

■ PART I

**DRUG REPOSITIONING: BUSINESS
CASE, STRATEGIES, AND
OPERATIONAL CONSIDERATIONS**

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Drug Repositioning: The Business Case and Current Strategies to Repurpose Shelved Candidates and Marketed Drugs

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1.1. INTRODUCTION

Drug repositioning or “repurposing” has become one of the major sources for revenue growth within the pharmaceutical industry [1]. Repurposing encompasses everything from new indications for failed compounds to line extensions for existing drugs and is expected to generate up to \$20 billion in annual sales in 2012 [2]. This opportunity for revenue generation has led to an increase in companies such as Biovista, Melior, Marco Polo Pharma et al., consortia such as CTSA (<http://www.ctsapharmaportal.org>), and specialist units within major pharmaceutical companies that are dedicated to bringing new life to existing compounds, as well as summit meetings specifically designed on this topic [3].

It is easy to understand why repurposing drugs is so attractive since those that failed have been through much of the preclinical and some early human clinical trials and in many cases have been found to be safe. In general, drugs that have been approved for an indication have a greater likelihood of being safe in a new indication and different patient population. This increased knowledge of a drug shortens its development cycle relative to new molecular entities (NMEs¹), bringing significant savings and lower risk to the cost of development. In addition, the continually evolving knowledge of targets and

¹ NME: new molecular entity, which includes new chemical entity (NCE) and new biological entity (NBE).

pathways means that developing drugs for rare diseases or stratified populations of common diseases has become a more technically viable research and development (R&D) strategy.

This chapter will begin with a historic overview of why drugs fail and will explore the reasons for failures at each stage in the development paradigm, highlighting differences in success rates between therapeutic areas. Next, we will discuss how some of these failures led to the drugs that are on the market today. Finally, we will identify some of the common themes of repurposing failed—or “shelved” compounds—with the goal of highlighting some of the key learnings from these failures.

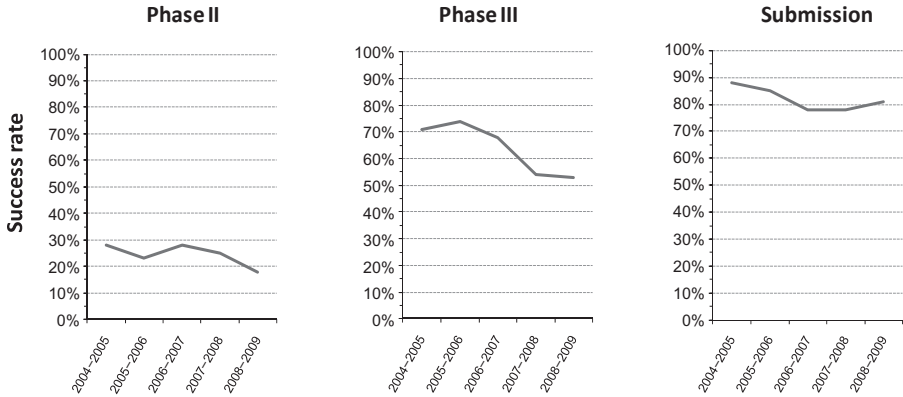
1.2. IS PHARMACEUTICAL R&D FAILING?

The only time you don't fail is the last time you try anything—and it works
—William Strong

Failure is a common problem in any research environment. Yet it is from these failures that many of the greatest successes are born. When Thomas Edison's experiments failed to produce a storage battery, he simply muttered, “I have just found 10,000 ways that won't work.” Failure is a fundamentally inherent property in the pharmaceutical research and development process. It is due to the difficult nature of the problems being solved that makes it so, and is not reflective of the work that goes into the process. Despite the working of some of the most creative scientific minds, most drug candidates fail. Statistically, after testing up to one million potential candidates, one is picked to enter clinical trials, and only 1 out of 20 compounds that enter into clinical trials goes on to be a marketed product [4, 5]. Put another way, 95% of new drug candidates entering human clinical trials fail. Furthermore, pharmaceutical research data [6] suggest that drug candidates are failing more often. As shown in Figure 1.1, the success rate for compounds progressing through clinical development from Phase II to Regulatory Submission actually decreased over the period from 2004 to 2009.

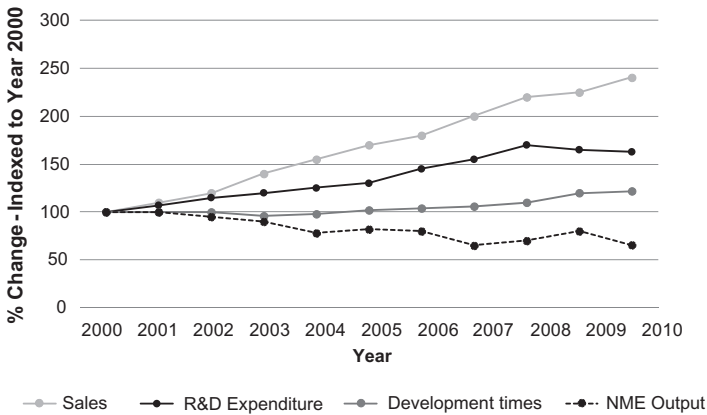
Success is not final, failure is not the end. It is the guts to carry on that counts.
—Winston Churchill

The pharmaceutical industry faces unprecedented challenges in its R&D productivity. Despite the continued increase in R&D investment up to 2008, with a slight flattening in 2009–2010, the number of NMEs approved globally per annum has fallen and cycle times for candidate development have risen [7] (Figure 1.2). The sales figures in Figure 1.2 would at first glance suggest a fairly optimistic future for R&D-based pharmaceutical companies; however the growth in sales of branded drugs is more than offset by patent expiry such that the majority of future sales growth comes from generic drugs and emerging



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FIGURE 1.1. Average success rates for compounds successfully advancing to the next phase of clinical trials for the years 2004 through 2009 for a cohort of 40 large and mid-sized pharmaceutical companies. *Source:* CMR International 2010 Global R&D Performance Metrics Programme. Reproduced with permission.



