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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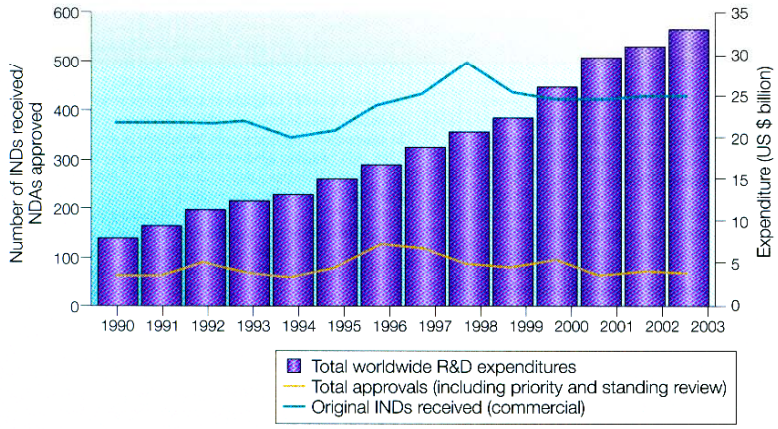

Figure 1 | **The growing productivity gap in the biopharmaceutical industry.** Despite enormous increases in spending in novel technologies over the last several years, R&D productivity has actually decreased since the mid-1990s, as measured either by the number of new drugs approved per dollar spent 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.

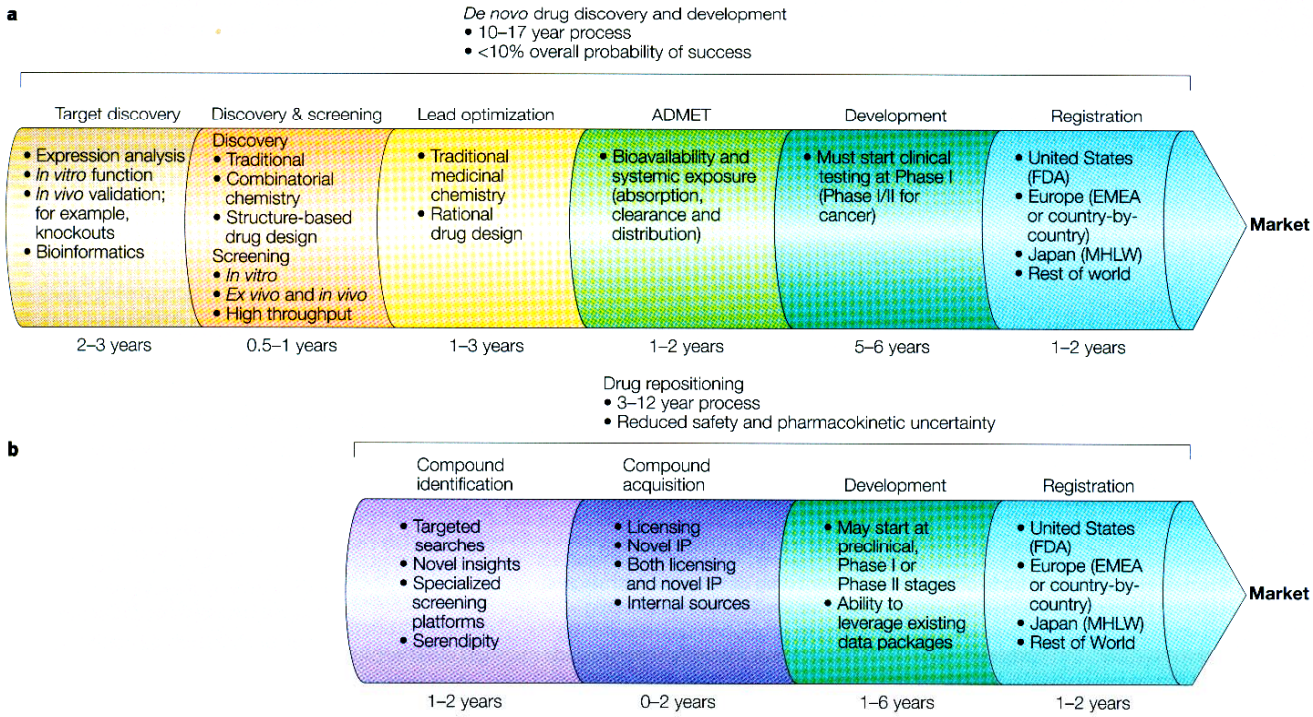

Figure 2 | **A comparison of traditional *de novo* drug discovery and development versus drug repositioning. a** | It is well known that *de novo* drug discovery and development is a 10–17 year process from idea to marketed drug[72]. The probability of success is lower than 10%[37]. **b** | Drug repositioning 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.

