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Regulatory challenges in pharmaceuticals: Navigating global compliance and approval

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***Abstract*---**Background _ The concept of repositioning or repurposing existing medicines for new disease indications has emerged as an attractive strategy in drug development. This approach can lead to significant savings in time and financial resources, particularly in the context of cancer treatments, where there is an urgent need for effective therapies. Repurposed medicines often prioritize effectiveness over safety considerations due to the critical nature of cancer care. Aim of Work – This paper aims to provide a comprehensive overview of the strategies employed by drug developers to secure financing, navigate regulatory affairs, and manage intellectual property regulations in order to successfully bring repurposed medicines to market as novel cancer treatments. Methods – The study involved a thorough review of financing options available for repurposing pharmaceuticals, including government grants and charitable organizations. Additionally, it examined historical instances where computer simulations predicted secondary applications of FDA- or EMA-approved therapies, which were subsequently validated through in vitro and in vivo studies. The paper also analyzed the tactics employed by the pharmaceutical industry to address regulatory challenges in bringing these medicines to market. Results – The findings indicate that various financing options exist for academic and business projects aimed at repurposing drugs for cancer treatment. Successful cases of repurposed therapies demonstrate the efficacy of computer simulations in predicting new applications. Furthermore, the pharmaceutical sector has employed specific strategies to manage regulatory issues effectively, facilitating the market entry of repurposed medicines. Conclusion – To optimize the benefits of repurposed medications for both patients and pharmaceutical companies, it is essential to carefully consider financing, regulatory navigation, and intellectual property management. This comprehensive approach can enhance the success of bringing effective cancer treatments to those in need.

***Keywords*---**Drug Repurposing, Cancer Treatment, Regulatory Affairs, Financing Strategies, Intellectual Property.

Introduction

The practice of repurposing drugs is becoming more popular as a strategy for creating new medications. Indeed, the approach of repurposing existing therapeutics for new uses has been proven successful in previous observational studies and instances of serendipity. For example, sildenafil (Viagra), a phosphodiesterase inhibitor originally designed to treat angina, has now been repurposed as a medication for erectile dysfunction. Similarly, metformin (Glucophage), a widely used diabetes medication, is currently being investigated as a potential cancer treatment in over 100 ongoing Phase II and Phase III clinical trials **(1)**. Optimal candidates for medication repurposing are substances that have completed clinical trials and have become unsuccessful due to reasons unrelated to safety, such as failure to meet effectiveness milestones. Given that these medications have previously been shown to be safe, the expenses associated with conducting studies for a new indication are lowered. As an illustration, repurposing mifepristone, an emergency contraceptive, for the treatment of Cushing's syndrome only needed a group of fewer than 30 patients to assess its effectiveness. In contrast, a clinical trial evaluating the safety and effectiveness of a new chemical compound called levoketoconazole for the same condition required approximately 90 individuals **(2, 3)**.

Discovering a novel use for an already established medication has several advantages. Usually, an existing drug has undergone thorough research to assess its safety, effectiveness, and toxicity. As a result, substantial data have been gathered to support its approval by the United States (US) Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA) for a specific use (4). Utilizing existing data via repurposing offers a time and cost-saving solution for patients with rare tumors, whose situations are financially impractical for new research. In addition, medications that have been repurposed are often granted approval in a shorter timeframe, ranging from 3 to 12 years, and at a lower cost, typically decreased by 50 to 60% **(5, 6)**. Furthermore, it is worth noting that only about 10% of new medication applications get market approval. However, roughly 30% of repurposed pharmaceuticals are approved, which provides firms with a strong market-driven motivation to repurpose their current assets **(5)**.

In the context of cancer, unusual or fatal oncological symptoms allow for more flexibility in terms of safety precautions owing to the urgent need for innovative treatments **(7, 8)**. Furthermore, cancer is a complex disease that progresses through several stages, providing opportunities for intervention at the onset, fast and diverse development, metastasis, and/or recurrence. The presence of these characteristics indicates that repurposing drugs with a focus on cancer would be advantageous for both patients and pharmaceutical corporations. The following sections will provide a summary of existing prospects and possible obstacles in this area.