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FIGURE 1.2. The percent change in pharmaceutical investment in R&D, drug development times, and global NME output over a 10-year period indexed to 2000 for a cohort of 40 large and mid-sized pharmaceutical companies. *Source:* CMR International 2011 Pharmaceutical Fact Book [7]. Reproduced with permission.

markets. Generic sales are expected to be worth \$400 billion by 2015. The shift from branded to generic drugs has a major negative impact on the profitability of traditional pharmaceutical companies [8].

Despite the steady increase in pharmaceutical R&D budgets over the last ~15 years, the number of new drug applications (NDAs) approved per annum

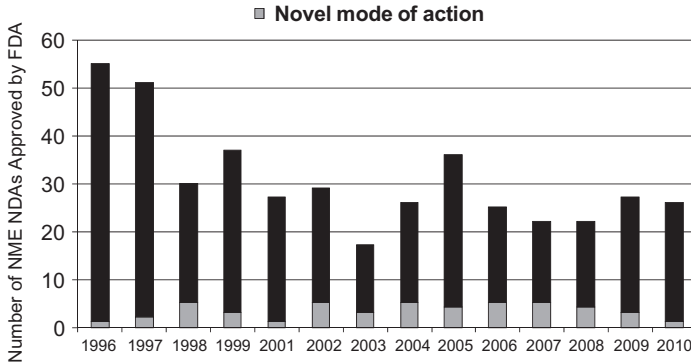


FIGURE 1.3. The number of NMEs approved in the United States by the FDA for the years 1996 to 2009 targeting a novel mode of action, and the total NMEs approved for a cohort of 40 large and mid-sized pharmaceutical companies. *Source:* Thomson Reuters Integrity database.

has remained reasonably constant (Figure 1.3). The only exception to this trend in output was in the period from 1995 to 1997 when output spiked to more than 50 NDAs per annum; the industry mistakenly thought that this was the dawn of a new and sustainably high output, but by 1998 output had fallen back to historic levels. Forecasts predict that the investment in R&D has no obvious signs of major decline [7], but the need to discover drugs to address unmet medical needs is even more urgent [9].

The consequences of the unchanging NDA output and the rise in R&D budgets results in an average cost per launch that has been estimated at as high as \$3 billion [10]. To add insult to injury, fewer approved drugs will recoup their R&D costs. Data from the Centre for Medicines Research (CMR) International [6] for the number of pharmaceutical projects at each stage of clinical development for the years 2002 through 2009 are shown in Figure 1.4. It can be seen from these data that despite a nearly 70% increase in the number of Phase II projects between 2002 and 2007, there has not been a commensurate rise in the number of Phase III starts or NDA submissions. Based on this analysis of attrition in early clinical development, the problem of stagnant NME output is unlikely to be reversed in the near term.

Many explanations are offered for this productivity decline, but in reality, it results from a combination of multiple factors. From a biological standpoint, “breakthrough” drugable targets are often elusive, particularly for complex multigenic diseases such as Alzheimer’s, cancer, and diabetes. There is also increased understanding of and attention to the safety risk–benefit profile of candidate therapeutics by the industry and regulatory authorities. Changes in strategic focus and cost reductions within corporate portfolios and ensuing reorganizations can halt entire therapeutic areas and delay progress in others. In addition, there is growing pressure from payers to reimburse only those new medicines that are clearly differentiated from existing standards of care,

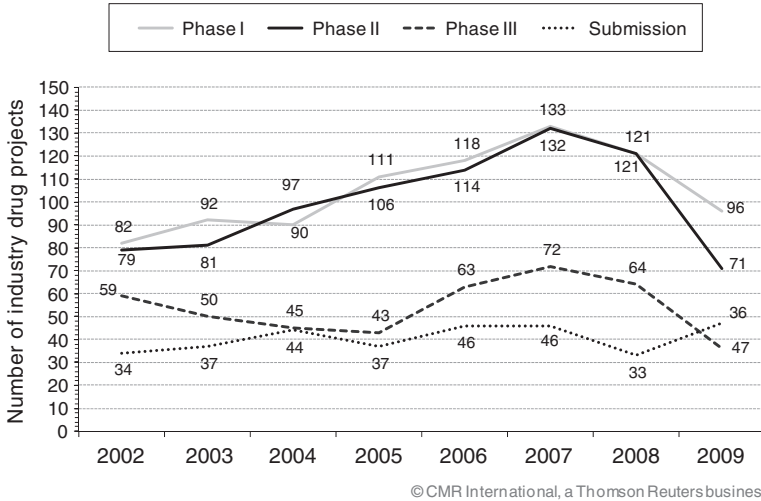


FIGURE 1.4. The number of NMEs entering each stage of clinical development from 2002 to 2009 for a cohort of 40 large and mid-sized pharmaceutical companies. *Source:* CMR International Global R&D Performance Metrics Programme. Reproduced with permission.

which themselves in many areas are increasingly dominated by lower cost generics as patents on branded medicines expire.

It is perhaps ironic that the current challenges are in part the result of past success. The pharmaceutical industry had a period of extraordinary growth in the mid-1990s, producing a far greater number of NDAs per year between 1995 and 1997 than ever before. In addition, a significant proportion of this cohort became blockbuster drugs, such as Lipitor®, Norvasc®, Zocor®, and Zoloft®. The underlying assumption at the time was that the discovery of new targets and new drugs was a “scalable commodity,” and to increase drug launches one simply needed to increase the number of compounds entering clinical trials. Thus, if it required 10 first-in-human (Phase I) starts to get one blockbuster drug then, according to this logic, 20 Phase I starts would produce two launches. What followed was a major increase in R&D spending and capacity, and in addition research groups within these companies began to be incentivized to produce more drug development candidates; the number of new drug candidates became a primary goal. This flawed basis for improved productivity was built around a “shots on goal” philosophy. Since the average research and development time for a new drug is nearly 12 years, it took a while for the industry to recognize that more early clinical programs per se was not resulting in the anticipated number of late stage programs and launches. The increased attrition of candidates in development and the flat NDA approval rates was not an aberration. It became apparent that pharmaceutical R&D productivity could not be enhanced solely by increasing the

number of candidates, but rather by producing quality candidates based on fundamental understanding of the human disease processes they are designed to affect. In this context, quality is defined in terms of appropriate toxicological, physicochemical, and pharmacological properties against a biological target(s) that has a validated role in causation of human disease/symptoms. Furthermore, a quality drug development program will evaluate such a drug candidate in well-defined patient populations in order to demonstrate that it is meaningfully superior to currently available therapies.