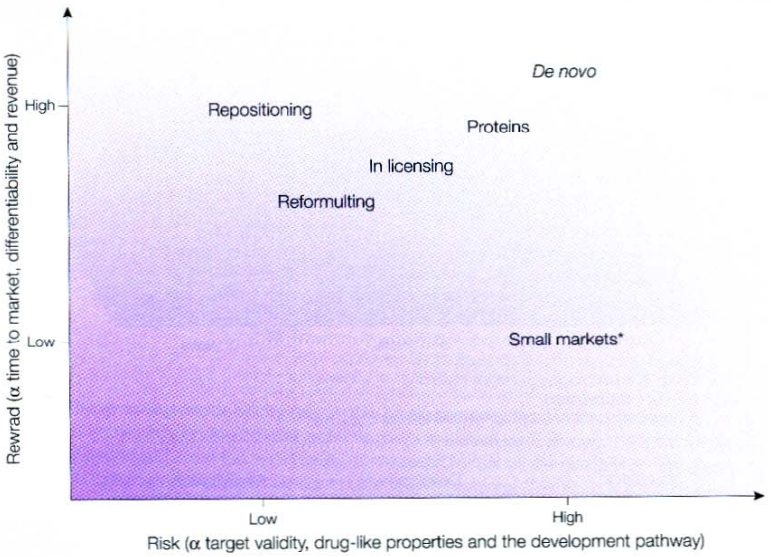

Figure 3 | **The risk-versus-reward trade off between different drug development strategies.** Drug repositioning offers one of the best risk-versus-reward trade-off of the available drug development strategies. It can offer lower risk than in-licensing strategies because repositioning candidates have 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.

Table 2 | **Repositioned neurological drugs (not including anti-depressants)**

Generic (MOA)	Original indication (trade name; originator)	New indication (trade name; repositioner)	Comments
Atomoxetine (NSRI)	Parkinson's disease (N/A; Eli Lilly)	ADHD (Strattera; Eli Lilly)	Approved by FDA in 2002 for ADHD[44]. Reached US $370 million in sales in 2003 (REF. 45), is projected to achieve US $1.15 billion annually by 2007 (REF. 43).
Chlorpromazine (dopamine receptor blockade[46])	Anti-emetic/antihistamine (Thorazine; Rhone-Poulenc)	Non-sedating tranquillizer (Thorazine; SmithKline)	Originally marketed as a general sedative and anti-emetic agent. After Paris surgeon Heri Laborit observed in 1952 that it had a tranquilizing effect, SmithKline marketed it for that indication and it became a standard element of psychiatric care, used to treat 50 million patients during the next 12 years*.
Galantamine (acetylcholinesterase inhibition)	Polio, paralysis and anaesthesia (Nivalin; Sopharma)	Alzheimer's disease (Reminyl; Johnson & Johnson)	Originally marketed in 1960s (REF. 47) and now approved in many countries for mild to moderate Alzheimer's disease[48].
Lidocaine (sodium channel blockade)	Local anaesthesia (Xilocaine; AstraZeneca)	Oral corticosteroid-dependent asthma (N/A; Corus Pharma)	Corus is reformulating lidocaine for use as inhalation treatment for oral corticosteroid-dependent asthma. This programme, known as Corus-1030, is in Phase II trials in the United States and Europe[‡,§]. In a non-trial setting at Mayo Clinic over four years, inhaled lidocaine was well tolerated, all but one patient continued treatment, and 47 out of 49 patients were able to stop corticosteriod use[49].
Ropinirole (dopamine-2 agonism)	Hypertension (N/A; SmithKline Beecham)	Parkinson's disease and idiopathic restless leg syndrome (Requip and Zepreve; GlaxoSmithKline)	Marketed for Parkinson's disease since 1997; currently in Phase III for idiopathic restless leg syndrome. Worldwide sales reached US $162 million in 2003.
Tofisopam (unclear)	Anxiety-related conditions (Grandaxin & Seriel; EGIS Pharmaceuticals)	Irritable bowel syndrome (N/A; Vela Pharmaceuticals)	Racemic tofisopam has been sold for over two decades in Europe and Asia for anxiety disorders. A Phase II trial in irritable bowel syndrome began in June with the R-enantiomer (dextofisopam)[50].

