The true cost of drugs that fail in clinical trials should be measured by far more than the cash poured into the development process. Everyone loses something, whether it be the patients who are waiting for new treatments or the companies losing resources that could have gone back into bolstering R&D. Some of the investment into these failed or shelved drugs can be recouped by giving them a second and often lower-risk chance in a new indication. This is known as drug repositioning, drug repurposing or drug rescue. It may be carried out by the company that invented the drug, but it’s more commonly pursued these days by smaller, more specialized companies. These companies take failed drugs back into basic research and search for new therapeutic uses for them. Some are drugs that were not effective or potent enough, while others have simply been shelved because the company has changed its focus. Repositioning can also involve relaunching already-approved drugs whose patents have expired.

One of the key advantages of repositioning is that drugs that have completed preclinical and Phase I trials are known to be safe and to have toxicity data that can be recycled. Repositioned drugs still have to go through preclinical trials to confirm and validate their activity in their new indication, or to investigate a new mechanism of action. But overall, companies can route the repositioned drugs into proof-of-concept trials more quickly, shortening the overall time to market.

“After we have made sure that the drug works in vitro, we can then move quickly to Phase I or Phase II clinical trials,” says Michel Souchet, CEO of France’s Harmonic Pharma, which focuses on drugs that have reached Phase II or higher in their original indication and have failed, or that are on the market as generics. Being able to move quickly into Phase II proof-of-concept trials can cut up to three years off the normal development timeline, estimates Farid Khan, CEO of PharmaKure, which was spun out from the University of Manchester in the United Kingdom in early 2013 and mines known compounds for potential new applications in Alzheimer’s and other diseases. PharmaKure has already identified a preclinical candidate for malaria, Khan says. The availability of toxicity and other research data not only speeds up the development process, but it also helps drug developers to make benefit/risk calculations more easily and accurately. That reduces the risk inherent in drug development and therefore cuts the attrition rate. This is reflected in the success rate of a drug getting to market, which is 25% for a repositioned drug versus around 10% for a new chemical entity.

This shortened timescale and lower development investment makes the process more cost-effective, allowing companies to recoup some of their already significant investment in the drugs. It also makes it more viable for companies to develop repositioned drugs for rare diseases and orphan indications.

“Drug repositioning allows drug developers to jump over much of the preclinical process, just using animal models to provide evidence of efficacy, and moving straight into human proof-of-concept trials,” says Andreas Persidis, CEO of Charlottesville, VA-based Biovista, which uses its systematic discovery platform to develop a pipeline of repositioned drug candidates in neurodegenerative diseases, epilepsy, oncology, and orphan diseases.
SOURCES FROM THE STOCKPILES

Companies looking for drugs to reposition are likely to find plenty of choices. “We totaled up all the drugs that have been tested in humans in the last 300 years, and it came to over 29,000,” Khan says. “In terms of repositioning this could be all we need to treat any disease.”

Finding candidates for repositioning among all these thousands of drugs can be serendipitous, as a result of observations and anecdotal reports or mentions in papers of interesting off-label effects of drugs. It can come from scientific breakthroughs, such as identifying new biological pathways and targets, or new mechanisms of action that point to new applications for shelved drugs. Or it can be more methodical, resulting from systematic searches through in-house, open-source or licensed databases of molecules.

Harmonic Pharma relies on its in-house library of around 14,700 compounds that cover a range of therapeutic areas. These have been profiled using the company’s proprietary platform to create molecular footprints, or “harmonics,” of the drugs, based on in silico, in vitro and in vivo data, Souchet explains. Each of these footprints includes a range of information on the drug, such as biological target, mechanism of action and therapeutic use.

Other sources include contract research organizations such as GVK Biosciences in India that have manually curated databases of drugs that are available for licensing to academia and industry. Academic institutions such as Johns Hopkins also make their libraries available for a small fee. It’s not just small biotechs and pharmaceutical companies that are showing an interest in drug repositioning, however. The large pharmaceutical companies are starting to see the value of the shelved compounds that they have in their fridges and cupboards, or even virtually in their databases. It’s estimated that Big Pharma’s libraries include around 2,000 or more failed or shelved drugs.1

Rather than developing these themselves, they are likely to pass them on to small companies and academics to develop, sometimes retaining some rights or options for products that make it beyond the development stage.

“Many large pharma companies are moving towards open innovation. They have realized that their failed drugs may be a resource with a lot of potential and have made them available to academia and small biotechs to prospect,” says Khan.

