



**MADE
WITH**
HEART & SCIENCE

WHITEPAPER

Drug repurposing trends and strategic approaches for shortening timelines

Anil Kane

*Executive Director, Global Head of Technical
& Scientific Affairs at Thermo Fisher Scientific*



Abstract

As the complexity of drug development increases, so does the industry's focus on strategies and solutions that can help bring advanced products to market as quickly as possible. Lowering the cost of R&D is also a key factor, as new chemical entities and de novo drugs in clinical phases face high attrition rates, with companies losing significant investments in non-viable candidates. One approach to avoiding this fate is drug repurposing, where known clinical candidates or commercially approved molecules are evaluated for new targets and indications. Understanding drug repurposing, how it can significantly reduce your time to market, and the important role established and knowledgeable CDMOs can play in this journey is critical to finding success with this emerging strategy.

The cost and benefit of failure

The failure rate for traditional new chemical entity (NCE) development is significantly high in the early stages of development, with 90% of NCEs failing before they even reach Phase I testing (Figure 1) based on poor exposure or animal toxicity. Once the molecule moves from Phase I to Phase II and safety issues are addressed, the failure rate drops to 34% and the efficacy testing of the drug candidate for the specific therapeutic indication becomes the primary goal.¹ We see about half of molecules survive past Phase II, where a critical decision on go/no is done by the clinicians and sponsor companies based on investment in expensive Phase III clinical study and CMC work. From there, the rate drops again to 41%, which could be related to a variety of reasons, such as safety and/or adverse side effects that were not prominent until the drug was given to a larger patient pool. A company's market strategy, competitive landscape in a specific therapeutic area, and business decision could also cause a program to be suspended prior to filing.

Failure during drug development, while costly and frustrating, does create opportunities to take advantage of a drug repurposing strategy (also known as drug repositioning or drug reprofiling), which redirects approved, failed, or shelved drugs and/or recycles existing compounds for novel indications. In fact, many successful drug candidates

have been largely serendipitous discoveries. For example, Sildenafil, which has been sold as Viagra since 2005, was tested as a treatment for erectile dysfunction only after the side effect emerged in Phase I trials for cardiovascular disease.² The antihypertensive medication, Minoxidil, was reformulated into the topical cream Rogaine after patients using it to lower blood pressure also experienced hair regrowth.³ Driven by these and other repurposing success stories, researchers are now taking more tactical approaches to pinpoint new uses for existing shelved or failed drugs and relying on new high-throughput techniques, such as large-scale screens and bioinformatic strategies, to mine data for drug disease connections.

The timeline and cost of developing a novel NCE only compounds the high failure rate. Between 10 and 12 years and approximately \$2 billion to \$3 billion is needed to discover a candidate compound and then take it through the necessary preclinical and clinical tests needed for FDA approval.⁴ To save money, companies, academic institutions, and even nonprofit organizations are getting into drug repurposing where a pharmaceutical company has already invested the resources for preclinical development as well as Phase I and, sometimes, Phase II and Phase III human trials. Repurposing drugs is a more time and cost-efficient strategy, as bringing a repurposed drug to market is estimated at \$300 million.