An examination of funding initiatives for cancer drug repurposing

The lack of sufficient financing possibilities for academic and business medication developers indicates that drug repurposing activities are still in their early stages of development. Academic laboratories have effectively incorporated repurposing programs into extended research funds provided by governmental bodies and patient advocacy organizations. These financing options are referred to as non-dilutive since the institution that receives the cash does not give up their ownership or "dilute" its shares. firms sometimes seek dilutive financing options, such as securing investment from venture capitalists and forming partnerships with bigger pharmaceutical firms, in return for giving up a portion of their ownership in the business. While these methods have made preclinical and clinical research easier, both non-dilutive grants and dilutive investments are very competitive and limited in availability. As a result, they do not provide enough financing to maintain worldwide initiatives. Pharmaceutical corporations do not provide financing for this kind of study due to restricted financial incentives caused by licensing and patent protection difficulties in repurposing generic medications **(9)**. Governmental and charitable groups have launched new financing schemes specifically for medication repurposing activities to support this business.

Governmental Granting Agencies

The US government initiated funding assistance for medication repurposing with the establishment of the National Centre for Advancing Translational Sciences (NCATS)2 inside the National Institutes of Health in 2012. NCATS supports the advancement of technology to assist in the creation and use of new treatments. NCATS has allocated specific funding for medication repurposing initiatives, however they are not specifically targeted towards research related to cancer. In addition, NCATS provides research funds for several phases of medication repurposing, ranging from initial in silico forecasts to advanced clinical trials. Several supplementary funding bodies, such as the National Cancer Institute (US) and the Ontario Institute for Cancer Research (Canada), exist. However, these agencies often do not provide grants or subsidies specifically focused on repurposing projects for academic or industry partners.

The Canadian Institutes of Health Research (CIHR) collaborated with Muscular Dystrophy Canada to create two grants specifically for drug repurposing programs. These grants are the E-Rare 3 joint translational call (JTC) and the North American Re:Rare (NAR:R). The JTC provides funding for Phase Ib or IIa clinical trials and is co-funded with European partners. On the other hand, the NAR:R was developed in partnership with philanthropic organizations such as Cures Within Reach (CWR), the Mindset Foundation, and Mitacs. It offers funding for proof-of-principle research. CIHR has not yet created funding opportunities specifically for fundamental science research focused on medication repurposing, including repurposing for cancer therapies, unlike NCATS.

Charitable Institutions

Philanthropic groups also provide assistance for drug repurposing research. CWR currently provides funding for ongoing clinical trials, such as the repurposing of mebendazole, an antiparasitic drug, for the treatment of brain cancer, specifically medulloblastoma and glioblastoma **(4)**. Other organizations with a similar mission include the Anticancer Fund based in Belgium, which focuses on repurposing drug combinations to treat cancer, such as metzolimos, metronomic cyclophosphamide, and methotrexate combined with sirolimus and zoledronic acid for osteosarcoma, and clarithromycin, pioglitazone, and treosulfan for non-small cell lung cancer **(5)**. Furthermore, Findacure, an organization based in the United Kingdom, launched their first grant opportunity in March 2017 to support research on repurposing drugs for rare diseases. Organizations such as the Stem Cell Network and Global Cures either fund a repurposing project on their own or collaborate with government agencies or patient advocacy groups to provide funding. This type of funding is characterized by short-term and highly specific goals, which limits its scope. Although medication repurposing is widely acknowledged as beneficial by many agencies, the majority of funding possibilities primarily focus on supporting late-stage initiatives. As a result, preclinical studies often have to depend on basic research grants. Nevertheless, as the industry continues to provide efficient and economical treatments to patients, it is probable that further financing possibilities specifically for cancer will arise.

Validation of drug repurposing candidates in oncology via preclinical studies
Computational Discovery and Experimental Validation