In 2011, AstraZeneca (AZN) announced an agreement with the U.K.’s Medical Research Council (MRC) to give academic researchers access to 22 shelved compounds free of charge. In November 2012, the MRC selected 15 projects and awarded a total of $11 million (£7 million) to fund the research.2 The drugs include zibotentan (which failed Phase III for prostate cancer therapy in 2010) and saracatinib (which was shelved after disappointing clinical trials in cancer).3

In a similar project in the U.S., the National Center for Advancing Translational Sciences (NCATS), part of the National Institutes of Health, has launched a pilot repositioning program called Innovation Drug Discovery (PD2) panel, part of Lilly’s Open Innovation Drug Discovery platform, which adds information on the molecules’ biological profiles, revealing mechanisms of repositioning this could be all we need to treat any disease.”

FARID KHAN, CEO, PHARMAKURE

DISCOVERING NEW THERAPEUTIC USES FOR EXISTING MOLECULES

It includes 58 shelved compounds from AbbVie ($ABBV, a spinout from Abbott, $ABT), AstraZeneca, Bristol-Myers Squibb ($BMY), Eli Lilly ($LLY), GlaxoSmithKline (GSK), Janssen Research & Development, Pfizer ($PFE), and Sanofi ($SNY). The program seeks applications for projects from both academia and industry.4

In June 2013, the NIH allocated $12.7 million to 9 projects that will match up academic groups and industry compounds as part of the NCATS pilot program.4 The NCATS Pharmaceutical Collection is an accessible database of 3,800 small-molecule compounds, focusing on 8 disease areas. These include many of the molecules that have been registered for human clinical trials or have been approved in the U.S., Canada, Europe, and Japan. The database has been screened using Lilly’s Phenotypic Drug Discovery platform, which adds information on the molecules’ biological profiles, revealing mechanisms or pathway activities of drugs.4 Roche ($RHHBY) has allowed the U.S.-based Broad Institute to screen 300 of its shelved compounds, known as the Roche Repurposing Compound Collection. Teva is also moving into drug repositioning, with 10 to 15 new programs planned during 2013, each of which is expected to take up to 5 years to move through clinical trials. Transparency Life Sciences is using open innovation and crowdsourcing to speed up drug development and lower costs, and is planning to validate its approach with studies on a series of repurposed generics. The first study will look at the antihypertensive agent lisinopril as a potential therapeutic in multiple sclerosis. The longer-term aim will be to use drugs from companies that lack adequate funding to continue development—another reason drugs get shelved.

FINDING THE ACTIVITY

In screening for potential hits, some companies use validated animal models of human diseases, while others rely on mathematical models that predict how a drug will act in a particular disease. SOM Biotech, a Barcelona-based drug repositioning company, uses a ligand-based virtual screening technology, and its typical repositioning program lasts around 9 to 16 months.

“Our in silico technology allows us to identify new biological activities of given drugs. We identify a disease and then screen our database of around 9,000 drugs to find candidates that are active in that specific disease,” says Raúl Insa, SOM Biotech’s founder and CEO.

According to Biovista’s Persidis, many companies use what he refers to as a single-dimensional approach, which he feels can overlook vital information. “Our approach is multidimensional, and we see this as important, since basic biological mechanisms are multidimensional, having evolved this way in the past to evade redundancy and other such
properties that are important to living organisms,” Persidis says. “Biology is complex and we need to look carefully at what we model and how we model it.”

Another approach to repurposing is to rescue molecules through engineering. For example, Dublin-based Alkermes used an existing, though underused, drug as a starting point for its molecule RDB 1419, an anticancer drug in preclinical trials. RDB 1419 is an engineered version of the IL-2 immunotherapeutic Proleukin. While not strictly a “failed” drug (it is still on the market for the treatment of metastatic melanoma and renal cell carcinoma), its use is severely limited by a black box warning about serious toxicity issues. Alkermes’ aim was to retain the powerful mechanism of action of IL-2 but create a less toxic drug that could be used for a wider range of cancers.

“Rather than repositioning [a molecule], we … build new layers of science and insight onto it,” says Richard Pops, chair and CEO of Alkermes. “IL-2 was a pioneer drug, and its efficacy promise was borne out, but this was limited by its toxicity.”

Alkermes has created a platform technology, known as Picasso, which can manipulate and improve biologics through circular permutation, a process of creating novel fusion proteins. IL-2 binds to two receptors. The engineered form of RDB 1419 had increased affinity for the “good” receptors, responsible for the activity, but wouldn’t fit as well into the “bad” receptors, which were responsible for the adverse effects. “We can demonstrate proof-of-concept much earlier, because we have known biomarkers and an established knowledge base, and we know the positives and negatives about IL-2,” says Pops. Alkermes expects to be ready to start human trials in early 2015.

