

FROM FORGOTTEN MOLECULES TO FRONTLINE MEDICINE: THE TRANSFORMATIVE POWER OF DRUG REPURPOSING

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Received: 15 July 2025 | **Revised & Accepted:** 4 October 2025

Keywords: Drug repurposing, Computational, Experimental, IPR, Off label, Sildenafil.

ABSTRACT

Drug repurposing, also known as drug repositioning, involves identifying new therapeutic uses for existing drugs, reducing time and costs compared to traditional drug discovery. This approach has gained importance, particularly after the COVID-19 pandemic, as pharmaceutical companies seek faster alternatives to meet growing healthcare demands. Repurposed drugs bypass several early-stage trials, reducing risks and accelerating approval. Drug repurposing utilizes computational and experimental approaches. Computational methods include signature matching, molecular docking, genetic association studies, and pathway mapping, leveraging bioinformatics and AI to identify potential drug-disease relationships. Experimental validation involves binding assays and phenotypic screening to test drug efficacy in new disease models. Retrospective clinical analysis, using electronic health records and real-world evidence, further aids in identifying promising candidates. Several drugs have been successfully repurposed, leading to new treatments for various conditions. Thalidomide, initially a sedative, was repurposed for multiple myeloma. Sildenafil, developed for hypertension, became a successful treatment for erectile dysfunction and later for pulmonary arterial hypertension. Advances in genomics, AI and big data analysis have further accelerated drug repurposing efforts. Drug repurposing offers a promising strategy to address unmet medical needs efficiently. Despite regulatory and patent challenges, it has led to groundbreaking therapies in oncology, neurology, and infectious diseases. The future of drug repurposing seems promising due to breakthroughs in AI genomics, and personalized medicine. While genomics could provide for specialized therapies for particular patient populations, AI will speed up the discovery of novel drug-disease combinations by examining enormous databases.

INTRODUCTION

Conventional drug discovery is expensive, time-consuming, and risky; because of its complicate chemical properties and manufacturing difficulties, it necessitates stringent regulatory compliance and substantial expenditure. The practice of finding new therapeutic uses for existing,

unsuccessful, or experimental drugs is known as drug repurposing, and it gained prominence during the COVID-19 pandemic. It is also referred to as therapeutic switching or drug repositioning, and it has had successful outcomes with minoxidil, aspirin, and sildenafil. Repurposing usually only comprises four

steps, as opposed to five in traditional drug research, which saves money, time, and failure risk. The first drug repurposing was observed serendipitously in the 1920s, the field has advanced with better methods. Repurposing efficiency has increased due to developments in cheminformatics, bioinformatics, and access to huge biological databases. The process is being further accelerated by artificial intelligence (AI), in silico techniques, and structure-based drug design (SBDD), which is making drug development more inventive and useful (1-4).

WHAT IS DRUG REPURPOSING?

Drug repurposing (or repositioning) means using an existing drug to treat a different disease than what it was originally made for. Sometimes, scientists actively test a drug to see if it can be useful for other diseases. When a pharmaceutical company first creates a drug, they test it for a specific disease. However, later, researchers may find that the same drug can also be useful for another condition. This discovery can happen in two ways:

1. Intentional Discovery
2. Accidental Discovery (serendipity)

Table 1: TRADITIONAL DRUG DISCOVERY VS DRUG REPURPOSING

Parameter Group	Traditional Drug Discovery	Drug Repurposing	Key Insight
Definition & Identity	Discovery of new molecular entities (de novo)	Finding new uses for existing drugs (repositioning/reprofiling)	One creates new drugs, the other repurposes known ones
Development Path	Full pathway: discovery → preclinical → clinical → FDA → post-market	Identification → acquisition → development → post-market	Repurposing skips initial discovery stages
Duration & Cost	10–17 years; ~\$1.2–\$12B	3–12 years; ≤60% cost; ~\$1.6B	Repurposing is faster and cheaper
Risk & Data Availability	High failure risk; limited initial data	Lower risk; available safety/PK data	Repurposing benefits from prior evidence
Clinical Trial Burden	Starts from scratch	Can bypass early phases	Faster transition to clinical use
Focus & Use Cases	Chronic/complex diseases	Rare, neglected, emerging diseases	Repurposing bridges unmet needs