Due to the growing amount of public and private data produced by in vitro, in vivo, and clinical investigations, it is becoming more usual to use biological multi-systems-level big data and in silico approaches to discover new treatments **(10, 11)**. Significantly, there are two primary tactics that may be employed: one focuses on gene expression, while the other targets specific drugs. The Connectivity Map (CMap) is a collection of gene expression patterns obtained from human cells that have been exposed to several bioactive small compounds **(12)**. Examining a drug's capacity to modify expression patterns in cancer cells enables us to draw conclusions about its mechanism-of-action. This methodology has resulted in the identification of the anticancer characteristics of trifluoperazine, an antidepressant that was previously authorized for the treatment of schizophrenia **(13)**. Trifluoperazine has been successfully tested in both laboratory experiments (in vitro) and live animal studies (in vivo). Additionally, it has shown to work well in combination with the current standard treatment, gefitinib. This information is supported by a study referenced as **(14)**. A different team utilized CMap to discover 28 compounds that showed activity against hepatocellular carcinoma in laboratory tests. Out of these, two compounds (chlorpromazine and trifluoperazine) have been confirmed to be effective in living organisms. Additionally, several other phenothiazines have demonstrated effectiveness in breast cancer cell lines that are resistant to tamoxifen. Additional algorithms based on gene expression are also available, including the Differentially Expressed Gene Signatures—Inhibitors (DeSigN). This tool has recently discovered that bosutinib, a kinase inhibitor currently used in leukemia

treatment, is effective in vitro on oral squamous cell carcinoma cell lines. This finding further emphasizes the effectiveness of these approaches **(15-17)**.

Computational drug-target methods have also shown positive results. Ke and colleagues discovered six compounds that effectively suppressed fibroblast growth factor receptor 3, a biomarker for bladder cancer. Out of these, two compounds were shown to be effective in laboratory tests, while another drug showed promising results in a mouse model with transplanted human tumor cells (xenograft model) **(18)**. Furthermore, cyclin-dependent kinase 2 (CDK2) has been identified as a biomarker for several types of malignancies, which makes it a desirable target for therapeutic development **(19–22)**. Shi and colleagues have created protein-ligand docking software that accurately identified adapalene as a CDK2 inhibitor in colon cancer and fluspirilene as a CDK2 inhibitor in liver cancer. These predictions were confirmed by experiments conducted in both laboratory settings (in vitro) and living organisms (in vivo) **(23–25)**. Due to the achievements mentioned, several research groups are now using computational methods to aid in the repurposing of current medications for cancer treatments.

Furthermore, multidisciplinary approaches have had positive results. Huang and colleagues integrated protein–protein interaction networks with CMap to discover 11 prospective medicines for the treatment of non-small cell lung cancer, out of which five demonstrated the ability to impede cancer cell proliferation in laboratory experiments **(23)**. Furthermore, Lan and his colleagues used machine-learning techniques to enhance systems biology data and identify genuine good results. The researchers discovered 87 possible treatments for nasopharyngeal carcinoma, with more than half of them already known for their anticancer capabilities **(26, 27)**. These examples highlight the significance of validation in consistently improving computational algorithms via empirical data.

Although several in silico triumphs have been emphasized, not all candidates undergo validation. Possible obstacles may arise when potential real positive matches are first assigned low scores and then eliminated. It is worth noting that certain chemicals function as pro-drugs and need activation inside a living organism. For instance, tamoxifen is an example of such a substance. Therefore, it is possible that some anticancer medications may not show effectiveness in laboratory tests (in vitro), but computer-based analysis of their active metabolites (in silico) might accurately predict their efficiency **(28)**. Therefore, due to its comparatively affordable nature compared to other approaches and its ability to successfully uncover promising therapeutic candidates, in silico technologies are well-suited for repurposing programs that have the potential to produce new medications authorized by the FDA and EMA.

Regulatory Affairs and Intellectual Property (IP)
Regulatory approval pathways

In the United States, there are three unique regulatory clearance procedures for registering different types of pharmaceuticals, as specified in the Food, medication and Cosmetics Act. However, only one of these channels, known as "505(b)(2)", is applicable to medication repurposing. Regardless of whether it is for cancer therapies or other illnesses, all medication candidates for repurposing

must be filed under Section 505(b)(2). The availability of Section 505(b)(2) was established in 1984 by the enactment of the Drug Price Competition and Patent Term Restoration Act (Hatch-Waxman Amendments). However, it is only in recent times that applications to this channel have gained prominence. Statistics indicate that the number of goods that gain FDA clearance via the 505(b)(2) pathway is almost double the number of products that go through the new drug route. Companies are seeking to gain more money and exclusivity by taking advantage of short approval processes, as indicated by the mention of "505(b)(1)".

