DRUG REPOSITIONING: IDENTIFYING AND DEVELOPING NEW USES FOR EXISTING DRUGS

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Biopharmaceutical companies attempting to increase productivity through novel discovery technologies have fallen short of achieving the desired results. Repositioning existing drugs for new indications could deliver the productivity increases that the industry needs while shifting the locus of production to biotechnology companies. More and more companies are scanning the existing pharmacopoeia for repositioning candidates, and the number of repositioning success stories is increasing.

The biopharmaceutical industry has a problem: output has not kept pace with the enormous increases in pharma R&D spending (FIG. 1)[1]. This gap in productivity exists even though pharma companies have invested prodigious amounts in novel discovery technologies, such as structure-based drug design, combinatorial chemistry, high-throughput screening (HTS) and genomics[2], which were sold on the promise of improving productivity. For example, many in the industry invested heavily in the idea that HTS technology would bring 20-fold improvements in throughput. Well over US $100 million has been invested to date in this technology[3]; so far, it has yielded few products[4].

This productivity problem — coupled with worldwide pressure on prices, challenges from generics and ever-increasing regulatory hurdles — has forced many drug developers to become more creative in finding new uses for, and improved versions of, existing drugs[5,6]. For example, extended- or controlled-release formulations of marketed drugs have improved drug attributes, such as dosing frequency — for example, once-a-day methylphenidate (Concerta; ALZA) for attention-deficit and hyperactivity disorder — and side-effect profiles — for example, extended-release oxybutynin (Ditropan XL; Johnson & Johnson) and transdermal oxybutynin patch (Oxytrol; Watson), both for overactive bladder. Drug developers are also creating new product opportunities by combining therapeutically complementary drugs into one pill — for example, Advicor (Kos Pharmaceuticals), which contains lovastatin plus extended-release niacin for hyperlipidaemia; Glucovance (Bristol-Myers Squib), which contains metformin plus glyburide for diabetes; and Caduet (Pfizer), which contains amlodopine plus atorvastatin for hypertension and hyperlipidaemia[7,8]. The process of finding new uses outside the scope of the original medical indication for existing drugs is also known as redirecting, repurposing, repositioning and reprofiling[8–10].

Repositioning success stories and companies leveraging repositioning strategies are increasing in number. This review focuses on repositioning and will describe its general advantages over *de novo* drug discovery and development; representative repositioning success stories; hurdles typically encountered during the repositioning process and approaches for overcoming them; the strategies applied by several biotech companies using this approach to drug development; and the relative merits of pursuing repositioning approaches inside pharmaceutical or biotech companies.

Faster development times *and* reduced risks

Attempts to reduce pharmaceutical research and development timelines are often associated with increasing risk. However, drug repositioning offers the possibility of escaping the horns of this dilemma. Specifically, development risk is reduced because repositioning candidates have often been through several stages of clinical development and therefore have well-known safety and

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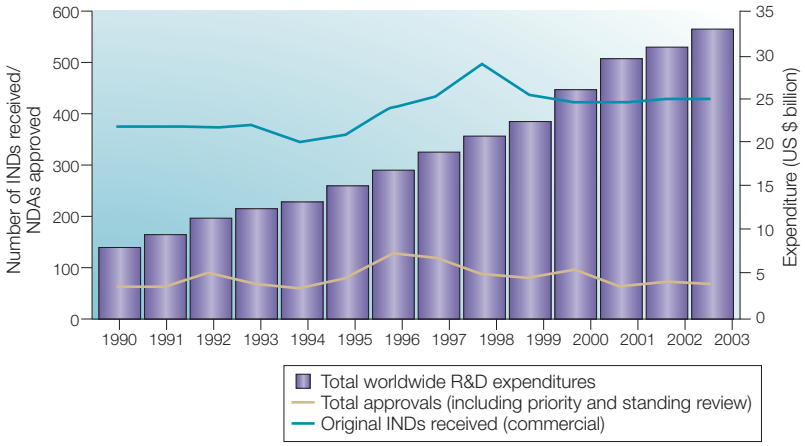

