) appears to be the earliest deuterated drug candidate to have entered clinical trials; however, very little data have been reported. Fludalanine, combined with cycloserine, displays **broad and potent antibacterial activity** [170]. The all-hydrogen analog 3-fluoro-D-alanine (Figure 10.7d) is a **highly effective antibacterial agent that acts against bacterial cell wall synthesis** [171]. However, preclinical studies reportedly showed that it was **metabolized to 3-fluorolactate** (Scheme 10.4), a toxin that caused brain vacuolization [172]. A recent letter reported that deuteration reduced 3-fluorolactate production to what were deemed acceptable levels in healthy volunteers [118]. However, higher 3-fluorolactate levels were observed in patients, which **may have resulted from metabolic differences between healthy volunteers and patients**. Studies on fludalanine were discontinued at Phase 2b.



Scheme 10.4. Proposed metabolic pathway for the conversion of fludalanine to L-(+)-fluorolactate.

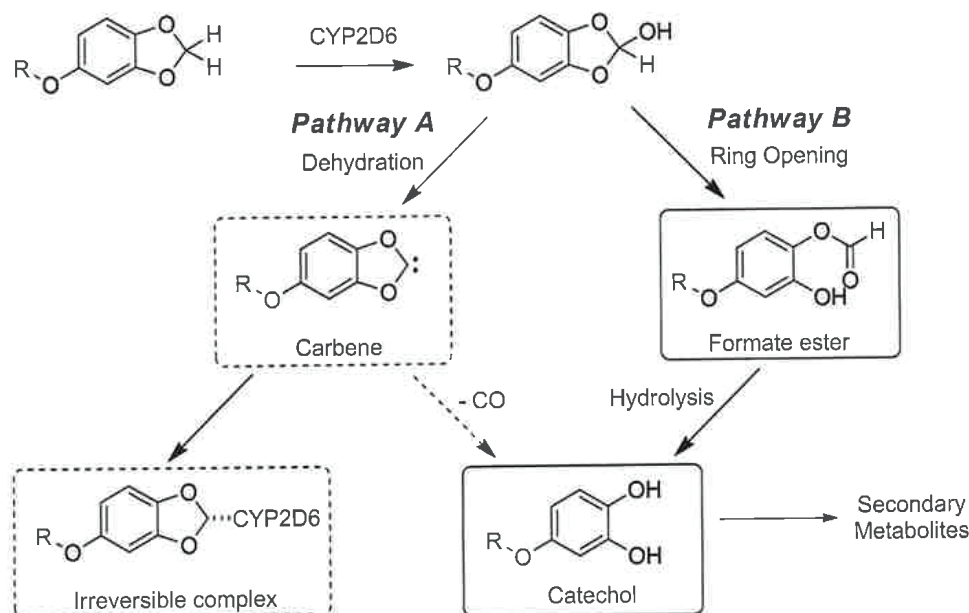
10.4.8. CTP-347, Deuterated Paroxetine

Paroxetine (Paxil®, Paxil CR®), shown in Figure 10.7e, is a centrally acting, SSRI launched in the United States in 1991 by GlaxoSmithKline and is labeled for the treatment of MDD, panic disorder, social anxiety disorder, and premenstrual dysphoric disorder [173]. As with venlafaxine, paroxetine has also been studied clinically for the treatment of hot flashes and neuropathic pain [163, 165]. Paroxetine is orally absorbed and extensively metabolized in the liver to produce a number of more polar and conjugated metabolites, which are readily cleared. The major metabolites have significantly less SSRI activity than paroxetine. Paroxetine is metabolized by CYP2D6; however, this enzyme is significantly inhibited by paroxetine. Therefore, co-administration of paroxetine with other drugs metabolized by CYP2D6 is contraindicated.