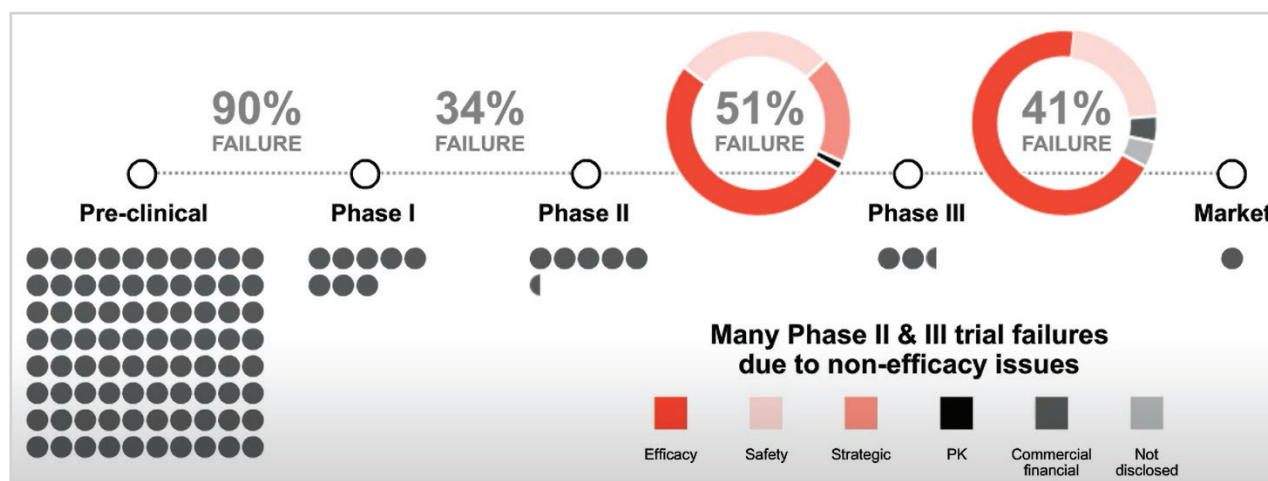


Figure 1: Failure rate of an NCE throughout clinical trial phases

Even with clinical data in hand, it is no small feat to conduct successful late-phase trials required by the FDA for approval of a new indication. In fact, these trials are arguably the most expensive phases of clinical testing, with a Phase III trial program costing anywhere between \$40 million to \$300 million.⁵ The attrition rate for repurposed drugs is estimated to be about 65% versus 90% to 95% of new chemical entities.⁶

The drug repurposing development pathway

A comparison of the pathways for the traditional development of a novel drug versus that of a repurposed drug highlights the advantages of the latter (Figure 2). For example, it is not necessary to carry out any safety studies on a repurposed drug, allowing you to potentially move directly to Phase II and Phase III clinical trials (based on the specific indication). There are cases when safety studies may be required, such as when the doses are significantly higher or if the single ascending dose and multiple ascending dose studies have not yet been conducted. Nevertheless, because safety studies do not need to be conducted on repurposed drugs, the regulatory pathway can be reduced from 10 to 15 years (traditional timeline for an NCE) to about three to eight years.⁶ A repurposed drug is often filed under the 505(b)(2) pathway and then filed as an NDA or BLA, depending on whether it is a large or small molecule.

It is currently estimated that 30% of FDA-approved, new drug products and repurposed drugs account for approximately 25% of the pharmaceutical industry's revenue. Data published by BCC Research (Figure 3) shows an increasing global market trend for repurposed drugs over the last several years.⁷

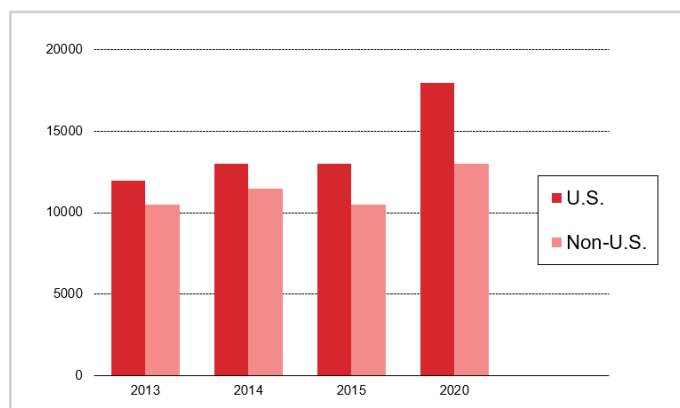


Figure 3: Global market trend for repurposed drugs

Figure 4 below shows the trends related to the application or the therapeutic category, where the top five indications stay the same, regardless of whether the drug is repurposed or an NCE.⁷

