Regulatory Actions to Advance Generic Drug Repurposing

Working Paper

Background

Generic drug repurposing can be a valuable approach for identifying new treatments, particularly in circumstances where access to therapeutic options is limited, unavailable, or unaffordable. *De novo* drug development is a risky and expensive process, costing as much as $2.8 billion to develop and taking 8-10 years to complete from start to finish.[1] Repurposing drugs that have already demonstrated safety allows for researchers to start in later stages of clinical trials, increasing their chances of success and reducing the cost and time for development. Furthermore, repurposing generic drugs provides a more affordable and accessible option for patients.

The literature surrounding 'generic drug repurposing' uses many different terms and definitions, so for the purposes of our work, we define 'drug repurposing' as the process of conducting clinical research on new uses for established drugs on the market. Additionally, we define 'generic drugs' as drugs on the market for which the originator has lost exclusivity and other industry sponsors and manufacturers may legally enter the market.

A recent example of repurposing generic drugs is the use of dexamethasone; originally used as a corticosteroid to treat conditions such as severe allergies, asthma, and arthritis, it was found to be effective for treatment of hospitalized COVID-19 patients.[2] Other prominent examples of generic repurposing is the use of thalidomide to treat multiple myeloma when it was originally developed as a sedative for pregnant women experiencing morning sickness, or the use of colchicine - a treatment for gout - for cardiovascular disease. Generic repurposing has also been gaining attention in the rare disease space, with recent Washington Post and New York Times articles reporting on repurposing success stories for rare diseases with no FDA approved treatments.

Despite the multiple potential benefits of generic drug repurposing, research on new uses of generic drugs is rarely conducted by traditional R&D-based pharmaceutical companies. Although cheaper than *de novo* drug development, drug repurposing still requires significant upfront capital to fund trials. Yet there is no financial incentive for companies to make this investment due to the presence of competitors and low price points in the generics market.

[1] Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018

[2] How Dexamethasone Used in Anti-COVID-19 Therapy Influenced Antihypertensive Treatment in Patients with SARS-CoV-2

Incentives for Generic Drug Repurposing
Additional efforts to address the incentives for traditional developers are needed, Duke-Margolis is exploring this challenge in a separate initiative.

As such, generic drug repurposing efforts are limited and typically only conducted by academic institutions or non-profit research organizations (as we will henceforth refer to as "nontraditional developers"). Although these nontraditional developers may be able to conduct rigorous clinical trials to demonstrate efficacy, they may lack the experience and resources necessary to navigate regulatory pathways and are not positioned to hold marketing authorization for the product.[3] Therefore, most generic drug repurposing studies are not intended to support label changes, which may hinder patient access, due to lack of insurance coverage, and limit provider education efforts. Additionally, there are limited resources and systemic efforts to identify repurposing candidates and conduct trials to demonstrate efficacy for a new use.

Disadvantages of Off-Label Prescribing

While prescribing drugs off-label is a common and efficient way for some physicians to provide patients with effective treatments, it also poses several disadvantages such as:

- *Lack of data generated on the drug's efficacy and safety for the off-label indication*
- *Uneven or slow uptake*
- *Reimbursement issues*
- *Limited awareness by providers and patients*
- *Patient concerns over using an unapproved therapy*
- *Supply issues (e.g., disruption or shortages from underestimated demand forecasting)*
- *Liability concerns from providers*

In recent years, a few initiatives have emerged in the United Sates to explore generic drug repurposing opportunities and support organizations conducting this research, such as the ACTIV-6 trial to explore potential repurposed treatments for COVID-19 and ARPA-H's support for Every Cure, a nonprofit organization developing an AI platform to support identification of drug repurposing opportunities.

These are important efforts, but addressing the barriers to generic drug repurposing is not a one-dimensional challenge and will require efforts across the biomedical system of researchers, developers, funders, regulators, and payers. In this paper, we endeavor to explore **the potential**

[3] Drug Repurposing During The COVID-19 Pandemic: Lessons For Expediting Drug Development And Access

role drug regulators, specifically the U.S. Food and Drug Administration, may play in unlocking the full potential of generic drugs to improve access to affordable treatments for patients.