Figure 1 | **The growing productivity gap in the biopharmaceutical industry.** Despite enormous increases in spending in novel technologies over the last several years, R&D productivity has actually decreased since the mid-1990s, as measured either by the number of new drugs approved per dollar spent or by the number of original Investigational New Drug (IND) applications received by the US FDA from commercial sources per dollar spent.

pharmacokinetic profiles. Shorter routes to the clinic are also possible because *in vitro* and *in vivo* screening, chemical optimization, toxicology, bulk manufacturing, formulation development and even early clinical development have, in many cases, already been completed and can therefore be bypassed. In sum, these factors enable several years, and substantial risks and costs, to be removed from the pathway to the market (FIG. 2). As such, repositioning can offer a better risk-versus-reward trade-off compared with other drug development strategies (FIG. 3).

These advantages have not escaped the notice of venture capital firms seeking near-term, high-value exits for their companies. For venture capitalists in 2004, it is hardly possible to invest in a therapeutics company without drug candidates in or near clinical trials because of the positive reception received by such companies from the public equity markets. Indeed, repositioning offers the opportunity to quickly create such a pipeline, and repositioning companies are having little trouble raising venture rounds[9].

Case studies

A novel 'below the belt' use for duloxetine. Duloxetine (Cymbalta and Duloxetine SUI; Eli Lilly) blocks the reuptake of both SEROTONIN and NORADRENALINE in the synaptic cleft. The Neuroscience Division of Eli Lilly discovered this compound in the late 1980s as a part of its efforts to find an improved version of fluoxetine (Prozac), Lilly's highly successful drug for depression. One of us (K.B.T.) was a member of Lilly's Neuroscience Division during the time that duloxetine was being developed for depression and reasoned that drugs with duloxetine's mechanism of action might also increase urethral sphincter tone and decrease detrusor activity. Serotonin and noradrenaline, although best known for their effects on mood, were also known to have significant activity in the spinal cord and, specifically, to exert an excitatory effect on urethral sphincter motor neurons, thereby increasing urethral resistance and protecting against leakage of urine. Preclinical studies showed that duloxetine potentiated the excitatory effects of serotonin and noradrenaline on sphincter motor neurons[11]. The Lilly group therefore proposed that duloxetine might be useful in the treatment of stress urinary incontinence (SUI), a condition characterized by episodic loss of urine associated with sharp increases in intra-abdominal pressure (for example, when a person laughs, coughs or sneezes). It is commonly seen in women who have experienced several child births and is caused by a weakening of the pelvic floor, which in turn compromises the angle of the bladder neck responsible for maintaining normal continence. As a result, SUI was largely considered to result from an anatomical defect, and it was widely thought that SUI would not respond to any drug therapy. Instead, SUI is treated with incontinence pads or adult diapers, pelvic floor Kegel exercises and surgery (for example, urethropexy or sling procedures). However, clinical trials in women showed that duloxetine was an effective therapy for treatment of SUI[12], and so Lilly decided to develop duloxetine for both SUI and depression. In September of 2003, Lilly received an 'approvable' letter from the US FDA to market duloxetine as Duloxetine SUI. If approved, it will be the first pharmacological treatment for SUI, and Lilly is currently anticipating worldwide sales of Duloxetine SUI to approach US $800 million within four years of launch[8].

Third time's the charm for dapoxetine. Dapoxetine is a selective serotonin-reuptake inhibitor (SSRI) that was originally developed by Lilly as adjunct therapy for analgesia, and discontinued for portfolio reasons. Dapoxetine was then considered as a follow-on antidepressant to fluoxetine. However, the rapid onset and short half-life of the compound did not allow for once-daily dosing, an absolute must for any competitive antidepressant, and it was again passed over. Fluoxetine was subsequently out-licensed to GenuPro, where one of us (K.B.T), who was then Chief Scientific Officer of GenuPro, proposed that a common side effect of SSRIs — that is, delayed ejaculation — could be turned into a therapeutic benefit in men with premature ejaculation, a disorder that is a problem for more than 20% of men in the United States[13]. Furthermore, it was proposed that duloxetine's rapid onset and short half-life would be a pharmacokinetic advantage for 'as needed' treatment, which led to the filing of a METHOD-OF-USE (MOU) PATENT. After obtaining Phase II proof of concept for premature ejaculation, GenuPro out-licensed dapoxetine in 2001 to ALZA Corporation (now a part of Johnson & Johnson), where it is now in Phase III clinical development for premature ejaculation. Johnson & Johnson is currently estimating peak sales of dapoxetine to approach US $750 million[14].