Declining productivity has been exacerbated by, or perhaps in part resulted from, the fact that few of the drugs launched over the last 10 years work via a new mode of action (Figure 1.3). The majority of new approvals are line extensions or “follow-on” compounds, including some that were not considered to be sufficiently differentiated from current therapies to receive reimbursement at a level that would make them commercially successful. Based on an analysis of Center for Drug Evaluation and Research NME Calendar Year Approvals [11], the number of NDAs approved for drugs that target unprecedented molecular mechanisms remains fairly steady at about 3–4 per annum. New regulatory hurdles now mandate that new drugs show superiority over existing therapies; the effectiveness of a drug (as measured in the United States) and the cost-effectiveness of a drug (as measured in the European Union) is the new standard for assessing drug value, further compounding the decline of drugs that are perceived to be only equal to or marginally more effective than currently available therapies. This greater need to differentiate from current therapy to enable reimbursement is driving the industry to a mantra of being “first and/or best in class” for each new drug candidate that it invests in. However in this regard, the concentration of research effort among companies working on the same mechanisms for the same or similar indications is a concern, since only a few of the drugs that come from this work will ever be approved and reimbursed. For example, according to an analysis by the authors in the Thomson Reuters Integrity database, 71 different organizations are listed as working beta-secretase as a drug target for Alzheimer’s disease. It is reasonable to assume that, at best, only a very small number of these efforts will result in a medically beneficial and commercially successful product; and even this is assuming that the target turns out to be a viable therapeutic approach.

In summary, new targets for the complex diseases that remain poorly served are elusive, as are the drugs to safely and effectively modulate their activity. Biological complexity and redundancy will likely mean that in many cases a single “magic bullet” will not be found. These factors have combined to contribute to the progressive decrease in drug candidate survival in most phases of development and along with it, the probability of success to market. To make matters worse, many of the blockbuster drugs launched in the 1990s reach the end of their period of exclusivity in the period from 2005 to 2013 and there are not enough new drugs of high value to replace these revenue streams for their innovators. Even the emergence of high cost per treatment

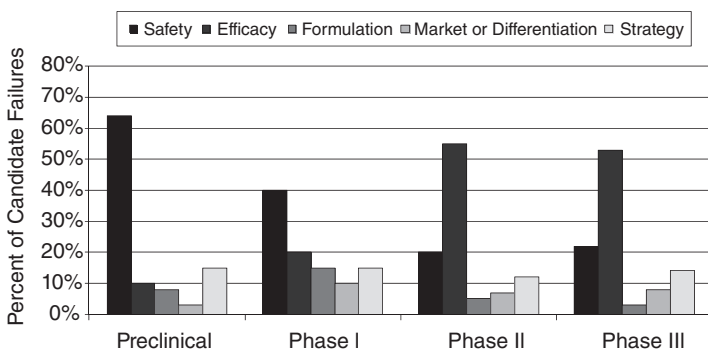
biologics is insufficient to bridge the revenue gap across the industry. The consequence of lower Pharma revenues, coupled with the higher cost of development, has led to reduction in R&D footprints, increased use of outsourcing, and a need to refill development pipelines using strategies such as company mergers and acquisitions, in-licensing, orphan drug approaches, and repurposing.

1.3. WHY ARE DRUGS FAILING?

Remember the two benefits of failure. First, if you do fail, you learn what isn't working and second, the failure provides you the possibility to try a new approach.

—Roger Von Oech

Data collected by Thomson Reuters have uncovered the reasons for failure from Phase I to submission over the last 6 years for a cohort of 20 pharmaceutical companies (Figure 1.5). The data highlight the fact that the causes of failure change during the course of development. Early in the process, compounds fail primarily for safety reasons. Compounds that successfully navigate Phase I increasingly drop out due to lack of efficacy in Phase II/III. As noted previously, this decrease in pharmaceutical industry productivity (as judged by the number of products approved per money invested) appears to have no obvious signs of an immediate upward inflection. Attrition is not just increasing in early development but also in Phase III and at the approval stage [12]. Despite being the most expensive phase of development, more than half of the compounds fail to move from Phase III to approval. Table 1.1 lists some of the more notable failures of 2009.



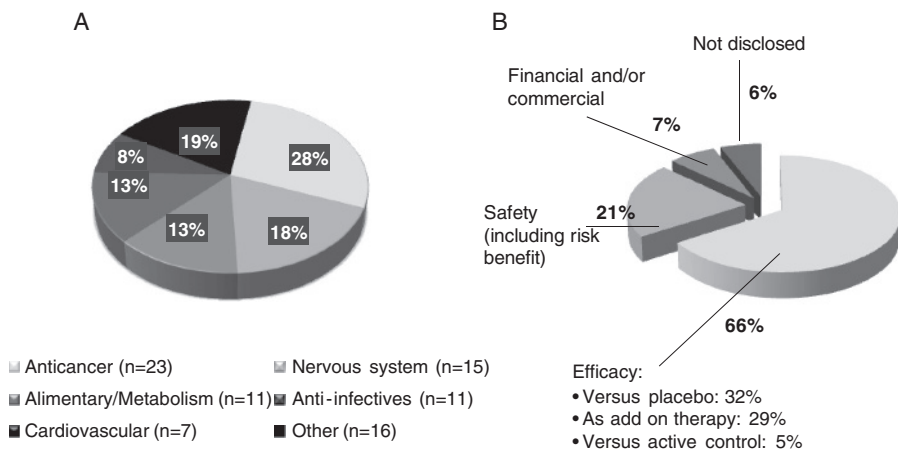
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FIGURE 1.5. A retrospective analysis of the reasons for a compound failing to advance to the next stage of clinical trials for the year 2009 as reported by a cohort of large and mid-sized pharmaceutical companies that represent approximately 70% of global R&D expenditure. *Source:* CMR International 2010 Global R&D Performance Metrics Programme. Reproduced with permission.