*WGBH. *A Science Odyssey: People and Discoveries*; website of the television programme (http://www.pbs.org/wgbh/aso/thenandnow/humbeh.html) accessed 19 Apr 2004. ‡Source: Clinical news: clinical status. 5 May 2003; available from www.biocentury.com. §Source: Clinical news: clinical status. *BioCentury* 22 Dec 2003; available from www.biocentury.com. ADHD, attention-deficit hyperactivity disorder; MOA, mechanism of action; NSRI, non-selective serotonin-reuptake inhibitor.

community, prior art might exist that can render a repositioning idea unpatentable. For similar reasons, pre-existing patents might also exist that could impede commercialization of the repositioned drug.

The process of defending repositioned drugs against competitors can be particularly challenging, even more than is the case with *de novo* drug discovery and development. Two general cases must be considered: either the COMPOSITION-OF-MATTER (COM) IP on the compound of interest is held by another party; or the compound is off-patent and therefore generic. In the former case, a deal must be struck to license or acquire that IP, and there are several strategies for dealing with the latter case.

If the repositioning candidate is off-patent, then the repositioner can rely on novel MOU protection or simply a 'use' patent to provide substantial barriers to entry if the drug has never been marketed. For example, many repositioned drugs are either on the market (for example, atomoxetine (Strattera; Eli Lilly)) or are in development (for example, duloxetine, dapoxetine and milnacipran (TABLE 1)) that rely or plan to rely on MOU patents for protection because their COM patents have expired or are close to expiring.

In addition, companies can invent new formulations, dosage forms, drug combinations or geographic strategies that create new barriers to entry. Still other companies, such as Sepracor, Sention and Vela Pharma, are developing isometrically pure enantiomers with fewer side effects or better efficacy than the corresponding racemic mixtures. New dosage forms can themselves be a source of new IP, as in the case of Propecia, Merck's drug for hair loss. In addition, companies developing drugs in combination might be able to obtain new COM IP. This is the development strategy that CombinatoRx is pursuing and the one that Dynogen used to create DDP200, which is being developed for overactive bladder. Finally, obtaining exclusive marketing approval in new geographic markets can also be effective in keeping out competition. For instance, in the United States, drugs can rely on six-month, three-, five- or seven-year marketing exclusivity awarded under 21 U.S.C. § 505(b)(2) for FDA approval of a new indication in a paediatric population[30], for a known compound for a new indication[31], a new chemical entity[32], or in a orphan population[33], respectively.

COMPOSITION-OF-MATTER PATENT (COM). A patent containing one or more claims directed to a composition of matter or product per se, such as a small molecule, protein, nucleic acid or particular formulation of an agent.

Potential intra-organizational hurdles

A repositioning programme must endure the same intra-organizational Darwinian struggle that every development programme endures for access to corporate resources. For an internal repositioning candidate to enter development, it not only has to clear the typical development 'fitness' hurdles, but it might also have to compete against itself. For example, a repositioning programme using a previously discontinued internal compound might encounter resistance from those who were involved in discontinuing the drug's initial programme. Furthermore, an additional indication can trigger concern on the part of the of the original development team regarding resource allocation, safety, pricing differences and patient perceptions. An example of the latter would be a concern about taking duloxetine, a psychiatric medicine, for an incontinence problem, and vice versa.