The fall and rise of thalidomide. It is remarkable that thalidomide could ever have a comeback after its tragic beginning. Thalidomide was originally marketed in 1957 in Germany and England as a sedative and targeted specifically to pregnant women to treat morning sickness.

SEROTONIN
Also known as a 5-hydroxytryptamine (5-HT), a chemical neurotransmitter contained in a specific subpopulation of neurons in the central nervous system and in the enteric nervous system. Because changes in serotonin levels in the brain can alter mood, medications that affect the action of serotonin are commonly used to treat depression.

NORADRENALINE
A catecholamine neurotransmitter contained in a specific subpopulation of neurons in the central nervous system and in sympathetic post-ganglionic neurons of the peripheral autonomic nervous system.

METHOD-OF-USE PATENT
(MOU). A patent containing one or more claims directed to a method of use (for example, a method of treating disease X, comprising administering a therapeutically effective amount of product Y to a subject in need thereof). The exclusionary right is limited to the particular use claimed.

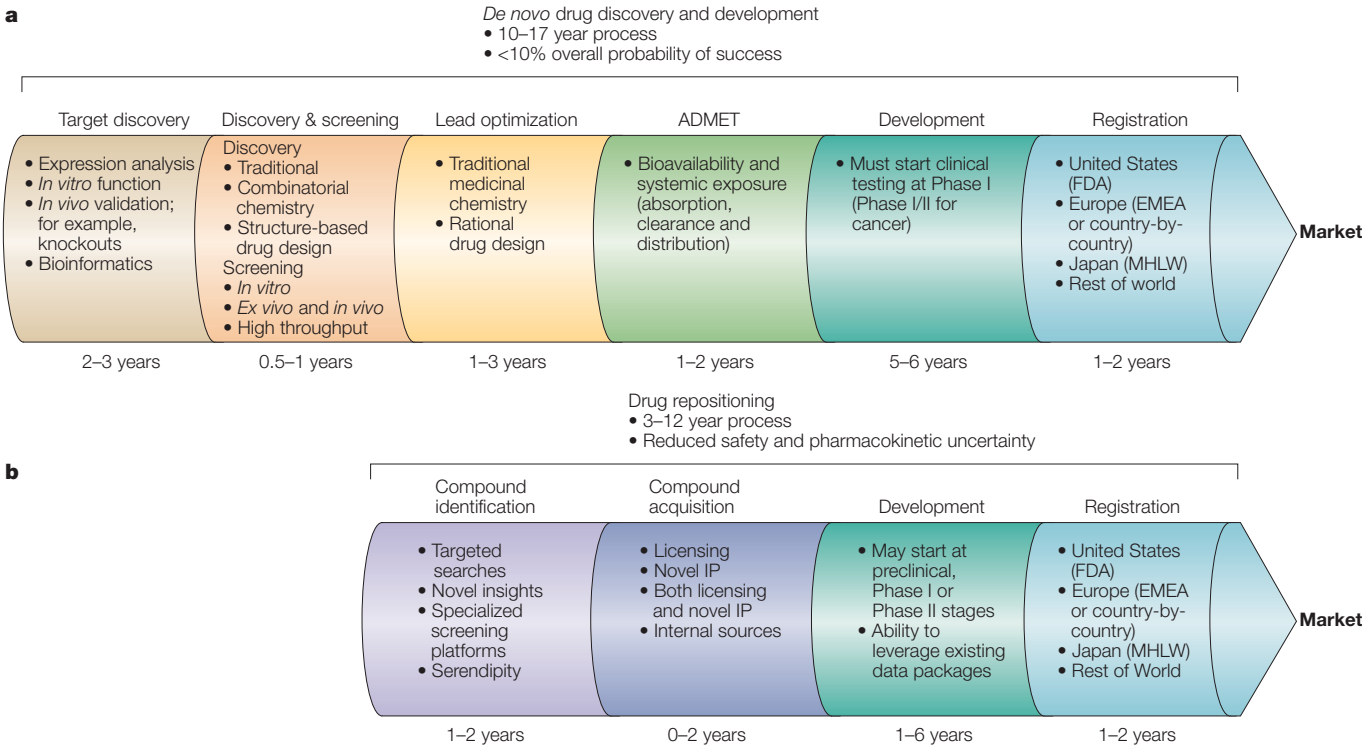

Figure 2 | **A comparison of traditional *de novo* drug discovery and development versus drug repositioning. a** | It is well known that *de novo* drug discovery and development is a 10–17 year process from idea to marketed drug[72]. The probability of success is lower than 10%[37]. **b** | Drug repositioning offers the possibility of reduced time *and* risk as several phases common to *de novo* drug discovery and development can be bypassed because repositioning candidates have frequently been through several phases of development for their original indication. ADMET, absorption, distribution, metabolism, excretion and toxicity; EMEA, European Medicines Agency; FDA, Food and Drug Administration; IP, intellectual property; MHLW, Ministry of Health, Labour and Welfare.

No regulatory approval was required — the drug was billed as "completely safe" — although the disaster that followed led to the introduction of the drug law known as the 'Arzneimittelgesetz', which requires that proof of safety be established for pharmaceuticals sold in Germany[15,16]. Taking the drug as indicated led to severe skeletal birth defects in at least 15,000 children born to mothers who had taken thalidomide during the first trimester of their pregnancies. Marketing in the initial indication went on until 1961, by which time the drug was being marketed to thousands of patients in 46 countries[16].