TABLE 1.1. Phase III Project Terminations Reported in 2009 and Reasons for Termination [12]

Product	NCE/NBE	Indication	Company	Status When Dropped	Reason
Mepolizumab	NBE	Hypereosinophilic syndrome	GSK	MAA Filed	Insufficient benefit—risk
Vandetanib	NCE	Non-small cell lung carcinoma	AstraZeneca	NDA/MAA Filed	No survival advantage
Vitespen	NBE	Renal cell carcinoma	Antigenics	MAA Filed	Negative opinion from CHMP
AVE-5530	NCE	Hypercholesterolemia	Sanofi-Aventis	Phase III	Lack of efficacy
Axitimib	NCE	Pancreatic cancer	Pfizer	Phase III	Lack of efficacy
Candesartan cilexetil	NCE	Diabetic retinopathy	Takeda	Phase III	Lack of efficacy
Desvenlafaxine succinate	NCE	Fibromyalgia	Wyeth	Phase III	Lack of efficacy
Dirucotide	NBE	Multiple sclerosis	Lilly/BioMS	Phase III	Lack of efficacy
DTP-HepB-Hib	NBE	Diphtheria tetanus, pertussis, Hep B, Hib	Sanofi-Aventis	Phase III	Reallocation of resources
Estreboxetine	NCE	Fibromyalgia	Pfizer	Phase III	Lack of superiority over existing drugs
Imagabalin	NCE	Anxiety	Pfizer	Phase III	Lack of superiority over existing drugs
Liprotamase	NBE	Cystic fibrosis	Altus	Phase III	Reprioritization of portfolio
Resatorvid	NCE	Sepsis	Takeda	Phase III	Lack of efficacy
Rosiglitazone	NCE	Alzheimer's	GSK	Phase III	Lack of efficacy
Saredutant	NCE	Depression	Sanofi-Aventis	Phase III	Negative study in combination with escitalopram
Sarpogrelate	NCE	Prevention of recurrent stroke	Mitsubishi Tanabe	Phase III	Lack of efficacy
Tanezumab	NBE	OA pain	Pfizer	Phase III	Safety—exacerbation of OA symptoms

MAA, marketing approval authorization; NBE, new biological entity; NCE, new chemical entity; NDA, new drug application; Hep B, hepatitis B; Hib, *Haemophilus influenzae* type B; OA, osteoarthritis.



Modified from Arrowsmith, J. (2011). *Nature Reviews Drug Discovery*, 10, (1), 87. *Nature Publishing Group*

FIGURE 1.6. Phase III and submission failures: 2007–2010, by therapeutic area (A) and reason for failure (B). Modified from Reference [12].

The failures at this late stage of development fall into a small number of categories, either lack of efficacy (defined as undifferentiated from current standard of care, no advantage as add-on therapies, or no advantage vs. placebo) or an unacceptable safety or risk-to-benefit ratio. The decrease in late-stage candidate survival seems to apply to both and large and small molecules and also occurs more frequently in complex, multigenic disorders such as neurodegenerative disease and cancer, where early promise in Phase II does not always translate into positive outcomes in larger Phase III trials (Figure 1.6). Another area of concern for cancer drug development is that the previously approvable endpoint of progression-free survival is being questioned for some tumor types where current therapies exist, and the higher hurdle of overall survival is now seen as the gold standard approvable clinical endpoint [13, 14]. This change in approval criteria has even impacted drugs that had previously been approved and marketed against the original endpoint of progression free survival.

To exacerbate the problem, even if a drug candidate successfully navigates its way through the R&D maze, the probability of it becoming a blockbuster drug has become increasingly difficult [15]. To maximize the potential for differentiated efficacy, it has also become increasingly important to stratify patient groups, which further compounds the challenge of producing a rapid rise in revenue after the initial launch of a new drug. Some companies have attempted to address this issue through launch of “incremental blockbusters,” whereby they focus on the drug target, leverage an understanding of disease pathways that are dependent on modulating that drug target, and then target the responder groups across numerous diseases. In this way, only those patients

that are likely to be high responders are selected, thus avoiding some of the major reasons for late-stage failure. The value of this approach is based on sound science where only those patients whose disease etiology is dependent on the pathway under investigation are included in trial. This is particularly true for rare diseases (see later sections) as well as for subpopulations of large disease groups such as breast cancer (e.g., BRCA1 vs. BRCA2), chronic obstructive pulmonary disease (COPD), rheumatoid arthritis (RA), and hypertension [16]. In the past, patients in trials for these diseases have often been treated as large homogeneous groups with similar symptoms but in practice may have differing underlying etiologies. The approach of sub-grouping patient populations in clinical trials has been demonstrated eloquently by Novartis with their novel IL-1 β monoclonal antibody, canakinumab (Ilaris®) for a spectrum of rare autoinflammatory syndromes, termed cryopyrin-associated periodic syndromes (CAPS).

1.4. OVERCOMING FAILURES

Failure is success if we learn from it.