Table 3 | **Repositioned non-neurological drugs**

Generic (MOA)	Original indication (trade name; originator)	New indication (trade name; repositioner)	Comments
Celecoxib (cyclooxygenase-2 inhibition)	Osteoarthritis and adult rheumatoid arthritis (Celebrex; Pfizer)	Familial adenomatous polyposis, colon and breast cancer (Celebrex; Pfizer)	Currently in Phase II trials for prevention of colon and breast cancer[43]. Pfizer intends to also test celecoxib for use in Barrett's oesophagus, actinic keratosis, bladder cancer and ankylosing spondylitis[51].
Eflornithine (ornithine decarboxylase inhibition)	Anti-infective (N/A; Bristol-Myers Squibb)	Reduction of unwanted facial hair in women (Vaniqa; Women First HealthCare)	Originally developed for use against West African trypanosomiasis[52] and also explored for antitumour effects[53].
Finasteride (5-α-reductase inhibition)	Benign prostatic hyperplasia (Proscar; Merck)	Hair loss (Propecia; Merck)	Originally approved for the treatment of enlarged prostate in 1992, Propecia (with a fivefold lower dose), approved in 1997 for the treatment of hair loss[54], had worldwide sales of US $239 million in 2003 (REF. 55).
Mecamylamine (nicotinic receptor antagonism)	Moderately severe to severe essential hypertension and uncomplicated cases of malignant hypertension (Inversine; Layton BioScience)	ADHD (N/A; Targacept)	Inversine was originally launched in the 1950s, and was one of the first orally active antihypertensives on the US market. It is currently used off label for Tourette syndrome and Targacept has a low-dose version of mecamylamine undergoing Phase II testing for ADHD.
Mifepristone (RU486) (glucocorticoid receptor type II antagonism)	Pregnancy termination (Mifeprex; Danco Laboratories)	Psychotic major depression (Corlux; Corcept)	Mifepristone was first synthesized in 1980 at Roussel-Uclaf in France as an oral abortifacient. First approved in France in 1988, it was only approved in the United States in 2000 (REF. 73). It has been used experimentally in cancer (for example, meningioma), endometriosis and Cushing syndrome. Corlux has been fast-tracked by the US FDA as a treatment for psychotic major depression. It is now in Phase III clinical testing and is also being considered for bipolar depression.
Minoxidil (β-adrenoceptor blockade)	Hypertension (N/A; Pharmacia & Upjohn)	Hair loss (Rogaine; Pharmacia & Upjohn (now Pfizer))	Originally developed for hypertension[56]; repositioned for both male pattern baldness and erectile dysfunction[57]. Rogaine was approved in 1998 for the treatment of hair loss[58] and had worldwide sales of US $162 million in 1996 (REF. 59).
Paclitaxel (disrupts normal microtubule dynamics by promoting the polymerization of tubulin)	Cancer (Taxol; National Cancer Institute/ Bristol-Myers Squibb)	Restenosis (TAXUS Express; Angiotech/ Boston Scientific)	The US FDA approved the TAXUS system on 4 March 2004 (REF. 60). Preliminary worldwide net sales during the first quarter were approximately US $216 million[61].
Phentolamine (α-adrenoceptor antagonism)	Hypertension (Regitine; Novartis)	Impaired night vision (Nyxol; Ocularis Pharma)	Phentolamine is used for the short-term control of hypertension in patients with pheochromocytomas. When delivered intraocularly, phentolamine inhibits pupil dilation, an action that might allow it to be used for the treatment of impaired night vision, which can occur following LASIK surgery[62].
Raloxifene (SERM)	Breast and prostate cancer (Evista; Eli Lilly)	Osteoporosis (Evista; Eli Lilly)	Revenue of US $922 million in osteoporosis in 2003 (REF. 63), with US $1.5 billion in annual revenue projected by 2007 (REF. 43).
Sildenafil (PDE5 inhibition)	Angina (N/A; Pfizer)	Male erectile dysfunction (Viagra; Pfizer)	Viagra, the first approved drug for male erectile dysfunction, achieved worldwide sales of US $1.88 billion in 2003 (REF. 51).
Tadalafil (PDE5 inhibition)	Inflammation and cardiovascular disease (N/A; GlaxoSmithKline)	Male erectile dysfunction (Cialis; Eli Lilly & ICOS)	Tadalafil transferred to ICOS after GSK did not see any potential in the initial indication areas[62]. L aunched in August, 2003. Sales in 2003 reached US $203.3 million[64].
Thalidomide (TNF-α inhibition)	Sedation, nausea and insomnia (Contergan; Chemie Grunenthal)	Cutaneous manifestations of moderate to severe erythema nodosum leprosum in leprosy and multiple myeloma (Thalomid; Celgene)	Approval by the US FDA in 1998 for cutaneous manifestations of erythema nodosum leprosum in leprosy[65]. It is now widely used to treat multiple myeloma and Celgene is now seeking US FDA approval for this indication. Thalomid sales reached US $224 million in 2003 (REF. 66).
Topiramate (state-dependent Na channel blockade, GABA stimulation and kainate/ AMPA antagonism*)	Epilepsy (Topamax; Johnson & Johnson)	Obesity (N/A; Johnson & Johnson)	Johnson & Johnson noticed that Topamax caused weight loss in overweight drug recipients. However, the side-effect profile was unacceptable using the initial formulation*. TransForm Pharmaceuticals received an approvable letter for a novel crystalline form of Topamax in late 2003‡, then signed a licensing agreement with J&J[62].
Zidovudine (reverse-transcriptase inhibition)	Cancer (N/A; Burroughs Wellcome)	HIV/AIDS (AZT/Retrovir; GSK)	Originally developed in 1964 in oncology and was found, in 1985 to be a potent drug for AIDS§. Became the first drug approved for treatment of HIV in 1987. Worldwide sales of US $100 million in 2003.