Without the fortuitous presence of the banned drug in a hospital's medicine cabinet, thalidomide might not have been revived. Thalidomide was next used to treat the condition erythema nodosum laprosum (ENL), an agonizing inflammatory condition of leprosy characterized by large, persistent, painful boils and inflammation so severe it often leads to blindness. Cases of ENL are now well managed as a result of thalidomide's new use. The discovery of thalidomide's activity in ENL could not have been more accidental[16]. In 1964, physician Jacob Sheskin in the University Hospital of Marseilles was desperate to treat a critically ill ENL patient whose pain had been so great that he had not slept for weeks. As a last resort, Sheskin used the only drug in the hospital's infirmary that he believed might help the patient sleep. Thalidomide not only allowed the patient a night's sleep; it also healed the patient's sores and eliminated his pain. Sheskin then conducted a double-blind study of thalidomide in Venezuela, and of 173 patients treated 92% were completely relieved of their symptoms[16]. A World Health Organization-sponsored follow-up study on 4,552 ENL patients showed that a full 99% of patients enjoyed a complete remission in less than two weeks[16]. Thalidomide is still the primary, indeed the only, drug used to treat ENL[16]. Female ENL patients who receive thalidomide also go on two forms of birth control before being prescribed the drug.

It was later shown that thalidomide is an inhibitor of tumour-necrosis factor-α (TNF-α)[17]; and that AIDS patients suffered as much as leprosy patients from the inappropriate production of TNF-α[16], which was known to be involved both in the development of AIDS-related mouth ulcers and cachexia in these patient populations[16]. But it was Kaplan's 1993 discovery that thalidomide suppresses the activation of latent HIV type I that sparked the interest of the company Celgene and led to the subsequent approval of the drug under the trade name Thalomid in 1998 for use in treating ENL[16].

In 1994, researchers at Children's Hospital in Boston discovered that thalidomide had anti-angiogenic properties that made it a candidate in oncology, and also began to explain its dramatic effects in limb development in the human foetus[18]. Celgene acquired the rights to Children's Hospital's thalidomide MOU patent in 1998.