REPOSITIONING AS A BUSINESS MODEL

The market for repositioned drugs was estimated to be worth $20 billion in 2012.1 However, it takes more than just finding the perfect drug for a disease to exploit this opportunity. “It can be difficult to make money, … particularly when working with drugs that are freely available,” Khan says. “It’s all about patentability. To make a business in this area you have to know the patent landscape.”

When it comes to intellectual property, repositioned drugs can be protected in a number of ways. For example, developing a new method of administration or assembling a combination of drugs that offers measurable and meaningful advantages to patients can extend a drug’s patentability.

Repurposed drugs can also gain a second-use patent in a different disease, though this was limited by its toxicity.”

Alkermes has a “not invented here” mindset, which does not allow the available technologies to be quickly advanced. “We have a ‘not invented here’ mindset, which does not allow the available technologies to be quickly advanced before discontinuing a program,” says Khan. Many drugs have failed in Phase II, only to be subsequently revitalized by a bioavailability enhancement or drug delivery technology that is optimal.

Formulation scientists need to be familiar with ALL of the technologies in the drug development toolbox, not just those that have been successful in their own experience or within their own organizations.” Dr. Kurt Nielsen, Chief Technology Officer and Senior Vice President of Innovation and Growth.

Formulation scientists must increasingly deal with the complex challenges of poorly soluble and poorly permeable drugs. Recent survey findings show that 74% of scientists have worked with poorly soluble/permeable compounds in the past year. These formulation scientists need to quickly assess a variety of drug delivery and bioavailability enhancement technologies to meet the regulatory and performance demands of the clinic, as well as, global commercial markets. There is a need to enable fast assessment of advantages and disadvantages of the available technologies to quickly advance compounds into the clinic. R&D teams have a responsibility to look at the rapid assessment of formulation technologies as an opportunity for creating treatments for patients, payors and the industry collectively. However many R&D teams have a “not invented here” mindset, which does not allow the available technologies to be quickly evaluated before discontinuing a program. Many drugs have failed in Phase II, only to be subsequently revitalized by a bioavailability enhancement or drug delivery technology that is optimal. Formulation scientists must increasingly deal with the complex challenges of poorly soluble and poorly permeable drugs.

Recent survey findings show that 74% of scientists have worked with poorly soluble/permeable compounds in the past year.

Partnering with companies focused on applying bioavailability enhancement and drug delivery technologies expands the realm of possibilities that your R&D scientists can explore to solve complex problems in drug development. These technology-driven companies have deep expertise not only in product development but also scale up and global commercial supply. There is no teacher like experience and pharmaceutical product development is no exception. Successful application of technologies like nanoparticles, hot melt extrusion, lipid based systems, spray drying, matrix tablets and beads all benefit from experience and expertise. Many of the failures that these technology companies have experienced occurred in the laboratory, where failures become R&D learnings. These are invaluable contributions to the organizational wisdom that are unnecessary to replicate in your organization. In today’s budget conscious environment, all companies have the opportunity via partnership to ensure the availability of a solution at a fraction of the cost (and risk) to develop the experience and expertise in-house. Accessing more solutions throughout product development enable better treatments to be reliably supplied. Catalent has developed a patent pending tool that enables scientists to look into how different bioavailability and drug delivery technologies could be applied to drugs based on characteristics of the drug substance and desired performance of the drug product. Formulators and process development scientists can easily utilize the tool by inputting chemical characteristics and products specifications generating recommendations based on Catalent’s 75 years of experience in bioavailability enhancement and applied drug delivery. Whether new drug or line extension, insights from using this tool typically suggest new approaches that benefit pharmacokinetics patient adherence and therapeutic profile.

If you would like to learn more about your molecule and how it can be given a new lease on life, please visit www.catalent.com/FormPro.
more user-friendly in the new indication. These decisions about differentiation have to be taken on a case-by-case basis and will depend on the drug and the indication.

Once a repurposed drug makes it to market, there’s still one more hurdle: getting the product reimbursed. “One of the issues with drug repositioning is overcoming the existing preconceptions held by payers and clinicians,” says Pops. “They have expectations about known drugs, so even when new value is created it may not be recognized.”

He cites as an example low-dose doxepin, which was relaunched and repurposed at an ultralow dose as a sleep aid. “But many physicians and patients are wondering why they can’t just use a split dose of the generic formulation. Drug developers need to do something important to the drug and really add value, not just change the dose or move from twice daily to once daily. The changes need to differentiate the drug in a really meaningful way, both for patients and payers.”

Insa says. “If it’s not clearly differentiated, then doctors will use the drugs or devices off label.”

