HOW REPURPOSED DRUGS

ARE CHANGING THE FACE OF MEDICINE AND CREATING INVESTMENT OPPORTUNITIES

EMBARK HEALTHCARE

Drug repurposing – uncovering new uses for already-approved medicines that could benefit patients facing a different need than originally intended – is bringing hope to millions of the desperately ill and their families.

This is especially true for those suffering from rare diseases – who can't wait a dozen or more years for a new treatment to be discovered, developed, and made available.

Drug repurposing not only offers advantages over traditional de novo drug development in terms of cost, speed to market and improved patient outcomes, it can provide unique investment opportunities.

We invite you to learn more about drug repurposing on the pages that follow.

For the last several decades, growth in the pharmaceutical industry has been driven by a convergence of factors, most notably a growing, aging population — as well as by advances in medical science and improvements in purchasing power and access to quality healthcare and medicines to poor and middle-class families worldwide, all of which has greatly expanded demand.

The global pharmaceutical market in 2020 is expected to top $1.3 trillion in annual sales.

The pharmaceutical industry clearly plays an important role in discovering and developing medications and vaccines that are helping to reduce the incidence of diseases, to cure diseases and to improve the quality of life for tens of millions of people around the world.

GOOD NEWS, BAD NEWS

That's the good news. The bad news is that it's a complex journey to find just one miracle cure – from that eureka moment of discovery in the laboratory to routine use in patients – and can easily take a dozen or more years and cost well in excess of $2 billion.

Moreover, this ignores the fact that along the way most drug candidates fall by the wayside, for any number of reasons, including safety issues, failure to show efficacy, and lack of commercial promise – which can be seen in increased R&D spending and decreased new drug output.

Developing a brand-new drug takes an enormous amount of time, money and effort, mainly due to bottlenecks in the therapeutic development process. Delays and barriers mean that translation of a promising molecule into an approved drug often takes more than 14 years. It is crucial to advance strategies to reduce this time frame, decrease costs and improve success rates.

Drug repurposing is one such strategy. Many agents approved for other uses already have been tested in humans, so detailed information is available on their pharmacology, formulation and potential toxicity. Because repurposing builds upon previous research and development efforts, new candidate therapies could be ready for clinical trials quickly, speeding their review by the Food and Drug Administration and, if approved, their integration into health care.

Source: Therapeutic Drug Discovery, *Drug Discovery World*

In the U.S., the number of new drugs approved per billion dollars spent on research has approximately been halved every 9 years since 1950, falling around 80-fold in inflation-adjusted terms. As a result, the number of new drugs coming to market has remained relatively flat for the last decade.

Even when a new drug makes it into commercial use, patents and other means of providing pharmaceutical companies incentives designed to encourage drug discovery and development only provide exclusivity for so long. Eventually competition is free to sell generic versions of the drug, thus eroding market share and margins.

Furthermore, in recent years, policy-driven changes in healthcare spending are putting pricing pressures on the industry.

THERE'S NO MAGIC WAND

With R&D spending down, with drugs going off patent, with pressure to grow their businesses, given that big pharma can't simply wave a magic wand and find and develop a new drug, they constantly need to fill their flagging drug pipelines — often turning to repositioning older drugs as one solution.

The long-standing objective of drug discovery and development is to identify a potential therapeutic agent using a one drug for one target model. However, most drugs have side effects, meaning their mechanism of action triggers other drug responses. Drug repurposing simply recognizes and exploits this common phenomenon.

For example, when scientists first developed sildenafil for cardiovascular disease, a side effect appeared that indicated the drug might treat erectile dysfunction, and thus the blockbuster drug Viagra was born.

One of the most astonishing cases of a repurposed drug involves thalidomide. Originally approved in Europe in the 1950s, doctors were infamously prescribing it to prevent nausea in pregnant women. It was later revealed to cause severe birth defects in newborns and was withdrawn from the market.

What researchers would discover is that thalidomide acts by promoting the degradation of an unexpectedly wide range of transcription factors – cell proteins that help switch genes on or off, including one that interferes with limb development and other aspects of fetal growth. In the 1980s, thalidomide gained a second life when it was found that this same mechanism of action inhibited the growth of blood vessels in tumors. As such, it has come into wide use as a cancer drug, primarily in the treatment of multiple myeloma.