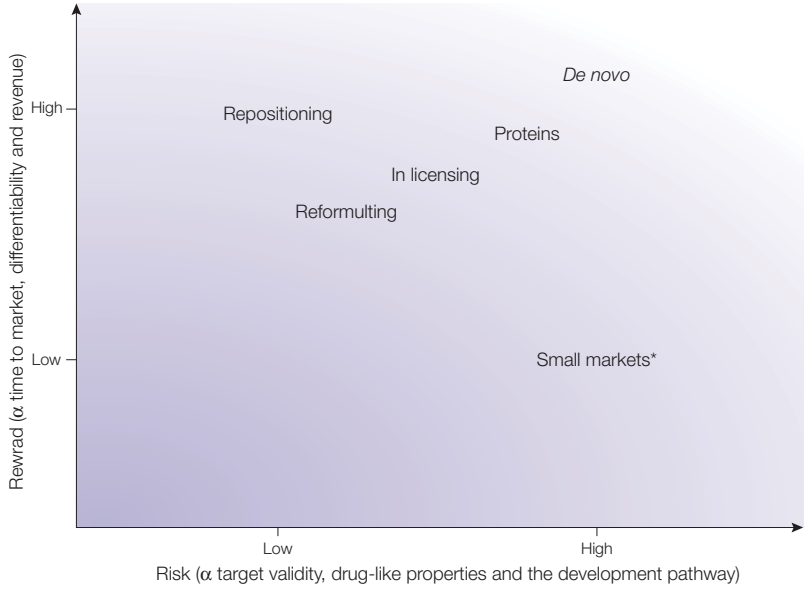

Figure 3 | **The risk-versus-reward trade off between different drug development strategies.** Drug repositioning offers one of the best risk-versus-reward trade-off of the available drug development strategies. It can offer lower risk than in-licensing strategies because repositioning candidates have often been through several stages of development and may even be marketed entities. In addition, repositioning offers the possibility of high rewards because of shorter times to market and higher possibility of differentiation as compared with in-licensing and reformulation strategies.*For example, rare diseases or diseases primarily incident in developing nations; government regulations have been enacted to reduce risk and/or raise potential reward for some small markets, for example, by conferring Orphan Drug status on certain drugs.

Celgene recorded 2002 sales of US $119 million for Thalomid, 92% of which came from off-label use of the drug in treating cancer, primarily multiple myeloma[19,20]. Sales reached US $224 million in 2003[21]. The lesson from the thalidomide story is that no drug is ever understood completely, and repositioning, no matter how unlikely, often remains a possibility.

An ineffective angina drug with an interesting side effect. Pfizer was seeking a drug for angina when it originally created sildenafil (Viagra) in the 1980s. As an inhibitor of phosphodiesterase-5 (PDE5), sildenafil was intended to relax coronary arteries and therefore allow greater coronary blood flow. The desired cardiovascular effects were not observed on the healthy volunteers tested at the Sandwich, England, R&D facility in 1991–1992. However, several volunteers reported in their questionnaires that they had had unusually strong and persistent erections. Pfizer researchers did not immediately realize that they had a blockbuster on their hands, but when a member of the team read a report that identified PDE5 as a key enzyme in the biochemical pathway mediating erections, a trial in impotent men was quickly set up[22]. A large-scale study carried out on 3,700 men worldwide with erectile dysfunction between 1993 and 1995 confirmed that it was effective in 63% of men tested with the lowest dose level and in 82% of men tested with the highest dose[23]. Of note, in many of these studies[22], Pfizer's researchers had difficulties retrieving unused sample of the drug from many subjects in the experimental group as they did not want to give the pills back! By 2003, sildenafil had annual sales of US $1.88 billion and nearly 8 million men were taking sildenafil in the United States alone[24,25].

COST OF GOODS SOLD (COGS). The expense a company incurs to manufacture a drug product for sale. Often includes labour, materials, overhead and depreciation associated with the manufacturing process.

PHARMACODYNAMICS The study of therapeutic and/or toxic effects that pharmacologically active substances have on biological systems. In other words, 'the study of what the drug does to the body'.

