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From Concept to Policy: **Pull Funding for Repurposed Generic Drugs**

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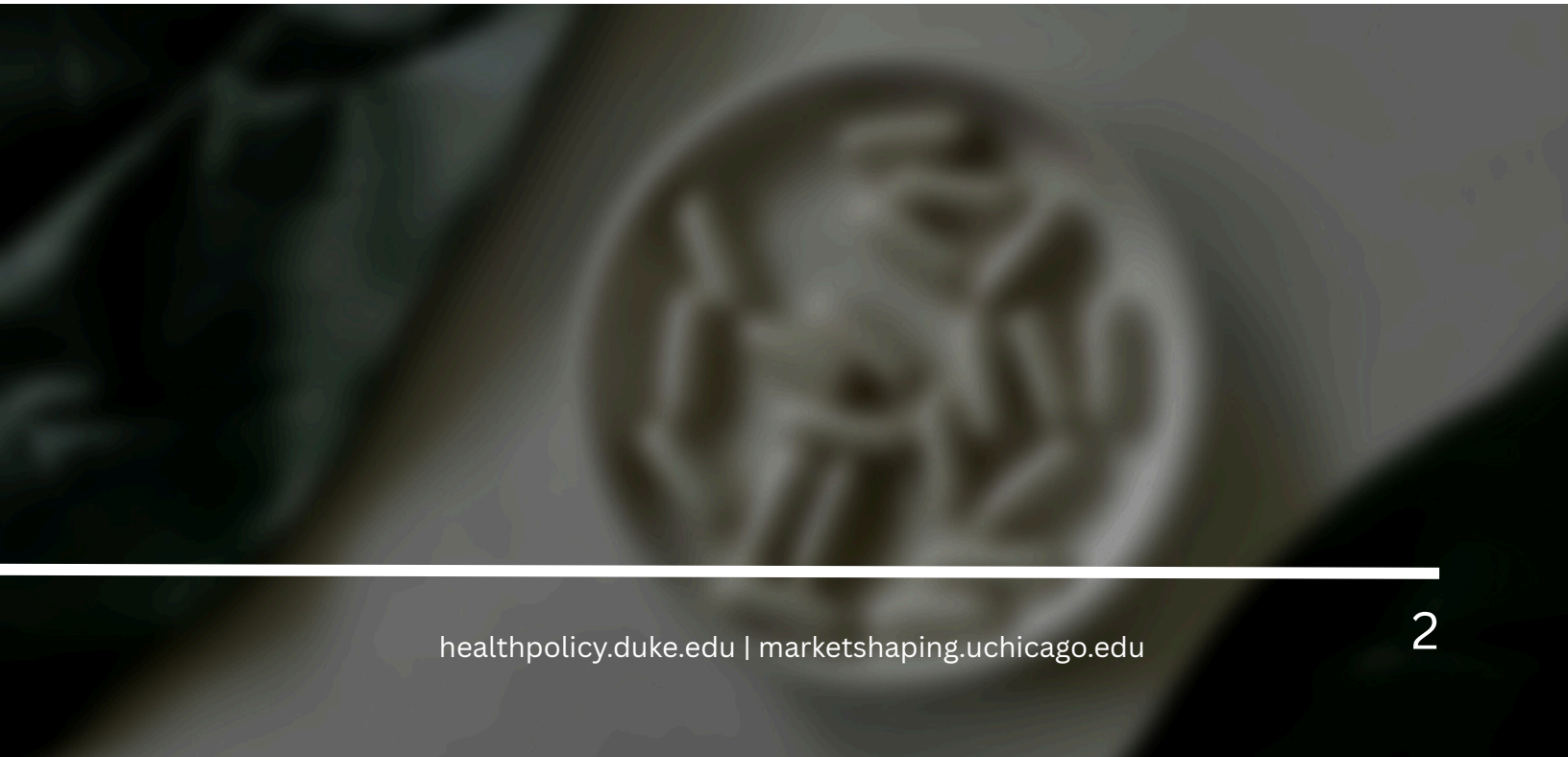


Introduction

Unlocking the untapped potential of generic drug repurposing

There is growing recognition that the medications already on our pharmacy shelves may hold new and powerful solutions to persistent health challenges. Generic drug repurposing – the process of identifying new uses for established medicines that no longer have market exclusivity – offers a promising and pragmatic path to expand treatment options for patients. It can even offer a pathway to find therapies for areas with significant unmet medical need. This approach has the potential to deliver safe, effective therapies at a fraction of the cost and time required to develop entirely new drugs, reducing risk for developers and investors.

In this paper, we define *generic drugs* as small-molecule compounds for which the original developer's patents and other exclusivities have expired, making them legally available for competition from follow-on manufacturers. Generic drugs are held to the same U.S. Food and Drug Administration (FDA) standards for safety and efficacy as their brand reference products, representing an underleveraged resource for innovation. Biosimilar products are not included in our definition of generics, since these products typically have different market dynamics around price and availability relative to small-molecule drugs that may require special considerations.

The opportunity

Generic drug repurposing presents a rare win-win opportunity across the healthcare landscape. Patients gain access to affordable and effective therapies, and payers benefit from both cost savings and improved population health. This dynamic may be especially powerful for diseases with few or no effective treatment options. For example, early research suggests nucleoside reverse transcriptase inhibitors (NRTIs) – typically used to treat human immunodeficiency virus (HIV) – may hold potential for treating Alzheimer's disease, a condition with limited therapeutic options and large social and economic burden.

For payers and health systems, generic drug repurposing can lead to lower treatment costs and fewer burdensome interventions for patients, such as hospitalizations or surgeries. Furthermore, repurposing has the potential to offer improved health outcomes by enhancing or replacing current standards of care or by offering treatment options for conditions that currently have no effective treatment options.