REPURPOSING GAINING GROUND

Given the high attrition rates, substantial costs and slow pace of new drug discovery and development, it's no wonder that drug repurposing is gaining in popularity.

For one thing, drug repurposing involves the use of de-risked compounds. A drug may be efficacious, but it has to be safe for use. Even drugs that get all the way to a Phase 3 study have a 17% failure rate due to safety. Repurposing starts with a drug that has a well-established toxicological and pharmacokinetic profile, and while they still need to undergo clinical testing for a new indication, the development timeline can be accelerated with less setbacks and lower cost than traditional drug development.

Because many of the early development steps don't need to be repeated, repurposing a drug can cut the critical time to gain approval, and at a fraction of the cost to develop a new drug from scratch.

Moreover, studies show a repurposed drug is two to three times as likely to gain approval for another indication than newly developed drugs.

> A bedrock principle of the pharmaceutical industry used to be the 'one drug-one target' paradigm. The continued rising costs combined with the catastrophic failure rates of de novo drug discovery and development have driven the pharmaceutical industry towards some exploration of [drug repurposing] strategies and their potential. The numerous benefits of [drug repurposing] are clear and documented. Entrenched, silo-structured pharmaceutical companies are not conductive corporate structures for [drug repurposing]. In addition, there appears to be a sentiment that [drug repurposing] is not an endeavor that produces innovative research and outcomes [scientific snobbery]. Widescale implementation of smart [drug repurposing] strategies could unleash a torrent of productive activity that enhances pharmaceutical company performances and provides significant opportunities for stakeholders.

Source: Therapeutic Drug Discovery, *Drug Discovery World*

Safer, faster to market, cheaper to develop, higher rate of approval – it's easy to see why, over the last 5 years, repurposed drugs have accounted for 45% of drug approvals in the U.S., generating some $500 billion in annual revenue.

DE NOVO DRUG DEVELOPMENT IS LONG, RISKY AND COSTLY

The best way to appreciate the benefits of repurposing drugs is to examine what it takes to bring a new drug to market.

Often the most important developments in medical science begin with investigators in basic research laboratories – sometimes at pharmaceutical companies, more frequently at universities – with the discovery of new biological molecules, processes, or pathways.
Armed with an idea, researchers work to identify biological targets underlying a specific disease or group of diseases.

After learning more about the disease pathway and identifying potential targets, researchers then create multiple potential drugs to act on that target.

They then seek to narrow the field to one lead compound – a promising molecule that could influence the target and displays the initial requirements to become an approved medicine.

Lead investigational compounds that survive the initial screening are then "optimized," to make them more effective and safer.

Once a compound is chosen, it's on to manufacturing, initially making the drug on a small scale to use in this preclinical stage. Later production of the medicine will need to be scaled up if it is approved for use in the general patient population.

Establishing the safety of a drug before use in humans is the next step. A candidate drug will go through a series of preclinical and toxicological tests to provide a preliminary assessment of safety, including the maximum tolerated dose -- before the candidate drug is allowed to be studied in humans.

Prior to any human clinical trial starting, a drug company must file with health authorities, demonstrating how the investigational medicine is thought to work in the body, a listing of any potential side effects as indicated by the preclinical studies, and manufacturing information. The submission also provides a detailed clinical trial plan that outlines how, where and by whom the studies will be conducted.

In addition, all clinical trials must be reviewed, approved and monitored by the institutional review board or ethics committee at the institutions where the trials will take place.

In Phase I trials, the candidate drug is tested in people for the first time. These studies are usually conducted with a small number of healthy volunteers. The main goal of a Phase I trial is to assess the safety of the medicine when used in humans. These closely monitored trials are designed to help researchers determine what the safe dosing range is and if the candidate medicine should move on to the next stage of development.

In Phase 2 trials, researchers evaluate the candidate drug's effectiveness in patients with the disease or condition under study. Many Phase 2 trials study patients receiving the drug compared with patients being given a different treatment, either an inactive substance, called a placebo, or a different drug that is usually considered the "standard of care" for the disease. If the trial meets its stated objective and drug continues to show promise, it's on to Phase 3 trials.