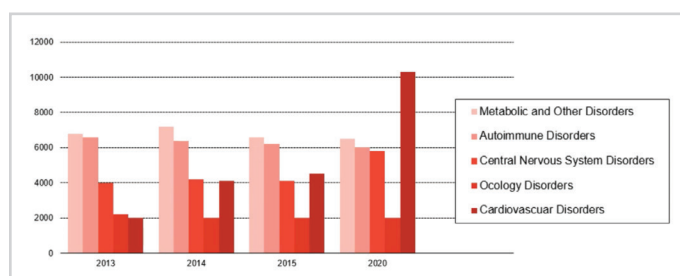


Figure 4: Top five indications targeted in today's pharmaceutical industry

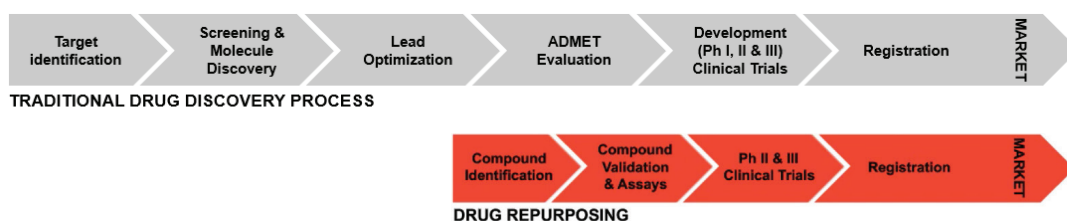


Figure 2: Pathway for a traditional drug discovery process versus a repurposed drug



Some approaches adopted by industry experts (more so in the last five to eight years than the past 10 to 15) to identify drugs for newer indications in drug design include the use of big data, quantitative structured activity relationship modeling, computational tools, machine learning, neural networks, artificial intelligence, and high-power computing techniques. Researchers, medicinal chemists, and pharmaceutical experts have also adopted many other computational and experimental approaches to use in drug repurposing. Some examples include molecular docking, genetic association, phenotype screening, signature matching, and retrospective clinical analysis. There are also many companies investing in artificial intelligence as well as partnerships forming among Big Pharma and even medium-sized companies with experts who can use artificial intelligence in drug discovery. Figure 5 shows the increase in investments in artificial intelligence and machine learning over the last 10 years.⁸

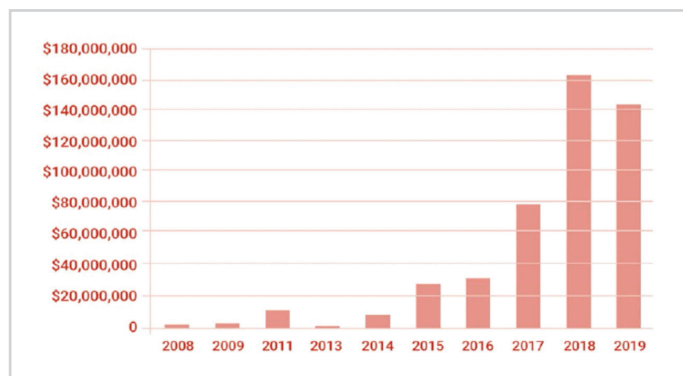


Figure 5: Trends in AI and machine learning investments from 2008 to 2019

AstraZeneca’s new R&D framework, termed the “5Rs,” has introduced an increased scientific rigor and emphasis on quality, driving an almost five-fold improvement in R&D productivity. This approach ensures each project team focuses on improving their understanding of a key set of criteria, which includes the right target, tissue, safety, and patient as well as having the right commercial strategy and a unique value proposition. The results of this effort led to an improvement in their Phase II failure rate, going from 85% between 2005 and 2010 to 60% between 2012 and 2016. There was also an overall improvement in their success rate of drug candidate nomination to Phase III study completion, which went from 4% to 19% over the same timeframe.⁹