Technologies Used	Lab-centric R&D	AI, in-silico, cheminformatics, SBDD	Repurposing is data-driven and computational
Regulatory Path	Full regulatory scrutiny	Reduced preclinical requirements	Regulatory acceleration
Success Rate	Lower due to unknown toxicity	Higher due to known safety profiles	Prior testing improves outcomes
Examples & Industry Impact	Statins, monoclonal antibodies; slow high-risk pipeline	Sildenafil, Minoxidil, Metformin; ~30% FDA approvals repurposed	Major growth area; projected \$31.3B market

HISTORY:

THALIDOMIDE'S UNEXPECTED SECOND LIFE: A TREATMENT FOR MULTIPLE MYELOMA

Thalidomide was first developed in 1952 and marketed as a sedative and treatment for morning sickness in pregnant women. However, the drug had been withdrawn in 1962 due to its teratogenic effect on foetus phocomelia. Further studies showed that the drug had anti-inflammatory and antiangiogenic actions because it inhibits tumour necrosis factor-alpha signalling. This led to its subsequent approval in 1998 for the treatment of erythema nodosum leprosum and in 2006 for the treatment of multiple myeloma. 30 more new indications for this drug are currently being investigated.

THE STORY OF SILDENAFIL: FROM HEART DRUG TO BLOCKBUSTER TREATMENT FOR ERECTILE DYSFUNCTION AND BEYOND

Sildenafil (Viagra), a PDE-5 inhibitor, is one of the oldest and most successful medication that was developed as a repurposed drug serendipitously. Pfizer originally developed it as an antianginal medication in the 1990s. The drug's

involvement in erectile dysfunction became clear throughout clinical trials. Over the following 20 years, sildenafil, which was approved in 1998 and marketed under its brand name "Viagra," has been a commonly prescribed medication for erectile dysfunction. The medication was later modified and approved as "Revatio" in 2005 for the treatment of pulmonary arterial hypertension (5-7).

VARIOUS WAYS IN UTILIZING APPROVED DRUGS FOR ALTERNATIVE INDICATIONS

1. Serendipitous Discoveries: Drugs created for one ailment can sometimes turn out to be beneficial for another. Example: Minoxidil was created for high blood pressure but was later found to help hair growth, leading to its use as Rogaine for baldness. This resulted in its FDA clearance in 1988 as a topical treatment for male paternal baldness.
2. Repurposing Unsuccessful Drugs: Drugs that fail in clinical trials for their original purpose may still have potential for other conditions. Example: sunitinib was initially unsuccessful in treating colorectal, breast, prostate, and non-small cell lung cancers. However, after repurposing efforts, it was approved for

treating gastrointestinal stromal tumors and renal cancers, and later for pancreatic neuroendocrine tumors in 2010.

3. **Post-Market Discoveries:** Adverse events may be documented during post-market surveillance studies, and these events may provide a new information which could be utilized to reposition the formulation using other drug development strategies. Example: pramipexole, used for the treatment of Parkinson's disease and restless legs syndrome, is sometimes prescribed off-label for depression. Because it acts on dopamine receptors, it may be an effective antidepressant.
4. **Off-Label Prescribing:** Off-label usage is a popular and lawful practice. Medication prescriptions for ailments not formally approved by regulatory bodies are occasionally written by Physicians. Example: the antidepressant amitriptyline is frequently administered as off-label to treat persistent back discomfort. Its effects on neurotransmitters involved in pain processing, including serotonin and norepinephrine, are connected to its efficacy in pain alleviation.

CRITERIA

- **Eligibility for Repurposing:** Repurposing is a good option for drugs that have successfully completed several stages of clinical development but failed for reasons other than safety.
- **Safety and Mechanism of Action:** A drug may be prohibited from comprehensive clinical testing if its safety and toxicity profiles have been established via previous trials; however, its mechanism of action still needs to be thoroughly studied.
- **Sildenafil is a notable example.** Originally developed to treat angina and

hypertension, sildenafil (Viagra) was successfully repurposed for erectile dysfunction during clinical trials.

- **Thalidomide is a controversial example.** Originally administered to treat morning sickness but then withdrawn due to teratogenic consequences. Thalidomide was later used to treat leprosy and multiple myeloma, which raised ethical concerns.
- **Regulatory and Ethical Considerations:** Before approving a repurposed drug, regulatory bodies must evaluate the benefit-to-risk ratio and decide whether it is safer or more effective than current treatments (8-11).