Phase 3 trials are designed to generate definitive data about the safety, efficacy and the overall benefit-risk relationship of the investigational medicine. Phase 3 trials may enroll hundreds to several thousand patients across numerous clinical trials sites. This stage of research is essential in determining whether the drug is safe and effective. It also provides the basis for labeling instructions to help ensure proper use of the drug.

After successful Phase 3 trials, the sponsoring company submits a marketing application to the health authorities requesting approval to market the drug.

BY COMPARISON

As can be seen, the process of going from laboratory to use in patients is both expensive and time consuming, and ends more often in failure than success. Only about 14% of the candidate medicines that enter clinical testing make it to approval.

That is what makes repurposing so attractive. By starting with an approved drug, most of the de novo drug development process, including the work involved in drug discovery, preclinical development, and often early clinical trials – which, in addition to being the most risky period in drug development, can account for half or more of the costs to bring a new drug to market as well as half the 10-15 years it usually takes to bring a drug to market, may be eliminated.

In the case of Embark Healthcare companies, while we seek out repurposing investment opportunities that have $500 million or more annual revenue potential, we stay away from "moonshots," i.e., heavily-pursued indications with high risk/high cost, or where there are huge technical challenges. Instead, we focus on development programs where an exit is reasonably achievable in 2-5 years with modest investment of $5 - $15 million.

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RARE FINDINGS

Besides addressing patients with conditions affecting a large number of people, repurposing offers a lifeline for many with rare diseases, where the relative risks and rewards of drug discovery versus the limited patient population might otherwise discourage research investment.

While untold millions of people are alive today and leading productive lives thanks to modern medical science, tens of millions more people worldwide continue to suffer, and in numerous cases, are dying, from an estimated 7,000 diseases for which there is no effective treatment. That adds up to some 7% of the world's population.

The National Institute of Health estimates that between 25 million and 30 million Americans suffer from rare conditions – termed "orphan" diseases. The burden of living with a rare disease can be immense – for those afflicted and for their loved ones. That's why finding cures takes on such importance.

“The pharmaceutical industry is still beleaguered by escalating costs, stagnant productivity and protracted timelines as it struggles to bring therapeutic drugs to market. This situation has been compounded by a ravenous generic drug sector.

…there is a morphing landscape dictated by more stringent regulatory oversight, demands for mechanism-of-action-based drug discovery and development and a patient population driven by the advent of personalized medicine and a consumer mentality. This has left the pharmaceutical sector scrambling for avenues of opportunity to minimize risk, reduce costs, and fill their pipelines with safe and efficacious candidate drugs.

Drug repurposing…is an attractive way to maximize return on prior and current preclinical and clinical investments in assets that were originally designed with different patient populations in mind.”

Source: Therapeutic Drug Discovery, *Drug Discovery World*

In case there was any concern that the industry might run out of diseases to cure, approved drugs offer help to only about 5% of patients with a rare disease. The vast majority of these patients have no therapeutic treatment options.

One bright spot in those grim statistics is knowing that with 30,000+ approved drugs and more either discontinued or abandoned for one reason or another, there's a rich pool of potential compounds for repurposing – so there's plenty of hope for the millions who continue to wait for answers.

PROUD PART OF THE INDUSTRY

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Advances in our understanding of human biology and disease are opening up exciting possibilities for potential new treatments and cures. While researchers are working every day in labs across the U.S. and around the world to turn scientific promise into new medicines for patients, at the same time, efforts are being made to make the best use of existing drugs.

We are proud to be a part of bringing hope to patients and their families desperately searching for answers. We are the companies of Embark Healthcare. We offer a unique approach to investing in the pharmaceutical industry.

Founded in 2001, Embark Healthcare is an "Indications Discovery Company." Embark Healthcare companies don't discover new drugs. Instead, they discover new ways to use existing drugs for other indications and then advance those drugs into late-stage development programs for the betterment of humankind.

If you would like to learn more about the investment opportunities in repurposing drugs, please feel free to reach out to us.

We're Embark Healthcare. Health. Caring.