Research Approach

Building off prior work on drug repurposing, the Duke-Margolis team wanted to better understand the current regulatory pathways and programs which may have relevance for generic drug repurposing. We set out to explore two initial areas where we felt there could be a role for the FDA: (1) expanding pharmacovigilance systems to detect potential new uses of drugs; and (2) regulatory pathways, particularly for nontraditional manufacturers, to expand labels of repurposed generic drugs. Following our initial research efforts, we identified substantial limitations and barriers in expanding current pharmacovigilance systems for identifying repurposing opportunities, and therefore focused our continued efforts on regulatory pathways and other potential roles of the regulator *(see Appendix for more on these findings).*

Our research approach consisted of a desk review, extensive expert engagement, and a private expert roundtable, building off previous Duke-Margolis drug repurposing research and publications. We began with a review of the available literature and publicly available information on current repurposing efforts and regulatory pathways, as well as on the barriers to data collection, incentives, and gaining approval. We conducted interviews with a variety of experts in the field to better understand the challenges and opportunities in conducting repurposing trials and pursing approval/label expansion for a new indication. In November 2024, we hosted a private expert roundtable to bring together a range of relevant stakeholders to highlight existing efforts and share ideas on further work needed to address issues around incentives, data sharing, and more. In this paper we present the initial findings and emerging recommendations from these efforts, as well as remaining questions to explore.

The Importance of Regulatory Approval and Current Pathways

Regulatory approval is an important step for generic drug repurposing in terms of clinical acceptance of the treatment and patient access. When a repurposed drug receives regulatory approval for a new indication, it opens up mechanisms for additional efficacy and safety monitoring, payment and reimbursement, greater awareness for providers and access for patients, and reduces prescriber liability concerns. Additionally, label expansion creates a clear path for proactive promotion of the treatment to providers, thereby supporting adoption into clinical practice and expanding patient access. Most importantly, it maintains the bar for necessary clinical evidence that a drug should demonstrate before being promoted and used in patients. A new label indication claim must demonstrate substantial evidence of effectiveness, which under certain circumstances can be accomplished with one adequate and well-controlled clinical investigation and confirmatory evidence.

Currently in the US, the 505(b)(2) regulatory pathway is the primary pathway for adding new indications to a drug's label. 505(b)(2) applicants can partially rely on FDA's previous safety and

efficacy data, along with additional publicly available data on efficacy in their submission.[4] This can allow a developer interested in pursuing a new indication to bypass nonclinical or clinical studies, or both, depending on available data. However, some repurposing advocates – particularly nontraditional developers – have pointed out several challenges in pursuing this pathway.

- First, use of the 505(b)(2) pathway requires extensive statutory and regulatory understanding, particular understanding of the reference drug, and specific bridging needs. Although the FDA has created guidance documents to assist researchers in understanding uses of both the Investigational New Drug (IND) processes and the requirements for approval through use of the 505(b)(2) pathway, a lack of expertise or experience in the navigating practical requirements with the pathway may discourage nontraditional researchers from pursing approval for a new indication.
- Second, the pathway is intended for industry sponsors and drug manufacturers versus nontraditional developers who are typically unequipped to manufacture or market the drug. This creates a hurdle for nontraditional developers who are conducting trials to demonstrate efficacy, but face challenges in completing the manufacturing requirements for a regulatory submission.

Given these challenges, nontraditional developers currently have two options for getting a repurposed drug to patients. The first option is to partner with a manufacturer or the original industry sponsor of the drug. It is beneficial for nontraditional developers to partner with the original sponsor for data sharing purposes and their expertise on both the drug and designing studies intended for regulatory submission. The sponsor or manufacturer is also able to provide the FDA with the chemistry, manufacturing, and controls (CMC) data, and the product samples required for the 505(b)(2) application. Additionally, they can conduct post marketing surveillance and market the drug for the new use.[5] However, there is often a lack of incentive for such firms to collaborate with nontraditional developers and invest the resources to pursue label expansion if the new indication is unlikely to provide them commercial benefit that adequately offsets the cost, liability risks, and uncertainty associated with additional clinical trials.

The second option is to rely on off-label use and/or inclusion on treatment guidelines. If nontraditional developers choose to not purse a label expansion, they will have to rely on the dissemination of their research and hope there is uptake in off-label usage and/or inclusion on treatment guidelines. This often results in uneven uptake and can still leave some patients and providers with concerns about using an off-label drug. Additionally, not pursing label expansion sets zero evidence standards for efficacy and leaves room for groups to make unsubstantiated claims based on insufficient trials.

[4] What is 505(b)(2)?
[5] Clearing the Path for New Uses for Generic Drugs

Insights from International Efforts to Support Generic Drug Repurposing

Interest in generic drug repurposing is not new and other countries have already taken notice of its potential value, and the challenges hindering it. Both the United Kingdom (UK) and European Union (EU) undertaking efforts to address these challenges.