VARIOUS APPROACHES IN DRUG REPURPOSING:

COMPUTATIONAL APPROACHES:

Computational techniques analyze several types of data, including gene expression, chemical structure, genotyping or proteomic data, and electronic health records (EHRs), to generate repurposing hypotheses. The most commonly used computational approaches, together with drug repurposing examples, are-

- a) **Signature matching:** By matching the characteristics of existing drugs to those of diseases, signature matching discovers novel applications for drugs. Gene expression matching determines if a drug reverses changes in disease-related gene activity. Chemical structure matching assumes similar effects by examining similar drug forms. Despite difficulties with data collecting, AI helps with side effect matching, which connects medications with comparable side effects.
- b) **Molecular Docking:** A computer-based technique called molecular docking predicts how well a drug will bind to a

protein linked to a disease. By testing drugs on different proteins, such as mebendazole's ability to inhibit blood vessel formation, it aids in the discovery of new therapeutic uses. Unknown protein structures and the adaptability of both proteins and drugs during binding pose challenges. Despite these challenges, advances in technology are increasing the accuracy and utility of docking in drug repurposing.

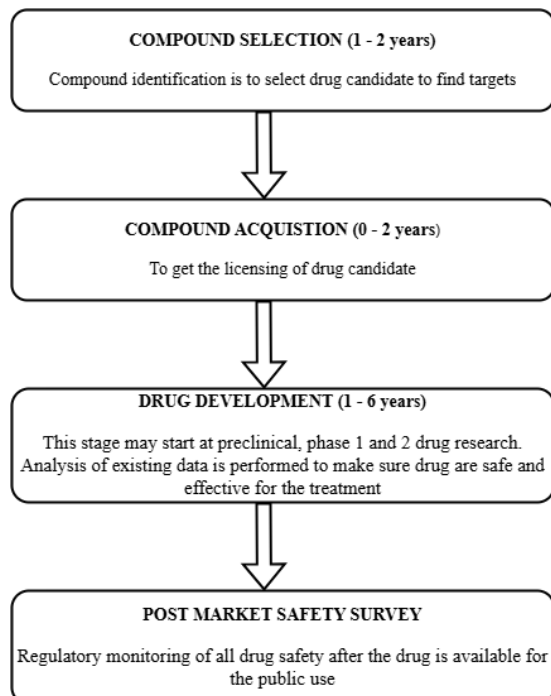
- c) **Genetic Association:** GWAS aims to identify genetic variations associated with recurrent diseases, which may lead to the discovery of novel therapeutic targets. Although there are still difficulties because of the lack of pathophysiological understanding, this can help with drug repositioning and calls for careful examination.
- d) **Pathway Mapping:** Network-based approaches find possibilities for drug repurposing by analysing information such as gene expression, disease pathophysiology, and protein interactions. By creating drug or disease networks, these techniques improve accuracy over GWAS alone. A more accurate method called NetWAS aids in identifying better pharmacological targets, such as those for high blood pressure.
- e) **Retrospective Clinical Analysis:** As demonstrated by the incidents of sildenafil and aspirin, retrospective clinical analysis leverages EHRs and clinical data to identify novel therapeutic uses. Comprehensive records aid in locating obscure drug-disease connections, such as terbutaline sulphate's role in ALS. Even if access limitations and unstructured data provide challenges, AI and machine learning are helping to improve this process.

- f) **Novel Data Sources:** Researchers are investigating novel applications for licensed medications by utilizing a variety of data sources, including genome-wide studies, biobanks, and cancer cell testing. These methods aid in identifying genetic connections between diseases and outcomes of treatment. Even though they might be untrustworthy, online patient reviews provide practical information that supports efforts to repurpose drugs.