“The IP aspect is getting harder for companies,” Persidis says. “In the past, originator companies could obtain patents that would include a very large list of claims for their drugs, even if so-called ‘possession of the relevant art’ was not clearly demonstrated. Competition and stricter governance now mean that strong proof must accompany each claim, and so a solid understanding of the mechanism of action of drugs becomes much more important.”

In the U.S., the Orphan Drug Act offers a period of exclusivity for repositioned drugs that have gained orphan drug status.1 “The best compounds are those that are off patent and have failed, because otherwise you are at the whim of the originator,” Khan says. Even once patent-protected and on the market, repositioned drugs still face challenges. “One of the challenges in drug repositioning is how to distinguish the new indication in the marketplace,” Insa says. “If it’s not clearly differentiated, then doctors will simply prescribe the old product.”

This differentiation can be achieved in a number of ways, including careful selection of the market. For example, if the originator drug is only available in Japan, the drug could be launched in Europe or the U.S. Or a repurposer can modify the formulation to make the drug

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1. The Orphan Drug Act offers a period of exclusivity for repositioned drugs that have gained orphan drug status.
The Future of Drug Repositioning

Some of the new technologies that are improving drug development could also affect drug repositioning, making the process of matching drugs and diseases faster and more accurate. One of these is data analytics, helped by the increasing speed and affordability of computer processors and falling costs of data storage, as well as an increased focus on big data across the industry. For example, data mining and pathway analysis allow researchers to make connections between drug structure and function, genetics and proteomics, and disease pathology. Advaita, a U.S.-based bioinformatics company, has received an award of $2 million from the National Institutes of Health to develop biological pathway analysis tools for personalized medicine and drug repositioning. The company will create tools to analyze the big data coming from gene sequencing technologies.\(^5\)

Researchers at Stanford University School of Medicine in California have combined data mining and preclinical models to reposition two older drugs as potential therapeutics for small cell lung cancer. The drugs, imipramine (a tricyclic antidepressant) and promethazine (an antihistamine and sedative), were found as part of a bioinformatics-based drug-repositioning project. The researchers got from the planning stage to Phase Ila clinical trials in just 20 months by using a computer program to scan hundreds of thousands of gene-expression profiles looking at specific pathways involved in small cell lung cancer. This shortlisted 6 drugs, and in preclinical trials in mice and in cell lines, imipramine and promethazine turned out to be the most active.\(^6\)\(^7\)

One of the applications for drug repositioning in the future could be to make treatments freely available in the developing world. This is one area in which the lack of patentability would be an advantage. Cures Within Reach, based in Skokie, IL, works with researchers institutes, clinicians and researchers to reposition off-patent drugs for orphan and rare diseases that have no effective therapy. “We approach drug repositioning as a not-for-profit entity with a philanthropic aim to provide low-cost medical solutions to physicians and therefore to patients,” says Bruce Bloom, president and chief scientific officer of Cures Within Reach. “We find and validate potential repositioning candidates, and fund and manage pilot clinical trials. We then publish the data, making it available to physicians who can then choose to use the drugs or devices off label.”

Khan is also working in the philanthropic repositioning field, via his other company, Lumophore, which is searching for treatments for microbial disease and malaria. Khan also has a position on the scientific advisory board of Findacure, a charity for rare diseases. “We have identified new repositioned antimarial drugs as a philanthropic venture, and we will publish the results so that they can be used by anyone in the developing world.” Drug repositioning is evolving, Persidis explains, and could even be moved earlier in the drug development process, so that it captures drugs that aren’t actually failing but that have other potential applications. “Initially, people talked about drug repositioning as a serendipitous process,” he says. “Repositioning can be used as a business tool earlier on in the drug-development process. Ultimately, some of the tools and methods of repositioning could move us closer to a state where better new chemical entities can be developed more efficiently.”

This means that companies can avoid missing opportunities, and they can license out indications that are outside their core area, providing an additional income stream. In a world of rising drug-development costs, diminishing pipelines and blockbusters vanishing over the patent cliff, drug repositioning could offer the industry a second wind. “Drug discovery in the future is not likely to be about large companies,” Khan says. “It’s more likely to be innovative compounds coming out of small companies, with a focus around … drug repositioning.”

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<thead>
<tr>
<th>Drug</th>
<th>Original indications(s)</th>
<th>Alpha-2-macroglobulin</th>
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<tr>
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<td>Morning sickness</td>
<td>Leprosy, multiple myeloma</td>
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**Table: Repositioning in practice**

Here are some repositioned drugs currently on the market.

- **Bibliography**