HOW THE NUMBERS FOR DRUG REPURPOSING ADD UP

1. **Repurposed drugs involve LESS RISK, because of their known safety profile.**
2. **To de-risk even more, we seek out drugs where HUMAN DATA exists for the new indication.**
3. **Repurposed drugs have a SHORTER ROUTE to approval and a HIGHER APPROVAL RATE.**
4. **Repurposed drugs can gain approval at a FRACTION OF THE COST of de novo drugs.**
5. **Adding IP (i.e., new patents) and gaining orphan drug designation and other regulatory protections (i.e., new chemical entity), provides MARKET EXCLUSIVITY.**
6. **Repurposed drugs bring PATIENTS IN NEED life-saving, life-changing therapy, HELP PHARMA fill their late-stage pipeline, all the while BENEFITING INVESTORS.**

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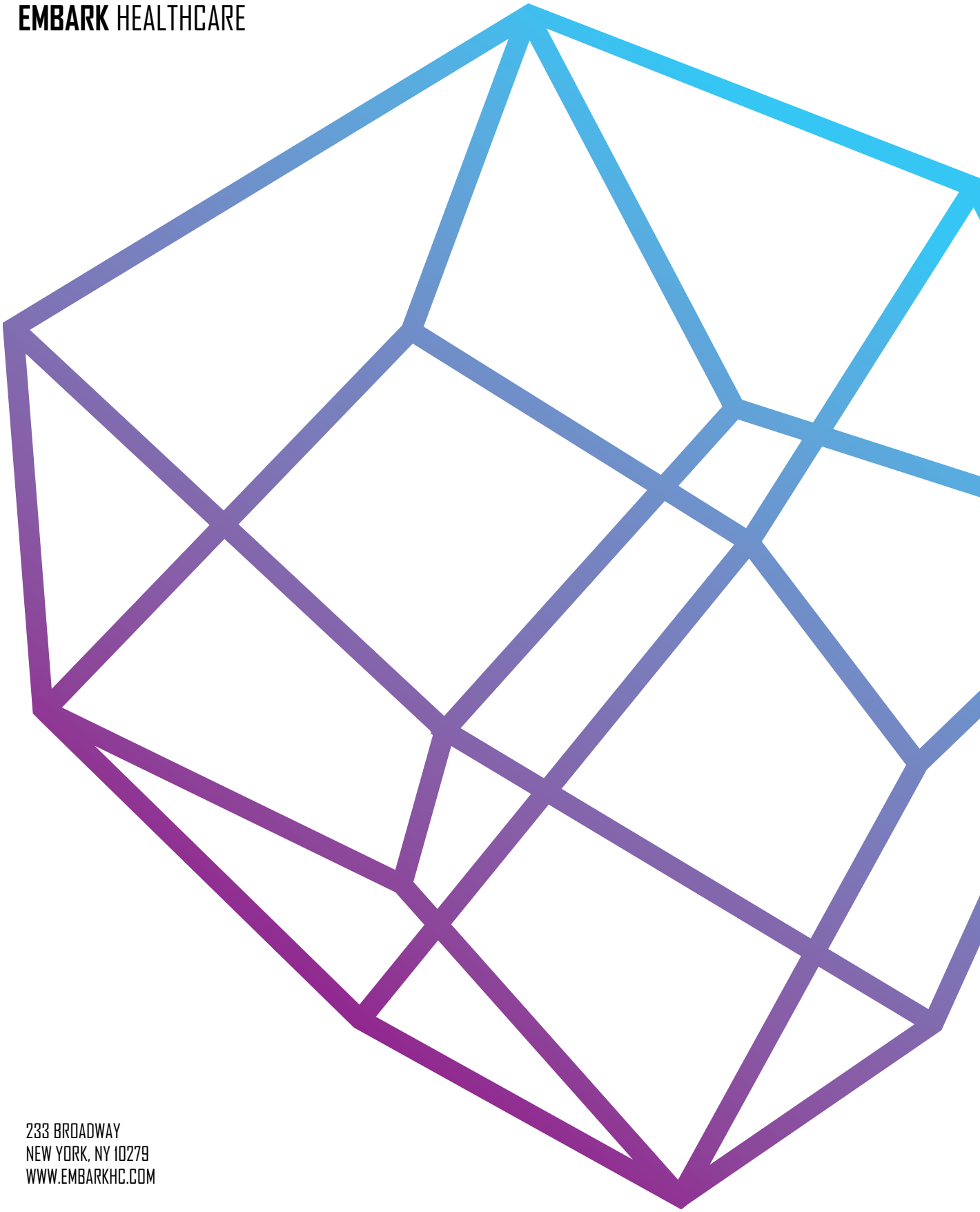

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