The 505(b)(2) pathway permits the registration of a drug even if the applicant did not conduct at least one of the studies required for approval. Therefore, applicants can use published literature and the FDA's previous safety findings on an approved product to support their data. Consequently, fewer supplementary investigations are necessary, leading to shorter timeframes and less expenses. In addition, in order to get the 505(b)(2) approval, drug researchers must provide a distinct method of administration or illness indication for their repurposed medicine in comparison to the main route and indication.

In Europe, the EMA regulates a separate approval process under Article 10 of Directive 2001/83/EC. However, unlike section 505(b)(2) of the Food, Drug and Cosmetics Act, which allows the use of previously conducted studies of high quality and safety to support various parts of an application, Article 10 specifically applies to drugs that require studies tailored to their differences from reference listed drugs. It does not provide a legal basis for the use of non-proprietary studies. Additionally, it is important to note that Article 10 cannot be used for new molecular entities, as it only applies to changes made from the reference listed drug. The EMA typically requires an additional 6 months compared to the FDA to get approval for new drug indications **(29)**.

Integration of Intellectual Property and Regulatory Exclusivities

When seeking to bring a repurposed medicine to market, it is crucial to take into account intellectual property (IP) and regulatory exclusivities. For instance, the use of a medicine for a different purpose might impact the exclusive rights of the original claims in the market. Shelved active pharmaceutical ingredients (APIs), which refer to previously abandoned or unapproved drug products, present a promising opportunity due to their ability to provide strong product protection. Additionally, repurposing an approved API for a secondary indication without the need for reformulation would benefit the original manufacturer, allowing them to generate extra revenue from new markets. Nevertheless, if innovators who are not affiliated with the original manufacturer alter the formulation of a repurposed medicine, they may be eligible for a new intellectual property (IP) protection. This is because the modified drug would be considered a unique composition of matter. Hence, patents provide the most effective security for protecting the composition of the API (29). Nevertheless, these patents are often filed at an early stage in the medication development process, resulting in a very limited patent lifespan once the product is ready for sale. Alternatively, new patents for composition of matter may be obtained when the repurposed active pharmaceutical ingredient (API) is combined with a new formulation. These

patents may qualify for a 5-year extension to make up for the time lost during the process of approving the medicine **(15)**.

While a strong patent offers protection against rivals, the regulatory exclusivities granted by the Hatch-Waxman Act may also provide significant protection. Even in cases when patent protection is not an option, the length of time during which a company has exclusive access to the market might nevertheless allow them to make a return on their original expenditures. In addition, new chemical entity exclusivity is awarded when the drug product contains an active pharmaceutical ingredient (API) that has not yet been registered by the FDA, regardless of the length of time it took to develop. This exclusivity ensures that other companies cannot use the safety and effectiveness data of the approved drug for a minimum of 5 years **(30)**. It also prohibits the FDA from accepting applications for generic versions during the first 4 years of the exclusivity period. On the other hand, the EMA will provide a maximum of 8 years of exclusivity. Furthermore, the US Orphan Drug Act offers incentives to pharmaceutical companies to repurpose drugs for rare cancers. These incentives include a 7-year market exclusivity and a 50% tax credit for expenses related to clinical testing. The recently passed Orphan Product Extensions Now Accelerating Cures and Treatments Act will extend the market exclusivity by an additional 6 months. If an anticancer drug proves beneficial for pediatric populations, an extra 6 months of exclusivity may also be granted. In Europe, there is a comparable designation for orphan medicines that provides 10 years of market protection and reduced costs for regulatory operations. If the orphan medication is specifically intended for pediatric populations, it will get 12 years of market protection.

In general, when a pharmaceutical company chooses to repurpose an existing medicine for cancer treatment, they must take into account intellectual property (IP) and market exclusivity rights, since these factors will impact the therapy's likelihood of success. APIs that have not yet been introduced to the market or received approval from the FDA or EMA provide the highest level of security. Significant safeguarding may also be attained by judicious utilization of novel composition of matter patents, enabling full assurance in the market long after obtaining regulatory clearance.