The UK National Health Service's (NHS) Medicines Repurposing Programme aims to identify and progress opportunities to use existing medicines in new ways, outside of current marketing authorization. The program selects and prioritizes medicines and provides tailored support including generating evidence, applying for a license variation, and facilitating equitable patient access. There is an open and competitive tender process to select a marketing authorization holder to submit to the Medicines and Healthcare Products Regulatory Agency (MHRA), providing a financial incentive for sponsoring the license variation. The program has already reported one success: anastrozole for breast cancer prevention.

The STAMP Pilot is an EU-based program which aims to support non-profit organizations and academia to collect and generate the evidence necessary to support submission to a regulatory authority for a new indication of an established medicine. The European Medicines Agency (EMA) and national medicines agencies provide regulatory support to participants to help them generate robust data packages which they can present to a pharmaceutical company in hopes of attracting them as a partner to submit the data package to the regulatory authority. Additionally, in the EU, there are legislative efforts to create a regulatory pathway for nontraditional developers. Article 48 is a proposal to the EU General Pharmaceutical Legislation that would offer a pathway for "not-for-profit entities" to submit data to their regulatory agency for repurposing products that meet unmet medical needs.

Existing US-Based Programs for Drug Repurposing

In the US, there has also been growing interest in generic drug repurposing and despite the lack of a coordinated, government-led effort, there have been a handful of disparate efforts to address some key challenges.

CURE ID

One such effort aims to curate a "treatment registry" of drugs that have been repurposed for rare diseases. CURE ID, a collaboration between the FDA, National Center for Advancing Translational Sciences (NCATS), the World Health Organization (WHO), and the Critical Path Institute (C-Path), provides a platform for healthcare providers, patients, and caregivers to share their treatment experiences with existing medications being used in new ways. Case reports are submitted directly through CURE ID's website or mobile app. This collection of real-world experiences captures treatment outcomes for medicines being used to treat diseases

beyond their original indication and serves as a resource to share information to patient communities where there is no FDA-approved product for treatment.[6]

Project Renewal

In the oncology space, many treatments are prescribed off-label yet are listed on the National Comprehensive Cancer Network (NCCN) Guidelines and have decades of real-world evidence as safe and effective treatments. Project Renewal is an FDA-led initiative through the Oncology Center of Excellence that aims to update the prescribing information for specific out-of-date oncology drugs to reflect these additional indications. The initiative reviews new post-market data to ensure the necessary prescribing and patient information is up to date for their safe and effective use.[7] The Project Renewal team works closely with the original drug sponsor to use this data to follow the proper regulatory pathway to update the reference drug's label.

Modern Labeling Act

Recent legislation has also targeted this challenge of updating drug labels. The Modern Labeling Act of 2020 granted FDA the authority to require updates to out-of-date drug labels of certain generic drugs in which the reference label drug has been withdrawn. Under this law, the label of the abbreviated new drug application (ANDA) submitted by generic manufacturers may be updated if it would benefit public heath, there is new scientific evidence available pertaining to the existing conditions of use that is not reflected in the labeling, or if there is a relevant accepted use in clinical practice that is not reflected in the approved label. However, to our knowledge, the Modern Labeling Act provisions have yet be utilized to update any drug labels. Reasons for this are unclear but based on interviews with experts it could be due to a lack of resources or a champion within the Agency to spearhead utilization of the authority.

While these existing programs show some promise for repurposing efforts, they are often met with limitations. While Cure ID is a great way to identify potential new indications, especially for rare diseases, it does not provide enough evidence for widespread adoption and still requires additional studies. Additionally, there remains lack of incentive or opportunities to ensure the drug label is updated for the new use. While Project Renewal is an effective, government-led effort to update drug labels, the effort is currently limited to the oncology space due to its uniquely large infrastructure, large population size, and clear ability to identify endpoints. Lastly, the lack of movement to utilize the Modern Labeling Act has left the authority of FDA to update labels of select drugs untapped.

A Range of Regulatory and Legislative Solutions

Our review of current government-led efforts to repurpose generic drugs and update their labels reveals that there are still significant opportunities for regulatory actions and polices to address the barriers and challenges, particularly for nontraditional developers. International examples offer inspiration to the types of actions which may be beneficial for repurposing efforts in the US. Additionally, experts convened in our roundtable provided thoughts on the

[6] Cure ID
[7] Project Renewal

potential role the FDA may play in 1) identifying **opportunities** for new uses of generic drugs, 2) creating opportunities for nontraditional developers to pursue regulatory **approval** for new uses and support for generating the satisfactory evidence to do so, and 3) encouraging the use of established evidence to update **labeling** to ensure responsible promotion and public health benefit. Based on these findings, we developed a framework of potential policy solutions that a regulator may undertake to address challenges in each of these three areas.