—Malcolm Forbes

Pharmaceutical companies have adopted a number of strategies in order to offset the issues caused by the fall in R&D productivity, price constraints, reimbursement issues, and generic intrusion. At a macro scale, companies are trying to maintain revenue streams and decrease a heavy reliance on a flow of novel drugs for the United States and Western European markets by moving more aggressively into emerging markets, building or buying generic drug capability, diversifying the business into animal health or consumer health, and focusing on rare diseases. There has been consolidation in the industry through mergers and acquisitions; there has been downward pressure on costs through staff reductions, outsourcing, and in-licensing. Many of the traditional “small molecule” companies have invested heavily in vaccines and biologics (“large molecules”). In addition, companies have increasingly extracted more value from their assets through life cycle management as seen in new indications (often related to the original indication), new formulations, combination products, and targeting new patient groups for previously approved products. Typically, this type of life cycle management used to occur as a product matured and the end of its period of exclusivity came closer, but in recent years the trend has been to advance these types of life cycle activities earlier in the period of patent protection. Clearly, life cycle management is dependent on a flow of new NMEs and so this practice will become more challenging as the flow of new products slows and exclusivity is lost. While biologics have remained relatively immune to generic intrusion, the recent introduction of legislation (U.S. Patient Protection and Affordable Care Act; European Medicines Agency guideline on similar biological medicinal products) [17, 18] will allow biosimilar production; and so this area is now under threat. Thus

premium pricing that drives the value of biologics is expected to face challenges. However, the cost of entry into biosimilar development remains very high compared with small molecules, so it cannot be assumed that market share for biologic innovator drugs will be eroded as quickly as has been seen for small molecules.

Fundamentally the industry needs more strategies from which it can develop new and commercially attractive drugs at reasonable cost. Traditional life cycle management was discussed above; however, one area that still remains relatively underexploited is drug repurposing. With better understanding of drug targets and disease pathways, there are potentially significant opportunities to take existing drugs, or previously discontinued candidates, and repurpose them in new indications with high unmet medical need and so complement the usual *de novo* approach to R&D.

1.5. DRUG REPURPOSING

Failure is a back road, not a dead-end street.

—Zig Ziglar

1.5.1. The Case for Repurposing

Table 1.1 provides a summary of the Phase III program terminations in the pharmaceutical industry in 2009. Although not exhaustive, the data clearly show that compounds are failing in Phase III primarily for efficacy reasons. While the detailed causes for each of these failures are beyond this chapter, the following points are noteworthy:

- The majority of these compounds were safe at the doses administered in the Phase II and Phase III trials.
- The compounds have desirable pharmacokinetic (PK) and pharmacodynamic properties.
- It is estimated that around 2000 failed drugs are sitting on companies shelves and that this number grows at the rate of 150–200 drugs per annum [19].

The drivers for repurposing highlighted in this chapter are:

- Pharmaceutical companies need to have additional strategies that will bring new and reimbursable drugs to market quickly.
- There is much substrate available on which to build a repurposing strategy.
- The science to evaluate or re-evaluate new diseases continues to evolve so that science-led repurposing (rather than random screening) is a viable business model.

- The risk of failure is decreased.
- The cost of a repurposing program is significantly cheaper than *de novo* R&D.
- The cycle time of a repurposing program is significantly shorter than *de novo* R&D.

With repurposing strategies, companies are going back to re-examine these failed drug candidates with an eye toward new indications. Current estimates suggest that around 2000 failed drugs are sitting on companies' shelves and this number grows at the rate of 150–200 drug candidates per annum [19]. Clearly not all of these failed drugs are amenable to repositioning; some were shown to be unsafe or have poor PK properties, but there are a large number of molecules that could be considered for science-led re-evaluation.

Drug repositioning offers an attractive route to halt the declining productivity trend. An analysis of the reasons for a compound's failure—particularly where safety was not the primary cause—can be used to turn these failures into insights into how to be successful in the future. There is a growing list of examples of drugs that were initially designed for one indication and have either been discontinued or gone on to be successful after repurposing in additional indications. Some of these examples are shown in Table 1.2.

And why wouldn't the pharmaceutical industry want to build on this model? The time and cost to re-evaluate shelved drugs is less than the time and cost required to create NMEs, and can be a highly effective approach to developing new or better drugs that meet medical needs and that are also reimbursable [1, 2]. With a robust rationale in place, including confidence in the target and its relationship to the disease state in humans, a drug candidate can get a "second chance" to make it to market or extend the franchise of an existing approved drug. This second chance will benefit from the continually evolving science on targets and pathways, which not only elucidates new pathways of disease, but also enables the repositioning of drugs to them.

Understanding why a drug fails will help identify whether it can potentially be repurposed and, if so, the most likely therapeutic applications based on its known mechanism of action. Clearly when a drug has been shown to be unsafe in humans (e.g., TeGenero TGN1412, [20]) it would not be considered for repurposing. However, when a drug is dangerous in specific populations (e.g., thalidomide in women of child bearing potential) it has been demonstrated that carefully selected alternative populations can benefit from such drugs [21]. The definition of a "safe drug candidate" can therefore be indication/patient population specific. There are also drugs that express pharmacology in humans but do not translate into meaningful clinical outcomes (e.g., thromboxane synthetase inhibitors) yet may be synergistic with other pharmacologically active agents. Finally there are potential repositioning candidates among assets dropped from a company's portfolio for strategic reasons (e.g., Roflumilast, a

TABLE 1.2. Examples of Repurposed Drugs and Their Original Indications

Drug	Innovator	Mechanism	Original Indication	Repurposed Indication
Gemcitabine	Eli Lilly	Inhibition of DNA synthesis	Antiviral	Anticancer
Raloxifene	Eli Lilly	Estrogen agonist/antagonist	Breast cancer	Osteoporosis
Bupropion	GSK	Norepinephrine–dopamine reuptake inhibitor	Depression	Smoking cessation
Dapoxetine	Eli Lilly	Selective serotonin reuptake inhibitor (SSRI)	Analgesia	Premature ejaculation
Fluoxetine	Eli Lilly	SSRI	Depression	Premenstrual dysphoria
Hydroxychloroquine	Sanofi	Lysosomal alkalization; TLR inhibitor	Antiparasitic	Antiarthritic
Doxepin	Boehringer Mannheim (Roche)	Serotonin–norepinephrine reuptake inhibitor (SNRI)	Antidepressant	Antipruritic
Bimatoprost	Allergan	Prostaglandin analog	Glaucoma	Eyelash growth

phosphodiesterase 4 [PDE4] inhibitor for COPD that was dropped by Pfizer but subsequently launched by Nycomed/Forest). Therefore, a thorough understanding of the reasons for termination provides a basis for rational decision making on future investments.