There are many potential drug repurposing pathways being considered. Authorized drugs can follow different repurposing pathways, depending on whether they are still under the protection of their original patent or whether they were adapted for the new use. If commercial strategies are applicable, it is likely that the repurposed drug will be developed and registered by the pharmaceutical industry. However, other options, such as off-label use and public promotion, should be explored. Promoting or publishing the positive outcomes, experience, and data of experience of use of the drugs and smaller clinical studies will help medical professionals and the healthcare industry evaluate the use of current drugs for newer indications. If the repurposing strategy does not meet the commercial/financial returns of investment for the pharma industry, then it is likely that the medical profession will use these studies and data for the sole benefit of the patient.

Shelved and off-label drugs

Many pharma companies shelve development programs of experimental drugs in Phase I or Phase II, and even sometimes Phase III, either because they do not work or are unsafe. In other cases, they just no longer fit a company's strategic goals. Many companies must then prioritize these molecules to determine where investments into large-phase clinical trials should be made. This creates opportunities to out-license these molecules to smaller players, such as startup companies, as well as open the door to spinout companies or new startup entities that then look at drug repurposing independently. For example, SpringWorks is a spinout of Pfizer focused on bringing new life to shelved drugs. Another example is iOnctura, a spinout company exploring new applications for shelved immuno-oncology drug candidates.

Many companies must then prioritize these molecules to determine where investments into large-phase clinical trials should be made.

Off-labelling drugs is another form of drug repurposing. According to the FDA, the term "off-label" can mean a drug is:¹⁰

- Used for a disease or medical condition that it is not approved to treat
- Given in a different way e.g., a drug approved as a capsule is given as an oral solution instead
- Given in a different dose e.g., a drug is approved at a dose of one tablet a day but a doctor prescribes a dose of two tablets a day

For example, Hydroxychloroquine is an FDA-approved drug for malaria and lupus but is now an off-label drug for COVID-19. Reports show that 30% of cancer drugs and 70% of pediatric antipsychotic drugs are prescribed for off-label uses.¹¹

There are pros and cons, of course, to this strategy. The biggest difference is that off-label drugs are not systematically evaluated for a specific indication, allowing drug repurposing companies to conduct clinical trials and include them on the new label indications for approval by a regulatory agency.

The promise of repurposed drugs

A drug repurposing strategy can result in new sales and market opportunities for shelved or abandoned compounds or drugs and, during that exploration, may also reveal major new mechanisms of action relative to new target disease indications. These discoveries could potentially lead to an intellectual property claim as well as extend the life of current marketed drugs by determining new indications and/or formulations. This depends, though, on several factors, including the component parts of the drug repurposing discovery process, the IP and the regulatory issues pertaining to the clinical trials, and suitable business models. Repurposed drug market exclusivity is of paramount importance and can also be achieved by a combination of IP and regulatory efforts executed via an appropriate business model.

In the case of NCEs, patent filing often occurs early in the discovery cycle of the candidate drug. This can result in a rather limited lifespan of composition of matter patent production for the NCE marketed drug. This is not the case with repurposed drugs. The repurposing process enables a later stage filing of a patent and significantly increases the patent production period of repurposed drugs. Yet, the success of such a strategy will also depend on the availability of genetic products that can be substituted by off-label prescription use by individual physicians.

Market exclusivity for an orphan disease drug is particularly attractive, regardless of whether the application was filed as a 505(b)(1) or a 505(b)(2).^{12, 13} It consists of a seven-year period that begins once the drug has been granted approval by the FDA and is independent of the drug's current patent status. A similar provision exists for pediatric drugs, which allows for an additional six-month exclusivity period. Drug repurposing companies are predominantly focused on producing robust clinical pipelines and market-driven therapeutic drugs. The drug repurposing sector is growing rapidly with an average of 14 to 16 new companies being formed every five years.¹⁴ Exit strategies for repurposing companies by acquisition have also been enormously successful.