The regulatory solutions framework (see Figure/Table) is organized into three categories based on the degree of effort required to implement: building on current processes and programs, new but within existing authority, and legislative action needed. Solutions under each of these columns is further organized by the level of resources needed to implement, from low to high. Color coding is used to represent which of the three regulatory role categories the solution addresses, with the shorthand titles: opportunities, approval, and labeling.

Generic Drug Repurposing: Regulatory Solutions Framework

	Building on Current Processes and Programs	New but Within Existing Authority	Legislative Action Needed
Low	**Programming –** A program offering advice on research protocols and evidentiary needs to obtain regulatory approval/attract manufacturer partner (NCATS/FDA joint effort?), including workshops, individual meetings, and guidance documents	**Disease Prioritization -** Identification of priority uses cases or conditions for repurposing efforts for Federal efforts (i.e., within FDA, NCATS, NIH)	**Expand Modern Labeling Act-** Expand modern labeling act beyond withdrawn RDLs (criteria TBD; may be based on # of years since first ANDA); OR expand to allow nontraditional developers to compile and submit the data to FDA (reduce workload on FDA staff)
		User Fee Waivers - Waive user for repurposed drugs that meet or advance public health needs as defined by FDA (see above); if a pathway is created for nontraditional developers, user fee not to be required	**New Regulatory Pathways -** "Labeling only" 505(b)(2) pathways (Reboot Rx proposal) OR creation of other new pathway for nontraditional developers (similar to Article 48 in EU proposal)
	Utilizing Modern Labeling Act – FDA can use authority provided to update labels of drugs with withdrawn RDLs based on existing data	**Sponsor Incentives –** Explore incentives for companies to partner with nontraditional developers on repurposing. This may include building on the "programming" solution to establish a program similar to the EU's STAMP Pilot.	**International Regulatory Reciprocity –** update labels based on evidence used for label expansion in other regulatory agencies (e.g., EMA, MHRA) for repurposed drugs that meet areas of unmet medical need
	CURE ID Expansion - link CUREID with government funding partner to pull out promising candidates and prepare research protocols to meet regulatory standards (may include match making conferences)		**Addressing Liability Concerns -** Addressing liability concerns for pharmaceutical companies to share data or study new uses of generic drugs
High	**Project Renewal Expansion –** Expand Project Renewal to other disease areas where there is sufficient data and clear evidentiary targets (i.e., infectious diseases)	**Expand Federal Programming -** Expanding NCATS, NIA Alzheimer's Repurposing Program, or ARPA-H to establish a government-led repurposing initiative	**New Federal Initiative -** Create a new large-scale government initiative (e.g., BARDA) to advance drug repurposing for unmet medical need

Legend: Opportunities Approval Labeling

Last updated: 5/14/25

In this working paper we explore each of the potential solutions we have identified so far through research and engagement. This framework will also serve the basis for a hybrid workshop on May 29, 2025. The goal for the workshop will be to pressure test the framework, identify any missing solutions, prioritize the most promising and feasible solutions for targeted recommendations, and propose actionable next steps.

Building on Current Processes, Programs, and Authorities

Some potential solutions can be built upon existing programs and efforts within the FDA and other health agencies. We imagine these actions to be the most feasible as they can leverage existing programs, authority, and resources in support of generic drug repurposing efforts, though recognize the significant additional resource challenges introduced by recent, large-scale reductions in Federal staff.

> *Opportunities:* The CURE ID platform has potential to be a significantly more utilized resource for sharing information on off-label use and identifying promising candidates for generic drug repurposing. With greater resources, the platform could garner more awareness and even more proactively gather potential repurposing candidates. The program could also be directly linked to clinical research funding within NCATS, or NIH more broadly, to pull out promising candidates, prepare research protocols that would meet regulatory standards, and fund trials.
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> *Approval:* The FDA could build upon existing knowledge development programs for patient groups, rare diseases medical product development, and small business support by developing additional programming and resources specifically for nontraditional developers interested in repurposing generic drugs. The program would include many services already offered by the FDA and heavily utilized by industry sponsors and manufacturers, such as guidance documents, workshops, and even tailored advice to investigators on research protocols and the evidentiary requirements for approval of a new indication. The program would consider the unique support needs of nontraditional developers and generic drug repurposing.
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> *Labeling*: The Modern Labeling Act grants the FDA the authority to use existing evidence to update drug labels for products with withdrawn reference drug labels (RDLs), enabling information about drug efficacy that emerges in the post marketing setting to be included in the label. This assists in FDA's mission of communicating accurate and reliable information to patients and positions when additional, new indications are well understood.[8] However, to our knowledge, this authority has yet to be utilized. FDA could work with external partners to identify opportunities among drugs with withdrawn RDLs and gather information to support label updates.