*Source: Maggos, C. Product development: formulation fix for Topamax. *BioCentury* 11 Feb 2002; ; available from www.biocentury.com. ‡Source: Company news: regulatory Johnson & Johnson. *BioCentury* 25 Nov 2003; available from www.biocentury.com. §Source: AIDS Healthcare Foundation versus GlaxoSmithKline PLC *et al.* No. 02-5223 TJH (http://www.aidshealth.org/newsroom/news/news_archive/N110702A.htm). ADHD, attention-deficit hyperactivity disorder; AIDS, acquired immune deficiency syndrome; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; GABA, γ-aminobutyric acid; GSK, GlaxoSmithKline; HIV, human immunodeficiency virus; MOA, mechanism of action; PDE, phosphodiesterase; SERM, selective oestrogen receptor modulator; TNF, tumour-necrosis factor.

Table 4 | **Biopharmaceutical companies repositioning drugs for neurological disorders**

Company (location)	Therapeutic focus	Approach	Comments
Cypress Bioscience, Inc. (San Diego, California)	Functional somatic syndromes and pain	Leverages expertise in the pathophysiology underlying functional somatic syndromes and their diagnoses and also animal models of fibromyalgia syndrome*.	Milnacipran, an antidepressant licensed from Pierre Fabre that is on the market for depression in Europe and Japan as Ixel, is in Phase III for fibromyalgia syndrome[67].
Dynogen Pharmaceuticals, Inc. (Boston, Massachusetts and Durham, North Carolina)	Genitourinary and gastrointestinal disorders	Leverages its knowledge of the nexus between neurology and genitourinary and gastrointestinal disorders, as well as its predictive pharmacology models to make informed decisions on potential research and development candidates‡.	DDP200, a proprietary combination of two generic neurological drugs which show statistically significant synergy in two *in vivo* models of overactive bladder, will be starting Phase IIa trials in overactive bladder in 2H:04. Dynogen has filed an IND application with the US FDA in 2004 for DDP225, a clinical stage antidepressant licensed from Mitsubishi Pharma Corporation which Dynogen is repositioning for diarrhoea-predominant IBS.
Sention, Inc. (Providence, Rhode Island)	Memory impairment and other CNS disorders	Applies a whole-animal assay system that identifies genes and proteins involved in memory consolidation and then identifies known drugs which modulate these targets[69].	C105, a stereoisomer of a known drug for a non-cognition related therapeutic indication, has received an Orphan Drug designation for a memory-related condition and is currently in Phase II. SN104, a proprietary component of a currently approved drug, has completed Phase I trials for attention deficit disorder[68].
Vela Pharmaceuticals, Inc. (Lawrenceville, New Jersey)	IBS, fibromyalgia, anxiety, menopausal symptoms	'Rediscovers' drugs by re-formulating de-prioritized compounds, seeking expanded geographic approval for drugs with limited distribution and exploring possible uses across multiple therapeutic areas§.	Dextofisopam, the R enantiomer of tofisopam, which has been sold in Europe and Asia for over two decades for anxiety-related conditions, is in Phase II for irritable bowel syndrome. Low-dose cyclobenzaprine has completed Phase II clinical trials for fibromyalgia syndrome. S-tofisopam, the S-enantiomer of tofisopam, is in Phase I for a variety of symptoms associated with menopause‖.