PHARMACOKINETICS The study of the rates of the movements of drugs within biological systems as affected by absorption, distribution, metabolism and elimination (ADME). In other words, 'the study of what the body does to the drug'.

Identifying repositioning opportunities

So where exactly do the ideas for repositioning and the actual repositioning candidates come from? Ideas for repositioning can come from serendipitous observations (for example, sildenafil)[22]; from novel, informed insights (for example, duloxetine)[11]; or from technology platforms established to identify repositioning opportunities (for example, CombinatoRx's cHTS system[26]). Once the repositioning idea has been generated, and the proposed approach scientifically validated, then a commercially viable target product profile for a candidate can be generated and a search conducted to identify compounds with the desired characteristics. This search often involves a review of the public and subscription-based information sources (for example, company websites, intellectual property (IP)[5] and scientific databases[5], and FDA Summary Bases of Approval and so on) to identify candidates within the generic and branded pharmacopoeia and also the pipelines of pharmaceutical companies.

However, discovering and validating the repositioning idea and identifying the actual repositioning candidate is just the beginning of the repositioning process. Market analyses, IP and regulatory diligence, and the formulation of new development plans, are all as much a part of the repositioning process as they are for *de novo* drug discovery and development. The same is true for selling the opportunity within one's own company. However, challenges associated with obtaining access and commercial rights to repositioning candidates can be unique to the process.

Due Diligence: 'is this dog gonna hunt?'

The next hurdle in the repositioning process is to evaluate the candidate's potential for attaining a competitive product profile in an attractive market with a reasonable COST OF GOODS SOLD (COGS). Part rigorous analysis and part crystal-ball gazing, market analysis involves three key elements: developing a detailed understanding of the current market; predicting what the market will look like when the repositioning candidate launches; and asking whether the market is large and growing rapidly, and/or whether it will support premium pricing.

Once a competitive product profile in an attractive market is identified, it must then be evaluated against the candidate's known PHARMACODYNAMIC, PHARMACOKINETIC and safety profiles. It is also important to understand what the candidate's potential COGS might be. Has production already been scaled to multi-kilogram levels? If not, does its current synthetic route involve a reasonable number of steps? Can its drug substance be formulated into drug product in a way that allows for attractive delivery and release characteristics?

The due diligence process can be one of the most challenging steps in the repositioning process, because it is almost impossible to gain a complete understanding of these issues; this can be because the data were never

Table 1 | **Repositioned antidepressant drugs**

Generic (MOA)	Original indication (trade name; originator)	New indication (trade name; repositioner)	Comments
Bupropion (enhancement of noradrenaline function)	Depression (Wellbutrin; GlaxoSmithKline)	Smoking cessation (Zyban; GlaxoSmithKline)	Approved as Wellbutrin for depression in 1996 (REF. 39) and as Zyban for smoking cessation in 1997 (REF. 39). Worldwide sales in 2003 for Wellbutrin were US $1.56 billion and US $125 million for Zyban[41].
Dapoxetine (SSRI)	Analgesia and depression (N/A; Eli Lilly)	Premature ejaculation (N/A; Johnson & Johnson)	Currently in Phase III. If approved, it would be the first approved agent for premature ejaculation. Peak sales are projected to reach US $750 million[42].
Duloxetine (NSRI)	Depression (Cymbalta; Eli Lilly)	Stress urinary incontinence (Duloxetine SUI; Eli Lilly)	Simultaneously in development for depression and SUI. Projected worldwide peak sales are US $800 million in SUI and US $1.2 billion in depression[43].
Fluoxetine (SSRI)	Depression (Prozac; Eli Lilly)	Premenstrual dysphoria (Sarafem; Eli Lilly)	Approved 6 July 2000 in the United States for use in premenstrual dysphoric disorder[44]. Sold in January 2003 to Galen, US $60 million of revenue reported by September 2003.
Milnacipran (NSRI)	Depression (Ixel; Pierre Fabre Médicament)	Fibromyalgia syndrome (N/A; Cypress Biosciences)	Marketed as Ixel for depression in Europe and Japan*; currently in Phase III trials‡.
Sibutramine (NSRI)	Depression (Sibut; Boots Company)	Obesity (Meridia; Abbott)	Bought in acquisition of Knoll Pharmaceuticals in 2001. Approved 24 November 1997 in the United States for the management of obesity.