As will be discussed in greater detail in subsequent chapters of this book, a number of technologies have been employed in drug repurposing, including computational approaches [22–26], *in vitro* and *in vivo* methods [27–29], and screening for synergies among combinations of existing drugs [30]. Success stories can be found in diverse therapeutic areas such as HIV [31], cancer [21, 32], diabetes, [33] and erythema nodosum leprosum (ENL) [21] among numerous others.

1.6. EXAMPLES OF SUCCESSFUL REPURPOSING

As discussed, repurposing or repositioning is a smart way to capitalize on the cost of developing a new drug or resurrecting a shelved candidate. It has become a major driver for increased revenue within the industry [2]. Numerous small companies have been started with the sole purpose of repurposing drugs, but increasingly larger companies are building this capability into their R&D function. Successful repurposing can result in three potential outcomes: (1) new indications for shelved candidates, (2) line extension for existing drugs, and (3) new targets and new indications for existing drugs. The first category, shelved drugs, can be further subdivided into those that failed for efficacy, safety, and strategic reasons. We will examine each of these in greater detail with examples.

1.6.1. Drug Candidates That Lacked Efficacy in their Primary Indications

1.6.1.1. Sildenafil Perhaps the most frequently cited example of drug repurposing is Viagra® (sildenafil), a phosphodiesterase 5 (PDE5) inhibitor that was under development for the treatment of angina in the 1990s. Clinical trials for the drug were suspended after it was shown that the compound had PK properties that were inconsistent with the prolonged control of angina in patients [34]. However, in these trials, researchers identified a striking side effect that helped define a new disorder—erectile dysfunction (ED). The poor PK properties that made the compound unsuitable as an antiangina treatment were ideal for a drug prescribed for ED. This case also exemplifies the point that some diseases are only considered as targets for therapeutic intervention when an efficacious drug is discovered, as was also the case for migraine prior to Imigran (sumatriptan). Subsequent to their use for ED, PDE5 inhibitors have been tested in a variety of other indications and found to be effective in pulmonary arterial hypertension (PAH) [34] for which sildenafil is now approved and marketed as REVATIO®.

1.6.1.2. Canakinumab Another recently discontinued drug that was repurposed provides a good example of a new paradigm for drug discovery. Canakinumab, (trade name, Ilaris®) is a recombinant monoclonal antibody developed by Novartis that works by blocking an immune system protein known as interleukin-1beta (IL-1 β). It was originally tested as a therapy for RA in a Phase II trial, where the drug failed to reach its clinical endpoints and was discontinued. Subsequently, a separate group of researchers at Novartis knew of a rare disease, termed Muckle–Wells syndrome, in which patients were genetically predisposed to high levels of IL-1 β [35]. Although this rare and potentially life-threatening illness affects only a few thousand patients worldwide, the researchers successfully argued for additional trials. The results of these showed that Ilaris® produced rapid and sustained remission of symptoms in up to 97% of patients, with most of them responding within hours of the first injection [36]. The U.S. Food and Drug Administration (FDA) has approved and given orphan drug status to the drug for two forms of cryopyrin-associated periodic syndrome (CAPS): Muckle–Wells and familial cold auto-inflammatory syndrome. It has also received priority approval in the EU. Novartis is now conducting trials to extend the drug to other inflammatory indications such as COPD, gout, RA, osteoarthritis (OA), and vasculitis in stratified groups of patients whose disease is highly dependent on IL-1 β overproduction. The lesson here is that a clear understanding of the disease pathway is an extremely important factor in *de novo* drug discovery and is essential to unlocking the full potential of the many thousands of drugs that are available for repurposing.

1.6.1.3. Pertuzumab Another recent example from Genentech involves pertuzumab, a first-in-class monoclonal antibody that acts as a “HER dimerization inhibitor”, which was intended to be the successor to Herceptin®. In 2005, the Phase II clinical trials of pertuzumab in prostate, breast, and ovarian cancers met with limited success [37]. However, when evaluated in newly diagnosed early stage HER-2 positive breast cancer, pertuzumab used in combination with other chemotherapeutic agents caused cancers to disappear in 49% of patients, compared with 29% of patients receiving Herceptin® and chemotherapy [38].

1.6.2. Drugs That Failed for Safety Reasons in the Primary Patient Populations

1.6.2.1. Thalidomide Thalidomide, launched by Grünenthal in 1957, was found to act as an effective tranquilizer and painkiller [21]. It was also found to be an effective antiemetic and had an inhibitory effect on morning sickness during pregnancy. Soon after launch, severe side effects began to be noticed as thousands of children were born with severe developmental abnormalities of the limbs and face (phocomelia) as a consequence of thalidomide use. The drug was withdrawn in 1962. Subsequent studies revealed the compound was

an enantiomer, and only one of the two optical isomers was responsible for the teratogenic effects [39]. Unfortunately the two isomers interconvert in humans, so it is impossible to separate the risk from the benefit in women of childbearing age. However, despite the catastrophic effects on the developing fetus, thalidomide has since been used successfully in the treatment of ENL, a painful complication of leprosy, and tuberculosis [21]. Mechanistic studies have revealed that the efficacy observed may be due to its ability to inhibit tumor necrosis factor (TNF) alpha signaling. Further studies have been carried out to develop the potential for thalidomide in Kaposi's syndrome (a complication of AIDS) and multiple myeloma [21, 40]. Sales of thalidomide produced \$550 million in revenue for Celgene in 2008. There is, therefore, renewed interest in thalidomide and its derivatives, and a recent literature search by these authors (Thomson Reuters Integrity database) has revealed investigation into its use in more than 30 alternative indications.