Commercial viability of repurposed drugs in the treatment of cancer

Despite substantial growth in expenditure in recent decades, pharmaceutical firms have seen a decline in the number of authorized medications **(31)**. Eroom's Law refers to the negative relationship between the amount of money invested in drug research and the slowing down of drug discovery **(32)**. As a result, the approach of repurposing existing medications is being investigated to address this tendency. Furthermore, pharmaceutical firms are now exploring the potential of repurposing pharmaceuticals for different types of malignancies. For instance, the producers of metformin, a medication used to treat diabetes, and celecoxib, an anti-inflammatory medicine, are now conducting clinical studies to assess the effectiveness of these treatments on patients with breast and colon cancer **(1)**.

Nevertheless, while modifying preexisting pharmaceuticals to enhance their financial viability, certain considerations must be taken into account **(33)**. firms

must be cautious of the expiration dates of patents on existing substances. Once a patent expires, other firms may manufacture generic equivalents at reduced rates. This was apparent in the case of celebrex, a drug developed by Pfizer. When its patent expired in 2014, Teva Pharmaceuticals introduced a generic version. As a result, Pfizer suffered a significant decline of almost 10% in operational revenue during the first quarter of 2015. Therefore, it is crucial for drug developers to employ proven strategies, such as reformulation and off-label usage, to successfully bring newly repurposed anticancer agents to the market. Alternatively, if there are financial disincentives such as patent expiry, legislation, guidelines, or levies that discourage or restrict continued research, it might significantly impede global medication repurposing efforts.

Industry Implementation Strategies

One important strategy for enhancing the economic value of a product is to get ownership rights via licensing. If ownership rights are already secured, another approach is to prolong the patent life cycle of the product. Notably, certain businesses, such as Sosei Co. Ltd., specialize in purchasing and then licensing drug libraries to organizations seeking to construct drug pipelines **(5, 36)**. According to reports, this method has led to an average yearly growth in the value of these assets by around 10% in the United States **(37).** Another adopted technique is specifically targeting orphan illnesses. In the United States, these conditions are classified as affecting fewer than 200,000 individuals and may include uncommon forms of cancer such as Ewing sarcoma, adrenocortical carcinoma, gastrointestinal stromal tumors, and chordomas **(25,26, 38-41)**. Due to the absence of competitive pressure and limited therapy options for certain disorders, regulatory agencies often expedite the clearance process for proposed remedies **(42)**.

The majority of prospects focused on developing cost-effective medications for rare illnesses mostly lie in the practice of repurposing medicines **(43)**. However, it is also possible for the converse to occur, where pharma firms tend to set prices for these medicines far higher than what an average middle-class person can pay, and insurance companies normally only provide partial coverage for the cost of treatments for these uncommon illnesses **(44)**. Furthermore, there are several disputes about the underlying goals of medication repurposing efforts. For instance, when a company realizes that an affordable medication can be used to treat a less common condition, the price of the medication can suddenly increase dramatically. This unethical practice, known as "price gouging," occurs when a company takes advantage of its monopoly position to inflate the prices of inexpensive products. Unfortunately, this does not benefit patients who have unmet medical needs **(43, 45)**. Currently, legislators are deliberating on measures to prevent similar incidents from becoming commonplace. Moreover, it is projected that by 2020, 20% of drug sales will be derived from medications for orphan diseases, including different types of cancers. This indicates a partial transition away from more prevalent conditions like diabetes, asthma, and cardiovascular diseases. Consequently, it is crucial to strike a balance between pricing and profitability in order to ensure that drugs remain affordable for both patients and pharmaceutical companies. Through the implementation of different mechanisms such as subsidies, tax credits, and expedited drug approval, drug

manufacturers are encouraged to invest significant time and financial resources in the development of drugs for rare and orphan diseases. As a result, patients with rare conditions can anticipate more affordable medications compared to a scenario where these incentives were not provided **(46)**.

After a new medicine has received approval for a different use, a common approach to optimize financial gain is to get a "specialty drug" classification, restricting its sale only to specialty pharmacies. This labeling leads to an increase in price, since these pharmacies need more financial resources to keep and manage these therapies. It also extends the period of patent exclusivity. This method has been utilized in the past for various anticancer medications, such as rituxan, which is used to treat non-Hodgkin's lymphoma and chronic myeloid leukemia.