CTP-347 is a deuterated analog of paroxetine for the treatment of hot flashes that has completed Phase I clinical evaluation [174]. Low-dose paroxetine reportedly has good efficacy in treating hot flashes [175]. However, in patients potentially benefiting from such therapy, such as postmenopausal women and cancer patients receiving endocrine disrupting agents, paroxetine use can be complicated or contraindicated as it causes extensive drug–drug interactions (DDIs) with other drugs. The cause of these DDIs is believed to be predominantly irreversible inactivation of the hepatic enzyme CYP2D6. While CTP-347 shows similar pharmacology to paroxetine with respect to inhibition of serotonin and norepinephrine reuptake [176], CTP-347 is reported to be the first example of the use of deuterium to mitigate CYP2D6 inactivation versus paroxetine in a clinical setting [177]. The structure of CTP-347 has not been reported; however, D₂-paroxetine and D₄-paroxetine (Figure 10.7e) have been disclosed in the patent literature [178].

Increased metabolism for D₂- and D₄-paroxetines versus paroxetine in human liver microsomes is reported in the patent. The greater stability of paroxetine results from irreversible inhibition of CYP2D6 whereas the decreased stability of D₂- and D₄-paroxetines results from reduced CYP2D6 inhibition. Metabolism experiments in human liver microsomes confirmed that paroxetine was a mechanism-based inactivator of CYP2D6 ($K_{\text{inact}} = 0.08 \text{ minute}^{-1}$); however, CTP-347 showed little or no CYP2D6 inactivation [179], possibly due to metabolic shunting that prevents the formation of a reactive metabolite that forms an irreversible complex at the active site of CYP2D6 (Scheme 10.5) [180].

A Phase I study was conducted to assess the effect of CTP-347 on mechanism-based inhibition of CYP2D6 in healthy women [176]. CTP-347 was administered (9/dose group) at doses of 10, 20, and 40 mg qd and 10 mg bid for 14 days. A 30 mg dose of dextromethorphan was administered orally on days 1 and 14. Dextromethorphan acts as a selective probe for CYP2D6 activity by measuring the urinary levels of dextrorphan, the metabolite formed by CYP2D6. Urine was collected for 8 hours and the amounts of dextromethorphan and dextrorphan were measured by liquid chromatography–tandem



Scheme 10.5. Proposed inactivation pathway for CYP2D6 by a paroxetine metabolite. Pathway A produces a putative reactive metabolite and resultant inactivated enzyme (structures in dashed-line boxes). Pathway B produces polar metabolites via formate ester hydrolysis to the catechol (structures in solid-line boxes) that are rapidly cleared as secondary metabolites. Some of the carbene metabolite may also form the catechol via decarbonylation.

mass spectrometry (LC-MS/MS). Subjects dosed with CTP-347 retained substantially greater ability to metabolize dextromethorphan than has been reported previously for paroxetine [181, 182], correlating well with *in vitro* data (see Figure 10.9). Minor CYP2D6 inhibition was observed at higher CTP-347 doses, which is consistent with the reversible, competitive inhibition seen *in vitro*.

The five case studies presented in this section serve as clinical examples of the potential benefits of deuterium substitution. Only fludalanine has progressed to clinical trials in patients; however, the PK data for the other four examples show the potential for tangible clinical benefits. Although no human data have been reported for CTP-518, the published PK data for D₁₅-atazanavir in primates show an increase in half-life and an improved exposure profile as schematized in Figure 10.5, Panel A. The reported PK for the deuterated versions of venlafaxine and tolperisone supports a deuterium effect that reduces first-pass metabolism and increases exposure without changing half-life according to Figure 10.5, Panel B. The last two case studies, fludalanine and deuterated paroxetine, are examples of a deuterium effect that results in metabolic shunting as shown in Figure 10.5, Panel C. In both cases, deuterium substitution reduced deleterious metabolic side effects: 3-fluorolactate production from fludalanine and CYP2D6 inactivation by CTP-347. These case