Repurposed drugs have proven valuable in the current COVID-19 pandemic, as scientists explore more than 140 drugs to combat this deadly virus. For example, drugs intended for other purposes, such as Chloroquine, Hydroxychloroquine, and Remdesivir, are now showing promise against COVID-19. Thermo Fisher Pharma Services is proud to state that we are actively working on more than 40 programs to support our partners in the pharmaceutical industry to treat COVID-19.



Drugs repurposed over the last 5 to 10 years have covered a wide range of diseases and therapeutic categories, and there is still opportunity with many others as well. In a recent study by a joint project between Harvard, MIT, and the Dana-Farber Cancer Institute, over 4,000 drugs used to treat conditions, such as diabetes, inflammation, alcohol abuse, and arthritis in dogs, showed an “unexpectedly high rate of anti-cancer activity.”¹⁵ According to an article about the study, these medications were tested “against 578 laboratory cancer cell lines spanning 24 tumor types, resulting in the identification of 49 non-cancer drugs that selectively killed cancer cells and whose activity against cancer could be predicted using molecular biomarkers. Another 103 compounds reporting less selectivity against cancer cell lines were also identified.”

The market potential for a repurposed drug is determined by the same market forces as a conventional NCE drug and includes drug differentiation, market need, patient acceptance, marketing strategy, and IP positioning. These products have the same opportunity to achieve blockbuster status as a de novo-derived drug. Table 1 shows just some of the brand names that have achieved mini blockbuster status with the annual sales shown on the right. The table also shows the indication for which it was originally developed and the new indication for which it was approved.²

Research shows a wide range of companies that have had success with repurposed drugs, from small to midsize all the way to Big Pharma.

| BRAND NAME | ORIGINAL INDICATION | NEW INDICATION (YEAR) | PHARMA COMPANY | ANNUAL SALES ^a |
|-----------------------|----------------------------------|-------------------------------|----------------------------------|---------------------------|
| GEMZAR | Anti-viral | Various Cancers (Various) | Lilly | \$1.72B |
| EVISTA | Osteoporosis | Invasive Breast Cancer (2007) | Lilly | \$1.09B ^b |
| PROSCAR ^c | Hypertension | BPH (1992) | Merck | \$741.4M |
| PROPECIA ^c | Hypertension | Male Pattern Baldness (1997) | Merck | \$429.1M |
| REVUMID | Structural Analogue ^d | Multiple Myeloma (2006) | Celgene | \$4.28B |
| REVATIO ^e | Angina/ED | PA Hypertension (2005) | Pfizer | \$525.0M |
| RITUXAN | Various Cancers | Rheumatoid Arthritis (2004) | Biogen/IDEC ^f & Roche | \$1.28B |
| TECFIDERA | Psoriasis | Multiple Sclerosis (2013) | Biogen/IDEC ^f | \$2.91B |
| THALOMID | Anti-Nausea | Leprosy (1998) | Celgene | |
| | | Multiple Myeloma (2006) | Celgene | \$535.2M |
| VIAGRA ^g | Angina | Erectile Dysfunction (1998) | Pfizer | \$2.05B |

Table 1: Examples of success in drug repurposing

CDMO support of repurposed drugs

Over the last couple of decades, outsourcing has been key to how the entire pharmaceutical industry — small and large companies — functions, with more than half of the industry forming partnerships with established CDMOs. This strategy gives access to the CDMO's integrated services supporting drug substance and drug product manufacturing for all clinical phases of the work as well as life cycle management approaches. Large and established CDMOs that have been doing this for years are a valuable partner, as they possess a considerable amount of data expertise, experience, and chemistry, manufacturing, and controls (CMC) knowledge. Because of this, many of the new chemical entities shelved in early phase studies due to safety and other reasons were likely supported as preclinical candidates at some point by a CDMO.