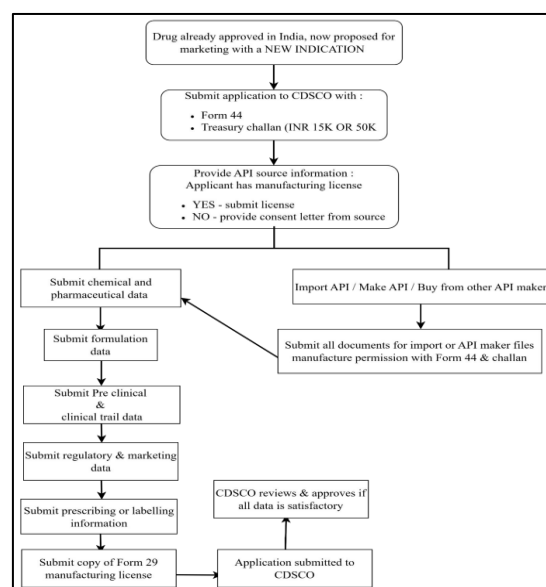
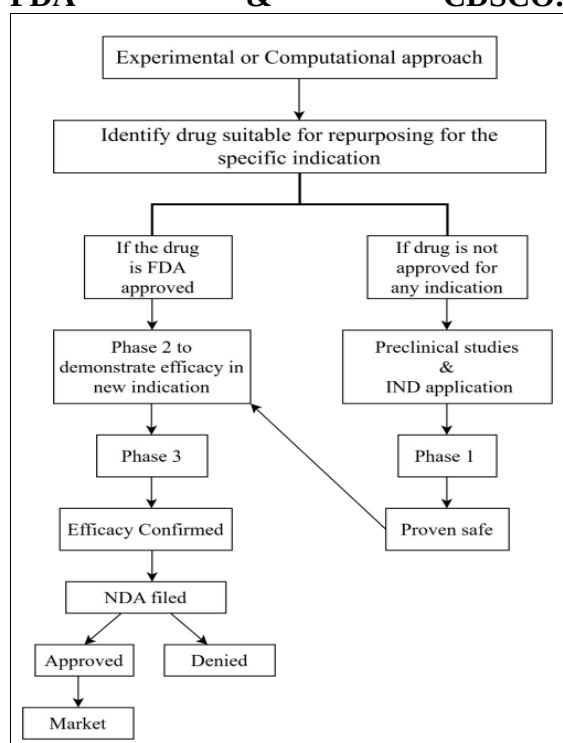
EXPERIMENTAL APPROACHES

- a) **Binding Assays to identify relevant target interactions:** In order to investigate drug-protein interactions and identify off-target effects, binding assays employ methods such as mass spectrometry and CETSA. By determining the broader impact of drugs, such as the use of imatinib beyond treating leukaemia, these techniques, alongside with instruments like kinobeads, facilitate drug repurposing. Additionally, high-throughput screening facilitates the investigation of drug responses, resistance, and novel uses, such as treating infections.
- b) **Phenotypic screening:** Using whole-organism or cell-based tests, phenotypic screening can identify drugs that influence disease despite having knowledge of their targets. Through the use of zebrafish models, it has revealed unforeseen uses for already-approved drugs, such as disulfiram's anti-cancer properties and drugs approved by the FDA that help treat tobacco dependence (12-14).

STAGES OF DRUG REPURPOSING:



REGULATORY PATHWAY FOR DRUG REPURPOSING AS PER US FDA & CDSCO:



The approval process for drug repurposing begins with the selection of an experimental or computational approach to identify potential drugs for a given indication. The drug enters directly into Phase 2 studies to determine its efficacy for the new usage if it has already received FDA approval. It must first go through preclinical research and submit an IND (Investigational New Drug) application before going through Phase 1 trials to confirm its safety if it is not approved. The drug proceeds to the Phase 2 and Phase 3 studies when safety is established. Once efficacy has been confirmed, a New Drug Application (NDA) is submitted. The drug is marketed if approved and not made available if rejected.

To propose a new indication for a drug already approved in India, the applicant must submit an application to CDSCO together with Form 44 and a treasury challan (₹15,000 or ₹50,000). Information about the API source must also be provided; if a license is granted, it is submitted; if not, a consent letter is needed. API may be imported, manufactured, or purchased, and related documents must be submitted. Then, together with Form 29 and labelling,

the applicant provides chemical, pharmaceutical, formulation, preclinical, clinical, and regulatory data. The application is sent to CDSCO, which authorizes the request if all the data is satisfactory.

ADVANTAGES

1. Saves Time and Money - Developing new drugs is expensive and time-consuming. Where Repurposed drugs have known safety profiles, which leads to reduction in cost and development time.
2. Higher Success Rate - Only ~2% of new drugs get FDA approval. Drug repurposing has a success rate of over 65%.
3. Reviving the Potential of Failed Drugs - Drugs that have failed for a condition may work for another indication.
4. Finds New Uses for Existing Drugs - Approved drugs can be repurposed to treat different diseases, expanding their utility.
5. Uses Advanced Technology - Tools like AI, genomics, and big data make identifying repurposing opportunities faster and more accurate.
6. Supports Drug Development - Repurposing is an effective means to overcome therapeutic gaps as new medicine approvals are declining.
7. Targets Multiple Diseases - Many drugs influence multiple biological pathways and can treat several conditions (average of 6–13 targets per drug).
8. Encourages Combining Different Approaches - The potential of success is increased when a combination of computational and biological methods is used.