*Source: Company web site: www.dynogen.com; accessed 15 Feb 2004. ‡Source: Company web site: www.cypressbio.com; accessed 15 Feb 2004. §Source: Company web site: www.velapharm.com; accessed 13 Feb 2004. CNS, central nervous system; IBS, irritable bowel syndrome; IND, Investigational New Drug.

It is not necessarily easier when a drug comes in from outside. Here the inevitable conflict of judgment between internal and external candidates can be encountered[9], which are often driven by biases against any drug 'not invented here'.

Again, we can use the duloxetine experience as case in point. When one of us (K.B.T.) originally proposed that an agent with duloxetine's mechanism of action could be useful for the treatment of SUI, it was met with a high degree of scepticism. Specifically, there were many, both inside and outside of Lilly, who felt that SUI could not be treated with a drug because SUI resulted from an anatomical defect. However, during the course of seven years, sceptics were converted into advocates as further data supporting the use of duloxetine in SUI became available and a development path for SUI became more clearly defined.

Finally, the new indications of repositioned drugs are often ones that have been overlooked in the past. If this is the case, then there might not be a lot of familiarity with the new indication and there might even be disbelief, either within the organization or the medical community at large, that the reposition indication will actually be addressing a disease or that the mechanism of action of the repositioning candidate represents a viable approach to treating it. However, history shows that such challenges can be overcome, as exemplified by drugs successfully repositioned for what were once overlooked or unrecognized diseases; these include attention-deficit hyperactivity disorder, fibromyalgia syndrome, hair loss, irritable bowel syndrome, male erectile dysfunction and premenstrual dysphoric disorder (TABLES 1–3).

Gaining access to repositioning candidates

Even after overcoming all of the above obstacles, gaining access to the repositioning candidate's patent estate and data package might at best be challenging and at worst impossible. Only a few pharmaceutical companies will even consider out-licensing their discontinued programmes. Within big pharma, only Eli Lilly and GlaxoSmithKline have dedicated out-licensing efforts, with Lilly having out-licensed more than fifty compounds in the past six years[34] and GlaxoSmithKline using its discontinued programmes as a 'currency' for making venture capital-like investments in biotech companies[35].

Big pharma companies that do not actively out-license discontinued programmes cite long lists of reasons why they take this position: "It is expensive to gather all of the required data"; "it is better for the organization to direct all of its resources towards internal efforts"; "people usually do not get promoted for getting rid of compounds"; "no one wants to be responsible for out-licensing a blockbuster"; "the Company is concerned about liability issues". Clearly these are real issues. Indeed, in our experience, some pharmaceutical companies will not even pull the paperwork for a compound unless the initial licensing fee will be US $1 million or more. But there are many strategies for managing these concerns, such as including 'buy back' options in the licensing deal and applying accounting methods that involve placing discontinued compounds to a non-basis asset pool and capitalizing the associated expenses[34]. In the end, good relationships between those seeking to license in a compound and their counterparts at the pharmaceutical company they approach often make the difference between success and failure[9].

Biotech approaches to repositioning

Repositioning stories have historically not been an area of great interest to venture capitalists, but they are now becoming increasingly attractive opportunities as therapeutics companies of all sizes, from start-ups backed by venture capitalists to publicly traded pharmaceutical and biotech companies, are now in favour of adopting this approach (TABLES 4,5). In addition, venture investors have lately become disenchanted by the long time lines and high development costs associated with *de novo* discovery and development. Indeed, development time lines have improved only slightly[36] and costs have risen dramatically[37], despite promising technological innovations in combinatorial chemistry, HTS and genomics. Furthermore, people are the stock in trade of venture capital start-ups as much as products. Cherry picking of excellent people from large pharmas has become easier as merger and acquisition activity in the industry has picked up. The same type of executive who would work well in a pharmaceutical company can also be an excellent candidate for a repositioning effort.