As a result, much of the intellectual knowledge about these molecules, although owned by the sponsors, is still stored in their databases. This creates opportunities for newer players and startup companies, as in-licensing and out-licensing of molecules can be leveraged from the CDMO's experience. However, it is important to remember that there are certain CMC regulatory requirements that may have changed since the drug was originally discovered and evaluated in clinical studies.

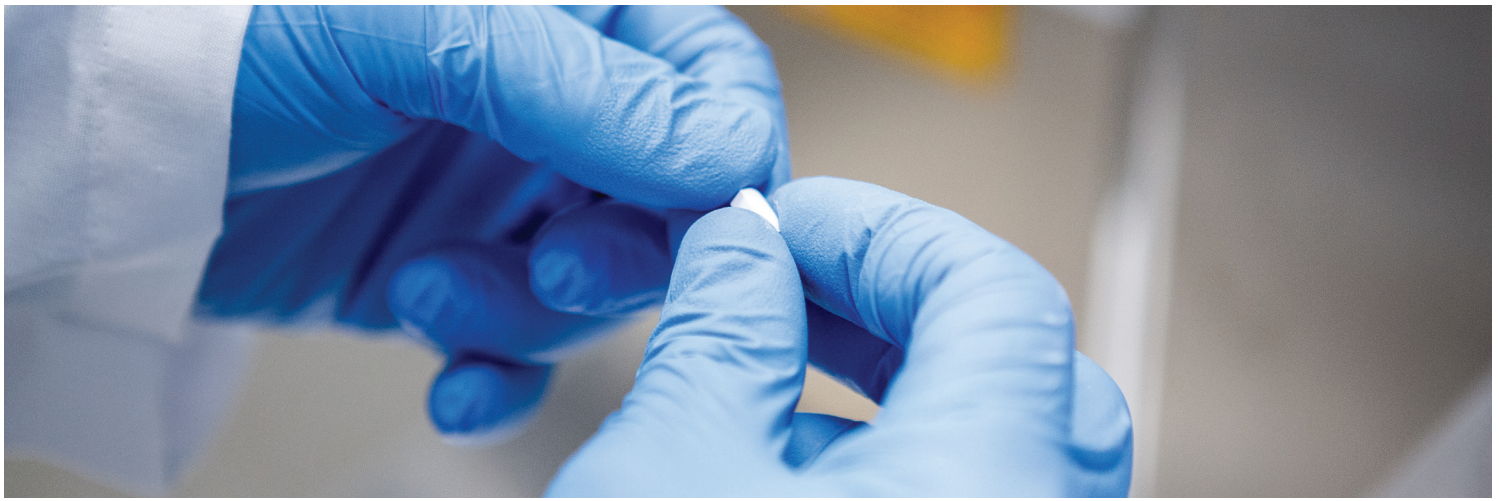
For example, compounds in the category of nitrites or amines that have the potential for n-nitrosodimethylamine (NDMA) formation must now have those impurities evaluated. Additional work, which could be conducted in parallel with clinical studies for the new indication, may need to be considered to ensure the repurposed drug is sufficiently evaluated against current regulations for clinical efficacy and/or safety. Other regulatory requirements that could have potentially changed since the original drug (for the old indication) was developed is the generation of the "robustness data" for the drug product. A systematic Design of Experiments (DOE) under the Quality of Design (QbD) principles will need to be performed for the new dosage strengths of the re-formulated drug product, process, and all analytical methodologies.

In many "drug repurposing" situations, the same molecules are being tested in clinical trials for a different indication and the dose of the drug is likely different than for the original indication. The CDMO is well positioned to reformulate the drug product with the new dosage strength, re-validate the analytical methods for the new dosage strengths for the phase appropriate requirements. This can significantly reduce the scope of work and the time / cost for the repurposed drug development.