CHALLENGES IN DRUG REPURPOSING:

Although drug repurposing has clear advantages - saving time, reducing costs, and increasing success rates, it still faces substantial barriers toward more implementation, particularly by pharmaceutical companies.

1. Risk of Failure in Later Stages:

- Clinical Uncertainty: Repurposed drugs may still fail in Phase II or III clinical trials if they don't demonstrate effectiveness for the new disease.
- Efficacy Problems: The drug that was proven safe in its initial use may not produce the desired outcomes in a different patient population or disease condition.

2. Patent Issues and Commercial Risks: One major problem with repurposing drugs is that pharmaceutical companies may not be able to secure patents or maintain market exclusivity for the new use of the drug. A patent gives a company the exclusive right to sell a drug, helping them recover research costs. These issues have demotivated active participation of the industries in repurposing of the drugs.

- Patent Expiry
 - Limited Exclusivity (3 years)
 - Commercial Disincentives
- #### **3. Difficulty in Patenting Repurposed Drugs:** Scientists can address new applications for old drugs in research articles before a company applies for a patent. Once the concept is public, it becomes "prior art," which means it can no longer be patented. To protect their repurposed drugs and prevent other corporations from replicating them, companies could
- Change the dosage or frequency with which the drug is administered.
 - Change the way the drug is administered, for example changing an injection into a tablet.

- Combine it with another medicine to achieve a new effect. These adjustments allow corporations to get new patents and continue making profits from the drug.
- 4. Limited Access to Data from Failed Drug Trials: Many drugs are abandoned during development because they don't work well or cause side effects. But often, the results from these trials are not shared with other researchers. If companies shared more data from preclinical and clinical trials, it would help researchers:
 - Learn from past mistakes & avoid repeating the same tests
 - Find new uses for old or abandoned drugs faster. Sharing this information could speed up drug repurposing and lead to better treatments.
- 5. Challenges in Computer-Based (In Silico) Drug Discovery: These include
 - Incomplete Datasets that often lacks failed drug outcomes.
 - Bias Toward Known Mechanisms that tend to identify drugs similar to those already known, limiting innovation.
 - Assumptions Can Be Misleading: The belief that similar molecules behave similarly doesn't always hold, especially for complex diseases.
- 6. Limitations in Experimental Testing Models:
 - Poor Human Correlation: Lab-based systems don't fully replicate the complexity of the human body.
 - Short Study Windows: Current models often can't simulate long-term conditions like Alzheimer's or cancer.
 - Immune Response Limitations: Key interactions with the immune system are often missing in experimental models, making it hard to study autoimmune or infectious diseases (15-17).

LIMITATIONS & BARRIERS

1. Intellectual Property (IP): Drug repurposing presents challenges from an intellectual property (IP) perspective since new indications could not be patentable, particularly if the original patent has expired. It is sometimes difficult for repurposed drugs to obtain Composition of Matter (COM) claims, which are essential for safeguarding new compounds. In order to minimize economic incentives, companies must demonstrate originality and therapeutic benefit beyond what is currently known by the public. Investment in repurposing initiatives may be hampered by this weak IP protection.
2. Financial and Commercial barriers: Even though drug repurposing can lower early development costs, hundreds of millions of dollars may still be needed to bring a repurposed treatment to market. Even though it reduces development risks, extensive research and complete regulatory approval are still required. Older, off-patent medications can lose priority in favour of newer, more profitable chemical compounds. Funding is still a significant obstacle, particularly among late-stage trials, especially if the initial indication was unsuccessful.
3. Regulatory and clinical trial hurdles: Regulatory approval for repurposed drugs is similar to that of new drugs which can be time consuming and costly. Designing appropriate clinical trials for repurposed drugs can be challenging and it needs careful consideration of parameters such as potency, target engagement and safety. Despite potential cost and time benefits, repurposed drugs might fail in clinical trials (phase II & phase III) leading to considerable financial losses.

4. Data Access barriers: The discovery of possible drug candidates may be hindered by limited accessibility of certain data types, such as clinical trial data. Because of computational constraints, non-standardized format and data quality issues, data mining and integration can be difficult. Data analysis in drug repurposing can be subjected to confounding and bias, that could end up in incorrect outcomes.
5. Other barriers: Insufficient knowledge, liability concerns, and uncertainty about the value of repurposing result in backing the development of drug repurposing.