Venture-backed start-ups applying repositioning strategies can be classified as those repositioning drugs for either neurological or non-neurological disorders and those using a technology platform or relying on expertise within a particular therapeutic area to make decisions on repositioning opportunities (TABLES 4,5). An example of a technology-based start-up is CombinatoRx, which uses HTS and other technologies to discover proprietary combinations of known compounds with novel therapeutic activity (TABLE 5). Companies focused on specific therapeutic areas, such as Cypress Biosciences and Sention (TABLE 4), use their extensive knowledge in particular diseases to be more opportunistic than pharmaceutical companies and claim rights to molecules that others would not expect to be active in the new indications. Sosei and Dynogen do not fall neatly into either of these categories. Sosei acquires molecules from the Japanese pharmacopoeia and Japanese pharma companies that have proven safe, and then makes them available for screening by companies interested in repositioning (BOX 1). Dynogen is using a hybrid repositioning strategy as one way to build its pipeline. This strategy uses a technology involving predictive pharmacological models of genitourinary and gastrointestinal disorders coupled with a deep understanding of the neuro-pathophysiology of, and clinical development challenges associated with, these disorders.

Simplistically viewed, the advantage of being a technology-based company is the greater likelihood of making discoveries that can be protected with patent claims. The disadvantage lies in the longer development times and increased costs of developing these new products from the beginning. The advantage of the indication-focused approach, by contrast, is that it has the potential to move the compounds very quickly through clinical trials on the basis of previously collected data. However, these approaches sometimes lack the ability to generate data able to support patent claims. Hybrid approaches can enjoy the best of both worlds, building on their indication-based repositioning successes to

Table 5 | **Biopharmaceutical companies repositioning drugs for non-neurological disorders**

Company (location)	Therapeutic focus	Approach	Comments
BioMedicines, Inc. (Emoryville, California)	Oncology and hepatitis	'Redirected development' of compounds bought or licensed from pharmaceutical companies*. Biomed 777/ Atamestane, acquired from Schering AG in 1999, is in Phase III for breast cancer.	Biomed 101, a cytokine inhibitor acquired from Searle in 1997, and Biomed 510, an omega interferon recombinant protein acquired from Boehringer Ingelheim in 1998, are in Phase I for renal cell carcinoma and hepatitis C, respectively. Collaborations with ALZA and Nobex[69].
Bionaut (Cambridge, Massachusetts)	Cancer and inflammation	Leverages its Sentinel Pathway Reporter System which consists of a library of human cell lines that report the activity of specific disease-associated pathways.	Funded research programmes with Eli Lilly, AstraZeneca and Biogen.
ChemGenex Therapeutics Inc. (Menlo Park, California)	Oncology	Uses gene-expression analysis, cellular screening systems and computational medicinal informatics software to recognize chemical structures with unique attributes‡.	Quinamed, a synthetic–organic compound with demonstrated antitumour and anti-viral properties, has completed Phase I/II studies. Ceflatonin, a natural-product with demonstrated clinical activity against haematological malignancies, is in Phase II clinical trials for chronic myelogenous leukaemia and myelodysplastic syndrome, and expects to begin trials in acute myeloid leukaemia this year[70,71].
CombinatoRx, Inc. (Boston, Massachusetts)	Oncology, inflammation, respiratory, metabolic and infectious diseases	Leverages a high-throughput combination screening system in conjunction with cell-based phenotypic assays to identify combinations of existing compounds able attack multiple disease pathways§.	CRx-026, a sedative and antibiotic combination product, is in Phase I/II for cancer. CRx-119 and CRx-139, low-dose steroids plus 'enhancer' molecule, is in Phase I for rheumatoid arthritis‖. Research collaborations with Sosei and DanioLabs¶.
Sosei Co., Ltd. (Tokyo, Japan)	Multiple	Uses an extensive network of biotech collaborations to discover new applications for a library of pre-commercialization stage compounds licensed from various Japanese pharma companies#.	SOU-001 originally failed efficacy standards in Phase II or a cardiovascular-related disease is in Phase I for in urinary incontinence. Several collaborations with Western biotechnology companies where each company is applying its own proprietary technology to Sosei's library**.

*Source: Company web site: www.biomedicinesinc.com; accessed 15 Feb 2004. ‡Source: Company web site: www.chemgenex.com; accessed 15 Feb 2004. §Source: Company web site: www.combinatorx.com; accessed 15 Feb 2004. ‖Source: Calkins, K. Emerging company profile: CombinatoRx: the art of the nonobvious. *BioCentury* 25 Nov 2003; available from www.biocentury.com. ¶Source: Company news: deals. *BioCentury* 20 Oct 2003; available from www.biocentury.com. #Source: Company web site: www.sosei.com; accessed 13 Feb 2004. **Source: Company web site: www.sosei.com; accessed 13 Feb 2004.