1.6.2.2. Plerixafor Plerixafor was initially developed at the Johnson Matthey Technology Centre for potential use in the treatment of HIV because of its role in the blocking of CXCR4, a chemokine receptor that acts as a co-receptor for certain strains of HIV. Development of this indication was terminated because of poor oral bioavailability, cardiac disturbances, and its teratogenic potential. Plerixafor (Mozobil®) was subsequently repurposed as an immunostimulant used to multiply hematopoietic stem cells in cancer patients and the stem cells are subsequently transplanted back to the patient [41]. Hence the limitations that resulted in failure as an oral drug were not relevant for this innovative application.

What all of these compounds have in common is that they previously failed to meet safety and/or efficacy goals for their original indication. Additional studies brought about by keen observations of the clinical data or a deeper understanding of disease pathways led them to this innovative application.

1.6.3. Drug Candidates That Were Discontinued for Strategic Reasons

There is a category of drugs that were discontinued during clinical development for commercial or strategic reasons. These include drugs:

- In therapeutic areas that were exited by a company.
- That were “backups” or “follow-ons” to lead candidates.
- Where the likelihood of getting a return on investment was low either because the target population is small or because the development costs were very high.
- That, based on data generated or timelines, were not going to be first- or best-in-class.

TABLE 1.3. Examples of Drug Development Candidates Discontinued for Strategic Reasons

Drug	Company	Indication	Termination Reason
Roflumilast	Pfizer	Reduced exacerbation of COPD	Pfizer's Phase III efficacy endpoints not reached. This PDEi has subsequently been launched by Nycomed/Forest Daxas®/ Daliresp®.
Alvespimycin hydrochloride	Kosan	Cancer	Hsp 90 inhibitor dropped due to reallocation of resources
AVE-0847	Sanofi-Aventis	Type 2 diabetes	Glitazar; reprioritization of product portfolio
INCB9471	Incyte	AIDS	Market potential; competing CCR5 antagonists already launched. Out-licensed.
TS-033	Taisho	Type 2 diabetes	Sodium-glucose transporter (SGLT) inhibitor dropped in Phase II in favor of backup compound

Drug candidates that have been discontinued during development for strategic reasons may be offered for out-licensing if a company assesses that there is no impact on their retained portfolio.

One example of a strategic discontinuation was Pfizer's Factor Xa inhibitor eribaxaban, which was shelved when a competing, but more advanced Factor Xa inhibitor, apixiban, was licensed-in from BMS.

Other examples of strategic terminations can be found in Table 1.3.

1.7. REPURPOSING EXISTING DRUGS

1.7.1. Line Extensions

A line extension is a variation of an existing product. The variation can be a new formulation of an existing product or an additional indication of an existing molecular entity [42].

It has been estimated that over half of the top 50 pharmaceutical companies expect to increase revenue by implementing some form of line extension on current products. This is clearly one of the best ways to maximize the potential of a compound, and this has not gone unnoticed by the pharmaceutical industry. One example of a drug that was extended beyond the original indication is bevacizumab, sold under the trade name Avastin®. The drug is a monoclonal antibody raised against vascular endothelial growth factor (VEGF), one of the

primary mediators of blood vessel growth (angiogenesis). It was approved by the FDA in 2004 for use alongside the chemotherapeutic drug 5-fluorouracil in patients with advanced colorectal cancer and in Europe in 2005 as a first-line treatment of patients with colorectal cancer in combination with chemotherapy. Since the initial approval, Avastin® has been approved for a variety of indications both as a first-line treatment and in combination with existing therapies. Table 1.4 lists a few other examples of line extensions to expand the monopoly that these drugs gained.

The advantages of a line extension are many. Approval rates are greater for line extensions than for first-in-class molecules. While a new development project has a 10% chance of going from Phase II to approval, a line extension or repurposed candidate at the same stage (excluding reformulations or new combinations) has a 25% chance of approval (Figure 1.7). Similarly increased approval rates are also seen for compounds from Phase III to submission. Line extensions also expand patient populations and increase revenues with lower development costs than a new drug.

1.7.2. New Indications for Existing Drugs

Human pathophysiology is complex, with many interconnected signaling pathways. Unfortunately for the drug discoverer, compounds often affect more than one pathway, which can have safety implications. Conversely, the same signaling pathway can be involved in different disease states, meaning that a compound used for one indication can just as easily be applicable to other diseases. One such example is Avastin®, which as described above, is used extensively in treatment for many types of cancer, but has shown promise as a treatment for macular degeneration.

Several additional recent examples of new indication approvals for existing drugs [40] include:

- Duloxetine (Cymbalta®), a selective serotonin and norepinephrine reuptake inhibitor (SSNRI) indicated for the treatment of major depressive disorder, neuropathic pain associated with diabetic peripheral neuropathy, and generalized anxiety disorder, has been approved for treatment of chronic musculoskeletal pain.
- Onabotulinumtocin A (Botox®) is a neurotoxin complex indicated for the treatment of cervical dystonia, severe primary axillary hyperhidrosis (underarm sweating), and upper limb spasticity, and has been approved recently for the prevention of chronic migraine.
- Finasteride, a 5-alpha reductase inhibitor, expanded use from prostate cancer (Proscar®) to hair loss (Propecia®).
- Hydroxychloroquine (Plaquenil®), a compound that increases lysosomal pH and inhibits toll-like receptors (TLR), expanded use from an antiparasitic to an approved antiarthritic agent.