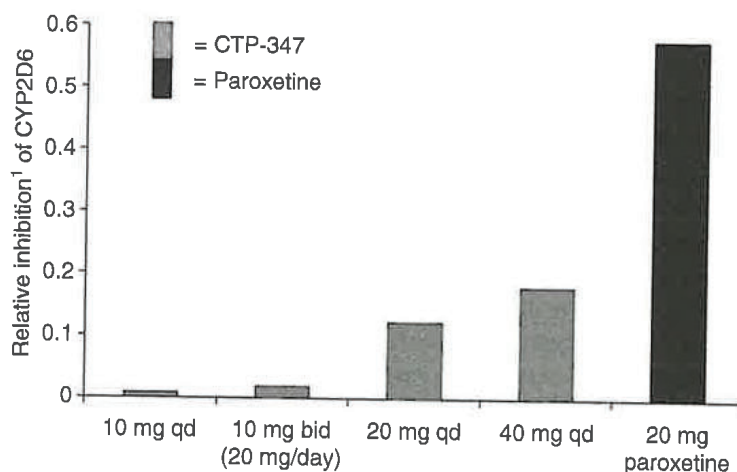


FIGURE 10.9. Drug–drug interaction between CTP-347 and dextromethorphan from Phase Ib study. ¹y-Axis shows the relative inhibition of CYP2D6 as the ratio of urinary levels of excreted dextromethorphan versus the CYP2D6 metabolite dextrorphan at four doses shown on the x-axis. The 20 mg qd paroxetine data shown are historical data from Reference [181].

studies support the ability of deuterium substitution to provide clinical agents with improved PK resulting in better efficacy, tolerability, and/or safety versus the corresponding all-hydrogen compound.

10.5. CONCLUSION

After a half century of drug discovery and development, the pharmaceutical/biotechnology industries have evolved to recognize the importance of drug repositioning as a new paradigm shift. Serendipitous discoveries, as well as concerted efforts, have led to strategies that capitalize on the advantages of repositioned drugs. The repositioning approach provides an attractive method for accelerating and concurrently de-risking drug development since these agents require less investment and time to develop and have a lower risk for late stage clinical failure. As such, repurposing offers an attractive risk-versus-reward profile in comparison with other drug development approaches and offers the potential to substantially improve performance metrics. As might be expected, there are a number of distinct challenges associated with any given repositioning strategy, which drives the development of creative approaches on the part of repositioning companies. The three strategies presented in this chapter highlight the continued progression of chemical platforms that may be utilized to facilitate these drug repositioning efforts.

The prodrug strategy has proven to be highly effective for solving many of the solubility, stability, permeability, and targeting problems necessary for certain repositioning strategies. This approach continues to yield successfully

repositioned agents as evidenced by the recent FDA approval of gabapentin encarbil for the treatment of restless leg syndrome. Increasingly, prodrugs are being utilized for targeting functions, including site-specific activation and tissue-specific delivery of anticancer agents, through their unique effects on transporters, and tumor- or tissue-specific enzymes. Such applications should further increase their utility for repositioning.

The conceptualization of the chiral switch strategy has evolved significantly over the past 20 years. To date, the chiral switch approach has provided a useful option to extend the profitable life of a pharmaceutical agent by providing compounds with improved pharmacological profiles, improved efficacy, and improved safety or tolerability. Although the approval of single enantiomer drugs has surpassed that of racemates or achirals, the prior success of the chiral switch approach ensures its utility as appropriate substrates present themselves.

Finally, the site-selective deuteration strategy has recently emerged as a platform with the potential to impact positively the absorption, distribution, metabolism, and excretion (ADME) profile of clinically validated compounds, thereby possibly conferring improvements in the efficacy, tolerability, and/or safety of the deuterated entity. The examples presented in this chapter demonstrate that, in some cases, the deuterated agents possess distinct clinical benefits over the corresponding all hydrogen analogs. With more of these deuterium-containing compounds progressing into clinical evaluations, the viability of this strategy as a repositioning approach should become more evident. As such, site-selective deuteration is poised to become a standard strategic approach for both drug repositioning and discovery.

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