Table 2: SUCCESSFUL EXAMPLES OF REPURPOSED DRUGS

Drug	Original Indication	New/Repurposed Indication	Year of Approval / Expansion
Galantamine	Chronic fatigue syndrome	Alzheimer's disease	2001
Amitriptyline	Antidepressant	Neuropathic pain	2005
Ropinirole / Pramipexole	Parkinson's disease	Restless leg syndrome	2005 / 2006
Thalidomide	Morning sickness	Multiple myeloma	2006
Pregabalin	Anticonvulsant	Fibromyalgia	2007
Amantadine	Influenza A	Parkinson's disease	2017
Esketamine (Ketamine)	Anesthetic	Treatment-resistant depression (nasal spray)	2019–2020 (FDA)
Colchicine	Gout / Familial Mediterranean fever	Cardiovascular inflammation (post-MI)	2020–2021 (expanded use)
Ruxolitinib	Myelofibrosis	Graft-versus-host disease	2021
Tadalafil	Erectile dysfunction	Benign prostatic hyperplasia	2020–2022 (expanded approvals)
Minocycline	Antibiotic	Neurodegenerative diseases (ALS, Parkinson's)	Ongoing / trial stage (2020 onward)
Metformin	Type 2 diabetes	Aging, anticancer prevention	Investigational (2020–2025 trials)
Rapamycin	Immunosuppressant	Aging, cancer, neurodegeneration	Ongoing trials (2020–2025)
Low-dose Naltrexone	Opioid/alcohol dependence	Autoimmune disorders, fibromyalgia (off-label)	Growing adoption (2020–2025)
Ivabradine	Heart failure	Stable angina	2020–2023 (expanded approvals)
Amantadine*	Influenza A	Parkinson's disease, traumatic brain injury	2020–2024 (expanded use)
Bexarotene	Cutaneous T-cell lymphoma	Alzheimer's disease (investigational)	Trials 2020–2025

Doxycycline	Antibiotic	Anti-inflammatory & neuroprotective uses	Expanded off-label use (2020–2025)
Topiramate	Epilepsy	Migraine prophylaxis, binge eating disorder	Expanded use (2020–2025)

FUTURE PERSPECTIVES

Computational advancements and integrated biological techniques are increasingly driving developments in drug repurposing. The selection of potential candidates is streamlined by artificial intelligence and machine learning, which improve the prediction of drug-target interactions and drug-disease connections. Improved understanding of disease mechanisms is made possible by the combination of multi-omics data and systems biology, which makes repositioning tactics more logical and mechanism-based. The validation of repurposed medications across a range of patient populations is further supported by empirical data and evidence. Precision medicine supports these initiatives by customizing treatments through biomarker-guided patient stratification. Concurrently, changing regulatory frameworks seek to establish more flexible and effective approval processes for medications that have been repurposed. Global data sharing and hypothesis-driven research are made easier by collaborative efforts and open-access platforms. Ethical considerations such as equal access, transparency, and patient autonomy remain critical, particularly in off-label use. In order to overcome resistance and increase efficacy, combination therapy and medication repurposing are also becoming more popular. In general, improving the clinical and translational success of drug repurposing requires the convergence of computational technologies, precision medicine, and international cooperation (18-20).

CONCLUSION

Drug repurposing, also known as drug repositioning, finds new therapeutic indications for the drugs that already have proven safety and pharmacokinetic profiles, providing a logical and economical alternative for traditional drug development. This approach is quite beneficial, especially when it comes to fulfilling emergency or unexpected clinical requirements, as it significantly decreases time-to-market and developmental attrition. The systematic investigation of drug-disease associations has been made feasible by advancements in computational methods, namely in silico molecular docking, gene expression signature matching, network pharmacology, and artificial intelligence (AI). These technologies improve the translational potential of repurposing candidates when used in addition to experimental validation methods such as target-based binding assays and phenotypic screening. Moreover, post-market surveillance and outcome evaluation are supported by the integration of real-world data (RWD) and real-world evidence (RWE) collected through electronic health records and retrospective clinical analysis. The clinical efficacy of the method has been proven by successful examples, such as the repositioning of thalidomide for multiple myeloma and the increased indication of sildenafil to pulmonary arterial hypertension. Developments in genomes, multi-omics, and AI-driven personalized medicine are driving drug repurposing despite existing regulatory, intellectual property (IP), and trial design barriers.

Harmonizing regulatory frameworks, enhancing inter-sectoral cooperation, promoting open-access data exchange, and ensuring ethical monitoring should be the main objectives of future perspectives. Drug repurposing has the potential to significantly boost therapeutic innovation and increase treatment accessibility across a range of disease domains when implemented strategically.

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