TABLE 1.4. Examples of Line Extensions and the Increased Years of Monopoly

Name (Marketed Since); Company	Monopoly Protection Until	Number of Monopoly Years	Second Drug (Marketed Since); Relationship to first drug	Monopoly Protection Until	Number of Monopoly Years	Additional Monopoly Gained
Citalopram (1989); Lundbeck	2002	13	Escitalopram (2002); (S)-enantiomer	2022	20	20
Omeprazole (1988); Astra Zeneca	2002	14	Esomeprazole (2000); (S)-enantiomer	2019	19	17
Risperidone (1993); Janssen Cilag	2007	14	Paliperidone (2007); active metabolite	2022	15	15
Loratadine (1988); Schering Plough	2002	14	Desloratadine (2001); active metabolite	2019	18	17
Paroxetine (1991); GSK	2003	12	Paroxetine CR (2002); controlled release	2017	15	14
Venlafaxine (1994); Wyeth/Pfizer	2006	12	Venlafaxine XR (2001); extended release	2017	16	11

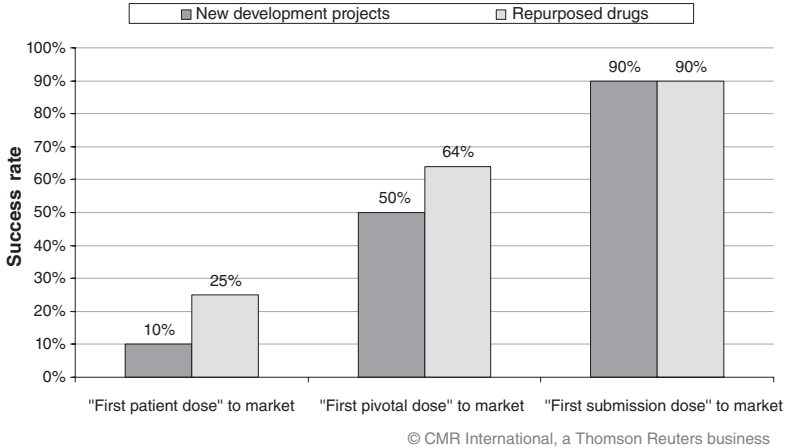


FIGURE 1.7. Probability of success to market for new development projects versus repurposed drugs for decisions made between 2004 and 2009. Repurposed drugs are defined as those drugs that have entered Phase II after the parent drug has been launched; it excludes reformulations, combinations, or same indications. *Source:* CMR International Global R&D Performance Metrics Programme. Reproduced with permission.

- Doxepin (Sinequan®, Adapin®), an SNRI, expanded use from an approved antidepressant to a topical antipruritic agent.
- Naltrexone, an opioid receptor antagonist, expanded use from an opioid addiction therapeutic to alcohol withdrawal therapy.

1.8. ORPHAN DRUGS

The focus of this chapter has been on repurposing failed drugs; some fail for safety reasons, some fail for lack of efficacy in the target indication, some fail because the patient population has not been appropriately stratified to eliminate nonresponders, and some fail because they no longer fit into a portfolio. The financial and time advantages of repurposing drugs have also been discussed. It is also appropriate to mention orphan drugs in the context of repurposing. The definition of an orphan drug in the United States is a rare disease with prevalence of less than 200,000 and/or for which drug development costs are unlikely to be recovered through sales in the United States. There are a number of incentives in the United States to encourage company involvement in orphan drug programs, including extended periods (7 years) of market exclusivity (and the potential for 10 years in EU/Japan), tax credits for 50% of development costs, R&D grants, fast track approval status with the FDA, and waived drug application fees. Similar concessions are available outside the United States. These incentives can make repurposing drugs to rare diseases

particularly attractive. It is estimated that there are between 5000 and 8000 rare diseases and there is already orphan drug designation for over 1800 of these in the United States [43].

Orphan diseases make a sound platform for a repurposing drug strategy since there are excellent exclusivity and R&D incentives offered with the Orphan Drug Act and price restrictions around such drugs are lacking. In fact, companies like Genzyme (acquired by Sanofi-Aventis) and Shire (through its acquisition of Transkaryotic) have made rare disease and orphan drugs their core business. Other major companies like Pfizer and GSK are aggressively entering this opportunity space. An important note here is that 90% of approved treatments for rare diseases were not originally developed for these rare diseases. Moreover, the strong rationale for a particular mechanism in a rare disease can provide an initial lower risk and quicker path to commercialization before expanding to more prevalent diseases where the rationale may not be as strong, as in the case of Ilaris®.

1.9. CONCLUSIONS

There will never be a shortage of discontinued compounds; this is simply the cost of doing business in the pharmaceutical environment. But if we learn from these failures and apply the constantly developing understanding of biology and human disease, value can be salvaged through repurposing efforts from these failed compounds, which is important in today's R&D environment where new drugs are difficult and expensive to develop and many medical needs remain underserved. Repurposing drugs, including those that have failed in their primary indications or have been shelved for strategic reasons, is an important part of a pharmaceutical company's R&D strategy and is also a key component of the operating model for several specialist companies, as well as numerous academic and foundation initiatives. Subsequent chapters of this book will explore examples of these in more detail.

While there are numerous diverse examples of successfully repurposed drugs, a number of key themes emerge from them:

- Keen scientific observation or specific detailed knowledge of disease states created new opportunities for R&D.
- The time to market was significantly shortened since fewer preclinical studies were needed and Phase I clinical trials were often unnecessary.
- Cooperation was imperative across the entire R&D organization to move these compounds through to market.
- There is plentiful substrate within large Pharma companies, or potentially available for licensing from other companies.
- Pharmaceutical companies are increasingly willing to explore opportunities for previously shelved compounds in which much investment has already been sunk.

Some key enablers of a repurposing strategy are to have:

- Support and belief in the value of repurposing from R&D leaders.
- Resources to execute high quality preclinical/human translational validation experiments, including exposure–response relationships, and proof-of-concept experiments.
- Access to one of the high quality databases, such as Thomson Reuters Integrity, that accurately curate and record R&D success and failure activity from across all of Pharma.
- Access to a high quality database that mines and analyzes the continually emerging knowledge in systems biology to understand the underlying biology behind disease pathways (see for example <http://www.GeneGo.com>).

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