Case study: Fast tracking a repurposed drug from development to approval

Once a company discovered that Thermo Fisher Scientific supported the CMC portion of a molecule they would like to repurpose, it is not uncommon for them to contact our team asking for specific data, so they can move forward with additional studies. As an example, a small biotech company came to Thermo Fisher Scientific about an orphan drug they wanted to repurpose for a rare pediatric indication. They had already conducted a Phase II study for rare disease as well as had discussions with, and received approval from, the FDA for fast-track approval.

They were able to use the data from Thermo Fisher Scientific to convince the regulatory agencies for a concurrent validation rather than waiting for the completion of the traditional number of validation batches. The company was then able to submit the validation data with the NDA as a small-volume product for a niche indication. Doing so significantly reduced not only the time needed for CMC activities, but also the overall time to market. There have been many other case studies at Thermo Fisher Scientific where new start-ups and medium-sized companies picked up molecules and products from the "shelved" list of drugs in the clinic and requested a speedy drug product development for new indication, filing, and approval.



Summary

Drug repurposing constitutes anywhere from 10% to 50% of the current R&D spending and is a determining factor in the life cycle management of pharmaceutical products.⁶ Many large pharmaceutical companies have embraced drug repurposing in either a formal or ad hoc manner. Some companies perceive candidate compounds for a polypharmacological perspective in parallel and, therefore, for a potential treatment for multiple diseases while simultaneously running clinical studies. Others have dedicated internal resources specifically to drug repurposing or, for smaller companies, found new opportunities with shelved molecules.

Drug repurposing has gained considerable momentum in the last decade, as it offers a great business opportunity for the entire pharmaceutical industry. Not surprisingly, the strategy has just been integrated in life cycle management of pharmaceutical products, with CDMOs playing a critical role as partners in the process by helping to quickly bring repurposed drugs to the market for the benefit of the patients and healthcare.

References

1. Takebe T., Imai R., Ono S. (2018). *The Current Status of Drug Discovery and Development as Originated in United States Academia: The Influence of Industrial and Academic Collaboration on Drug Discovery and Development*. Clin. Transl. Sci. 11:597–606. doi: 10.1111/cts.12577. <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6226120/>
2. Dhir, Neha et. al. (April 23, 2020). *Drug Repurposing and Orphan Disease Therapeutics, Drug Repurposing - Hypothesis, Molecular Aspects and Therapeutic Applications*. Farid A. Badria. IntechOpen. DOI: 10.5772/intechopen.91941. <https://www.intechopen.com/books/drug-repurposing-hypothesis-molecular-aspects-and-therapeutic-applications/drug-repurposing-and-orphan-disease-therapeutics>
3. Bryan, J. (2011). *How minoxidil was transformed from an antihypertensive to hair-loss drug*. Pharmaceutical Journal. 287. 137-138. https://www.researchgate.net/publication/289021851_How_minoxidil_was_transformed_from_an_antihypertensive_to_hair-loss_drug
4. Nosengo, N. (2016). *Can you teach old drugs new tricks?* Nature. 534, 314–316.
5. Azvolinsky, Anna. (January 1, 2017). *Repurposing Existing Drugs For New Indications*. The Scientist. <https://www.the-scientist.com/features/repurposing-existing-drugs-for-new-indications-32285>
6. Naylor, Stephen et. al. (2015). *Therapeutic Drug Repurposing, Repositioning and Rescue Part III: Market exclusivity using Intellectual Property and regulatory pathways*. Drug Discovery World. <https://www.ddw-online.com/therapeutic-drug-repurposing-repositioning-and-rescue-part-iii-market-exclusivity-using-intellectual-property-and-regulatory-pathways-1239-201508/>
7. Walker, Nigel. (December 7, 2017). *Accelerating Drug Development through Repurposing, Repositioning, and Rescue*. Pharmaceutical Outsourcing. <https://www.pharmoutsourcing.com/Featured-Articles/345076-Accelerating-Drug-Development-Through-Repurposing-Repositioning-and-Rescue/>
8. Jefferies Financial Group. (March 2, 2020). *AI and Machine Learning in Drug Development: The Decade Ahead*.
9. Pangalos, Menelas al. (2018). *AstraZeneca R&D – Improving Drug Development Productivity With Better Predictivity*. Drug Discovery World. <https://www.ddw-online.com/business/p322382-astrazeneca-r&d-improving-drug-development-productivity-with-better-predictivity.html>
10. FDA. (February 5, 2018). *Understanding Unapproved Use of Approved Drugs “Off Label.”* <https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label>
11. McKeegan, Nick. (October 19, 2017). *Promise In Off-Label Drugs For Alzheimer’s*. Cognitive Vitality. www.alzdiscovery.org/cognitive-vitality/article/promise-in-off-label-drugs-for-alzheimers
12. EvaluatePharma®. Orphan Drug Report 2019. (November 2020). ©Evaluate Ltd. and Informa PharmaProject database.
13. Drew, Angela and King, Jennifer. (April 8, 2018). *505(b)(1) versus 505(b)(2): They Are Not the Same*. Camargo Pharmaceutical Services. <https://camargopharma.com/resources/blog/505b1-versus-505b2/>
14. Culbertson, Adam et. al. (August 3, 2007). *Personalised Medicine – Technological innovation and patient empowerment or exuberant hyperbole?* Drug Discovery World. <https://www.ddw-online.com/precision-medicine/p322685-personalised-medicine-technological-innovation-and-patient-empowerment-or-exuberant-hyperbole.html>
15. Clinicalomics. (2020). *Drugs Developed for Other Illnesses Might Be Repurposed for Cancer Treatment*. <https://www.clinicalomics.com/topics/translational-research/the-drugs-tested-in-the-study-spanned-a-wide-variety-including-medication-designed-to-treat-diabetes-inflammation-alcohol-abuse-and-even-arthritis-in-dogs/>