*Source: Company news: deals. *BioCentury* 2 Feb 2004; available from http://www.biocentury.com. ‡Source: Edelson, S. Strategy: Cypress — the channel's the thing. *BioCentury* 12 Jan 2004; available from www.biocentury.com. MOA, mechanism of action; NSRI, non-selective serotonin-reuptake inhibitor; SSRI, selective serotonin-reuptake inhibitor; SUI, stress urinary incontinence.

collected, because the data that are available do not directly address issues specific to the new indication or because necessary data are not available in the public record. Indeed, if the availability of public data is limited, which is often the case, then the current or original developer of the compound must be approached to obtain the needed information. This can be a delicate process, to say the least. For older compounds, even if the data are available, it might not meet current regulatory standards.

Clinical development challenges

The reduced risks and development times associated with repositioning can sometimes come at a price. Success stories such as sildenafil occurred in therapeutic areas in which drug therapy was unavailable or inconvenient: no oral drug had even been tested for erectile dysfunction. In the case of duloxetine, SUI was not thought to be treatable with drug. For dapoxetine, premature ejaculation was not widely recognized as a medical disorder. What makes the development path for such indications challenging is that they require novel designs for clinical trials. For example, criteria for patient inclusion in trials of premature ejaculation needed to define a maximal time to ejaculation as an entry criterion, even though the Diagnostic and Statistical Manual IV does not stipulate ejaculation time in its definition of a time limit. In addition, it was important to ensure that a single partner was maintained throughout the duration of the study to prevent partner-induced changes in ejaculatory latency. Novel study endpoints and efficacy measures must also be developed. In the case of duloxetine for SUI, dapoxetine for premature ejaculation and sildenafil for erectile dysfunction, it was necessary to develop psychometric instruments to measure patient-perceived benefit; that is, the Incontinence Quality of Life[12], the Premature Ejaculation Questionnaire[27], and the International Index of Erectile Function[28], respectively. Without these measures, it is difficult to determine, for example, whether a 50% reduction in incontinence episodes or a 2-minute delay in ejaculation is meaningful to the patient.

In addition, the reduced risk offered by well-known safety and pharmacokinetic profiles of the repositioning candidates can be offset by the lack of a clinically validated mechanism of action. Furthermore, even basic data on toxicology or pharmacokinetics that were collected for the repositioning candidate in the original indication might be unacceptable due to the changes in regulatory standards. However, such pioneering efforts can pay off handsomely: achieving first-in-class status can allow for a significant head start on the competition, as exemplified by the roughly five-year head start that Pfizer's sildenafil had on Lilly and ICOS's tadalafil (Cialis) and GlaxoSmithKline and Bayer's vardenafil (Levitra).

There have also been instances in which the timing of regulatory review of the original and repositioned indications overlap. Needless to say, such circumstances can cause headaches for both the developers and regulatory agencies. As an example, duloxetine's NEW DRUG APPLICATIONS for depression and SUI were filed within about a year of each other with different sections of the FDA. Typically, if the same drug is being considered by two different sections, the FDA creates an 'oversight committee' to coordinate the two. However, in this case, the vastly different responses coming from the two sets of FDA reviewers posed a significant challenge for Lilly[29].

IP issues particular to repositioning

Both blessings and unique challenges surround IP issues associated with repositioning. On the plus side, new IP in the repositioned indication can create substantial value for the repositioner, particularly if the candidate has never received marketing approval. However, because the candidate is usually not new to the scientific

NEW DRUG APPLICATION (NDA). An application to the US FDA to market a new drug in the United States that contains data gathered during the animal studies, human clinical trials of an Investigational New Drug (IND) and also data on chemistry, manufacturing and controls (CMC). Every new drug since 1938 has been the subject of an approved NDA before US commercialization.

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