It is worth mentioning that after finding a medicine that may be used as a cancer treatment, several academics and firms choose to form collaborations with suitable leaders in the oncology pharmaceuticals market **(47)**. This phenomenon is evident in companies that prioritize repurposing, such as BioVista, which has formed partnerships with Pfizer and Novartis, and NuMedii, which has collaborated with Astellas Pharmaceuticals. By joining forces with larger and more established organizations, these companies gain access to extra resources and funding that can support the process of translating research findings into practical applications, such as conducting functional validation studies and eventually carrying out clinical trials.

Summary

While navigating the intricate ecosystems of medical regulations and commercialization procedures, it is crucial to carefully consider the process. However, drug repurposing for cancer indications has the potential to greatly benefit a large number of patients who are currently in urgent need of medical treatment. It is crucial to acknowledge that when repurposed treatments exhibit enhanced effectiveness, safety, and/or cost compared to the existing standard(s) of care, both patients and drug developers alike gain advantages. Pharmaceutical firms may optimize the efficiency of drug development by simplifying validation tests, eliminating the need for duplicating safety investigations conducted on humans. This allows patients to benefit from innovative and expedited methods for treating their specific diseases. In addition, with the emergence of new technologies in the current era of comprehensive biological analysis, large-scale multi-system data will continue to be used to achieve further success in repurposing approved, investigational, and potentially hypothetical drugs for multiple uses in cancer treatment.

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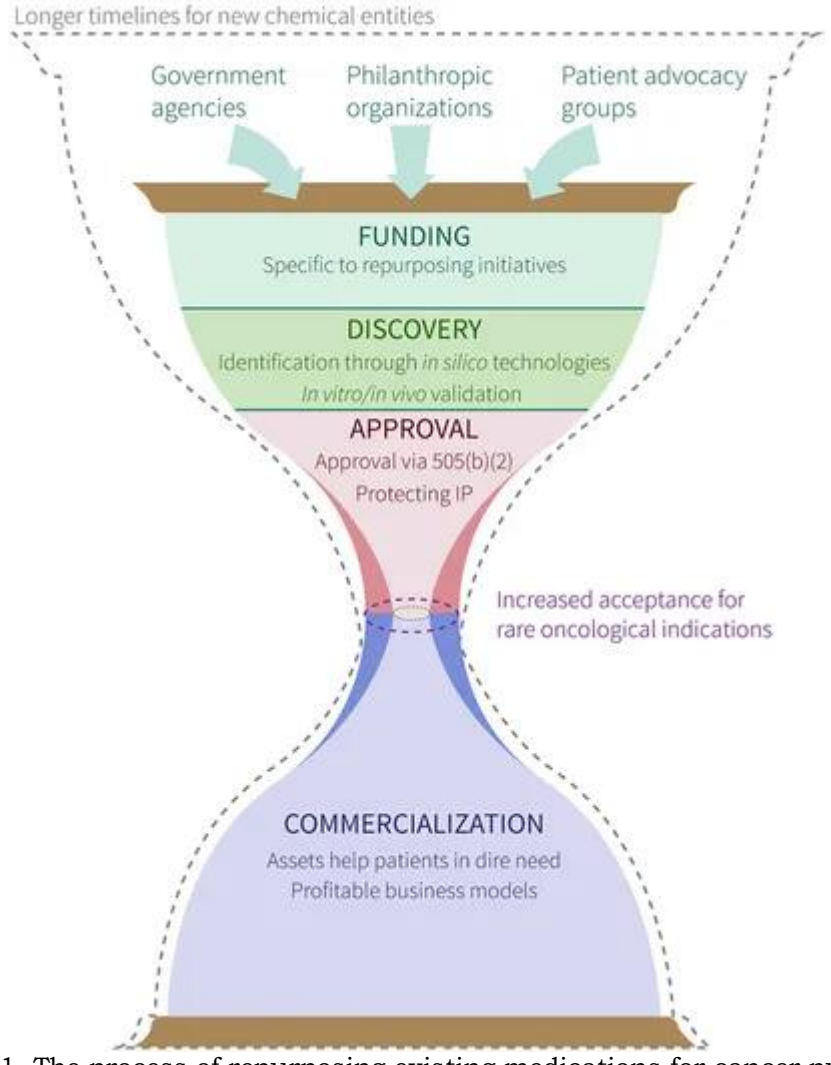

Figure 1. The process of repurposing existing medications for cancer purposes