About us

Thermo Fisher Scientific provides industry-leading pharma services solutions for drug development, clinical trial logistics and commercial manufacturing to customers through our Patheon brand. With more than 55 locations around the world, the company can provide integrated, end-to-end capabilities across all phases of development, including API, biologics, viral vector services, formulation, clinical trials solutions, logistics services and commercial manufacturing. We give all sizes of pharma and biotech companies instant access to a fully integrated global network of facilities across North America, Europe, Asia and Australia. Our global leadership is built on a reputation for scientific and technical excellence. This includes

specialized capabilities for highly potent and controlled substances, viral vector expertise, aseptic filling and lyophilization, complex formulations, solubility enhancement and difficult-to-manufacture APIs. We also offer integrated services for drug development that aligns development of drug substance and drug product in a coordinated drive toward proof of concept that can reduce development timelines. We have more than 17,000 scientific and professional staff and over 40 years of experience. As a leading global CDMO, we deliver unrivaled quality, reliability and compliance. Together with our clients, we're rapidly turning pharmaceutical possibilities into realities.



Anil Kane, Ph.D., MBA

*Executive Director, Global Head of Technical Scientific Affairs
Thermo Fisher Scientific*

Dr. Kane has more than 25 years of experience in the science and business of taking molecules through the entire drug development process. His extensive knowledge spans early stage development to scale-up and commercial manufacturing, and includes technical transfers between global sites and drug life cycle management. Dr. Kane received his Bachelors, Masters and Ph.D. degrees from the Bombay College of Pharmacy, University of Bombay, India, and served as a post-doctoral fellow at the School of Pharmacy, University of Cincinnati, Ohio. He has also earned an executive MBA from Richard Ivey School of Business, University of Western Ontario, Canada. Dr. Kane is a member of various international pharmaceutical professional organizations, and is often asked to speak about scientific topics on formulation, technology other technical aspects, QbD, etc at major industry events. He has also published many articles in International journals and delivered many talks at meetings and conferences cross the globe.