Box 1 | **Sosei's novel reposition strategy**

Founded in 1990, Sosei Co. Ltd. is meeting the enormous demand for repositioning candidates by sourcing the Japanese pharmacopoeia. As of late 2003, Sosei had obtained non-Japanese rights to more than 2,000 compounds already marketed in Japan and an additional 50 unmarketed compounds out of Japanese pharmaceutical companies that are thought to be drug candidates[38]. These compounds form the basis for no fewer than 17 collaborations with US and European biotech companies. At the outset, these collaborations are non-exclusive — each partner can screen the entire library for hits in their indication of choice — but exclusivity is assigned on a first-come, first-served basis. At the same time, Sosei in-licenses compounds from outside of Japan and markets them in its home market. Finally, Sosei has used its own drug development expertise to reposition SOU-001, a drug that had reached Phase II trials in a cardiovascular indication but was repositioned by Sosei and taken through pivotal trials in stress urinary incontinence. Part out-licenser, part in-licenser and part drug developer, Sosei has found favour with investors, raising more than US $27 million in its history from both international and Japanese venture capital groups. The company filed for an Initial Public Offering on the Tokyo Stock Exchange in June, 2004.

generate the revenue needed to develop early-stage compounds that take advantage of their technological expertise. However, the number of opportunities for hybrid approaches might be limited.

A question of venue

As we have seen, repositioning is an increasingly popular strategy in both biotech and pharmaceutical companies. But which venue — pharma or biotech — is the most appropriate for repositioning? We believe that the answer is self-evident: pharmaceutical companies might own most of the raw material for repositioned drugs, but the initiative and insight to screen them for novel uses usually comes from biotech companies. Furthermore, like regulatory agencies, pharmaceutical companies have not traditionally been organized along lines conducive to repositioning.

By contrast, biotech companies would seem to possess the ideal combination of incentives to pursue new indications for existing drugs given their level of entrepreneurship, motivation (succeed or die) and institutional flexibility. In the short-term, then, biotech is the place to look for the fastest-moving repositioning stories.

In the long term, repositioning in biotech could become a mergers-and-acquisitions game. Given that pharmaceutical companies are gobbling each other up, as well as acquiring product-oriented biotech companies, to fill their yawning productivity gap, the best biotech repositioning efforts are likely to be attractive takeover targets. The benefit is likely to become even more pronounced once the biotech-based repositioning model has been validated by some approvals. Pharma companies might find it more efficient and lucrative to own the repositioning engine rather than sharing rights and royalties. It is easy to imagine each of the remaining five or ten big pharma companies having its own in-house repositioning effort driven by a former biotech company it has acquired.

Conclusions

During the past several years, there has been a surge of interest in repositioning. Both pharmaceutical and biotech companies have recognized the advantages of repositioning, and activity in the area has increased dramatically. There are a number of examples in which serendipity or directed efforts have led to successful launches in new indications. The strategy is economically attractive when compared with the cost of drug development based on *de novo* drug discovery and development. Unique challenges are associated with repositioning strategies, which demand creative approaches and great dedication on the part of drug repositioners inside and outside pharmaceutical companies. Institutional bias often militates against developing a drug in a new indication in the same pharmaceutical company in which the drug was developed for the initial indication. But for those outside of big pharma, the challenge is equally great. Without a sense of trust based on a long-term relationship, pharmaceutical executives could be reluctant to make the deals with outside companies that are required to create out-licensing opportunities.

The current boom in repositioning raises an existential question about the approach: when the obvious candidates for repositioning have been exhausted, will anything be left to reposition? Fortunately, the number of potential indications for repositioned drugs exceeds the current screening capacity of most companies. Although the boom will consume the most obvious candidates, it is likely that repositioning opportunities will continue to present themselves, albeit possibly at a lower rate. Those companies that have sufficient biological and technological expertise should be able to develop early-stage discovery compounds to fill their pipelines while still taking advantage of repositioning strategies. The full potential of the existing pharmacopoeia will not be unleashed for a long time to come.

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Competing interests statement

The authors declare competing financial interests: see Web version for details.

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