New but Within Existing Authority

Other solutions may require the creation of something new, but still possible within the current authority granted to the FDA. We imagine this would be a heavier lift than just expanding an existing program as it would require allocation of resources and ownership by an office or senior official.

[8] Outdated Prescription Drug Labeling: How FDA-Approved Prescribing Information Lags Behind Real-World Clinical Practice

Opportunities: As part of a coordinated government effort on drug repurposing, agencies such FDA, NIH, and CDC could coordinate to identify and align on priority use cases or conditions where repurposing may have public health benefit. With more resources, repurposing programs in NCATS and/or the National Institute for Aging (NIA) could be expanded into a broader government-led drug repurposing initiative that could identify targets in addition to support across a wide range of generic drug repurposing challenges.

Approval: Building on the "programming" and resources proposal in the previous section, a dedicated program may be established with the goal of supporting nontraditional developers to prepare a ready-to-submit package of data that meets evidentiary requirements which can be used to incentivize a developer to sponsor the label expansion (similar to STAMP Pilot in EU).

Legislative Action Needed

Finally, there are also some solutions which would require legislation and/or appropriations from Congress to enact policy challenges. Pursuing legislation takes a considerable amount of effort and faces multiple hurdles from drafting legislative language and finding bipartisan Congressional sponsors, to making it through committees and both houses of Congress. Legislation also requires a good implementation plan or else it may not have the intended impact or benefit (as was the case of the Modern Labeling Act).

Opportunities: No recommendations explored thus far for identifying opportunities would require legislative action, although it could be the component of a large-scale government initiative focused on repurposing drugs.

Approval: One such action would be the creation of a new regulatory pathway for nontraditional developers to pursue label change, such as one proposed by RebootRx in a recent article.

Labeling: The Modern Labeling Act could be expanded beyond withdrawn reference drug labels or to allow nontraditional developers to compile and submit the data to the FDA. Additionally, evidence used for label expansions by other regulatory authorities, such as the European Medicines Agency (EMA) or the Medicines and Healthcare products Regulatory Agency, could be used to update labels in the US for repurposed drugs that meet areas of unmet medical need.

Encompassing all three categories and more, there have also been suggestions that the US government create a new large-scale government initiative focused on generic drug repurposing, similar to how The Biomedical Advanced Research and Development Authority (BARDA) was created specifically for development of medical countermeasures. Such a program could focus on advancing generic drug repurposing for areas of unmet medical need and include a wide range of programs and solutions, including target identification, research, label expansion, responsible promotion, incentives, and more. This program could draw inspiration

from the NHS's Drug Repurposing Programme which offers a range of supports for repurposing efforts that will benefit the NHS.

Next Steps

Duke-Margolis welcomes input on the ideas and framework presented in this paper. We will be hosting a public workshop on May 29, 2025 to continue conversations around the role of the regulator in generic drug repurposing and the feasibility of the solutions/policy recommendations laid out in the framework above. Based on the results of the public workshop, we will publish a final white paper presenting a prioritized set of actionable policy recommendations by Fall 2025.

Appendix: Findings on Expanding Pharmacovigilance Systems

In exploring expansion of pharmacovigilance systems, we first sought to better understand the current systems in place and how they operate. Pharmacovigilance is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other medical product related health problem. To fulfill these responsibilities, FDA reviews post marketing safety information through a range of systems and processes – most notably FDA's Adverse Event Reporting System (FAERS), Sentinel, and Biologics Effectiveness and Safety (BEST) systems – and conducts adverse event reporting inspections, among other activities. Our goal was to explore the possibility of expanding the current pharmacovigilance systems to go beyond tracking safety signals, and to also capture positive efficacy signals that may inform research on new uses of generic drugs.

Upon exploring the expansion of pharmacovigilance systems with experts, the use of pharmacovigilance systems to include positive indicators for new uses in their surveillance mechanisms was not deemed as feasible at this time. There are a few issues with this approach, the first being there is no code within the system to track off-label usage of drugs. Additionally, the systems are already operating on limited resources, and any expansion to the system would require significantly more resources. There is also the remaining challenge of sharing data from these systems with interested researchers which involves numerous legal hurdles which may are viewed by many as insurmountable. Finally, though these systems may be capable of demonstrating an efficacy signal, the data would be quite rudimentary and thus still require confirmatory, well-controlled clinical trials to determine whether substantial evidence was demonstrated.