Notably, this can be achieved at a significantly lower cost than traditional drug development. While bringing a new drug to market often requires $1.1 to $2.5 billion in investment, repurposing a generic drug can reduce those costs by up to 85%, in part because the early phases of

development, focused on safety and toxicology, are often already completed.

Generic drug repurposing represents an underutilized but powerful opportunity to improve public health, reduce healthcare costs, and drive innovation using tools we already possess. Yet despite its promise, generic drug repurposing remains the exception, not the rule. Promising opportunities often stall or go unpursued entirely, not because of scientific limitations but due to persistent structural and market barriers.

In this paper, we (1) **examine the current landscape and barriers for generic drug repurposing,** (2) **describe our proposal for a "pull" mechanism to help overcome these barriers**, and (3) **outline a practical pathway for implementing this solution** through the U.S. government.

Current landscape

The market failure

Even though repurposing generic drugs can improve health and lower patient costs, drug developers rarely invest in generic drug repurposing trials because there's no clear way to profit. When a drug's patents expire, cheaper generic versions enter the market, driving down drug prices and profits. This makes it nearly impossible to justify financing the clinical trials needed to find new uses. While new uses can be patented, these patents are difficult to obtain and enforce. This is because generic manufacturers can rely on "skinny labeling," which means they can carve out patented uses on their FDA-approved label and still sell the drug for the other unpatented uses. At the same time, doctors prescribe drugs by name only and do not specify the indication for which it is prescribed. Furthermore, pharmacies often dispense the lowest-cost version of a drug, usually a generic. Together, these practices make it hard to enforce new use patents on generic drugs. Knowing this, companies stop funding repurposing trials once generic competition is imminent.

This pattern is well documented by economists, legal scholars, and health researchers. One study found that the likelihood a company will invest in identifying new uses drops to near zero once generic competition begins (see Figure 1). Notably, longer patent life is associated with more repurposing activity, suggesting promising opportunities remain. Another study estimates that if developers were compensated similarly to how they are for new, patent-protected drugs, there would be 200 to 800 additional drug-use combinations in clinical practice today. The health value of this forgone innovation is estimated at $5 to $20 trillion.

Financial incentives for drug development:

Push funding: upfront funding to de-risk development (e.g., grants for clinical trials

Pull funding: funding allocated based on results (e.g., prizes for successful drug development)

Limitations of existing efforts to address this market failure

Governments and foundations have attempted to address this gap by providing research grants, a form of "push" funding "(see definitions in the box above). These programs typically pay academic and/or nonprofit organizations upfront to test new uses for generic drugs. Existing push funding efforts, such as grants provided by the National Institutes of Health (NIH), place financial risk on the funder. If a trial is unsuccessful, the funder is on the hook. These push funding efforts suffer from three major limitations:

- **Limited scale:** Grant budgets are small relative to the number of promising opportunities, and often don't fund through to regulatory approval. This leaves many promising opportunities under- or unexplored.

- **Disconnected from patient adoption:** Grants are usually awarded to academic or nonprofit researchers who lack the incentives and resources to navigate regulatory approval, pursue inclusion on clinical guidelines, and drive real-world adoption. As a result, even when new uses are discovered, they often receive little adoption (e.g., metformin for prediabetes).

- **Information gaps:** Grant makers and awardees lack access to important information that private developers possess, such as unpublished clinical trial data. Without these insights, funders and researchers risk duplicating previously failed studies and missing promising signals that could help them identify promising potential uses.

Designing pull funding

Pull funding proposal

We propose using pull funding to incentivize the repurposing of generic drugs. Unlike grants, which pay upfront based on proposals, pull funding pays based on results. In this context, pull funding is only paid when a developer (a) successfully demonstrates a new use for a drug and (b) achieves real-world, patient adoption. By shifting financial risk from funders to developers, pull funding better aligns incentives for the following reasons:

- **It motivates adoption:** By linking payments to adoption, our proposal encourages developers to take steps necessary to promote adoption. These steps may include regulatory submissions, efforts to get a drug covered and reimbursed by payers, and promotion to healthcare providers.

- **It unlocks private information:** When developers hold the financial risk, they are motivated to comb through proprietary resources, such as unpublished clinical trial data, RWE, and genomic analyses, to identify the most promising repurposing opportunities. This creates an early filtering effect. Companies with strong signals move forward into trials, while those without strong signals naturally move onto other opportunities. Private information guides investment before costly research begins.

Our proposal includes four core features:

1. Any drug for any disease. The mechanism would reward the repurposing of any drug for any condition. This avoids the need for funders to pick which of the tens of millions of drug-use combinations to fund. Instead, it allows companies to use their resources and expertise to efficiently search for potential drug-use combinations across the landscape of possibilities. In practice, the target diseases/conditions may be influenced by the priorities of the pull fund implementer.

2. Payments linked to value. Payments would follow a "value-based payment" model approach, in that payments would be tied to the measured cost savings and/or health impact generated by the new drug. While transformative innovations should be generously rewarded, budgetary constraints may necessitate limits. Funders could therefore set a cap on total payments for any single drug-use combination.

3. Reward goes to the developer. The company that funds the research and pursues label expansion is solely eligible for the pull mechanism payments regardless of the presence of other manufacturers selling the drug. This safeguard is essential to ensure that those who discover new uses remain properly incentivized, while maintaining generic competition and therefore affordability. The type of developer would not be specified, but we anticipate a range of developers, including de novo developers and generic manufacturers with development capabilities having interest in this incentive.

4. Regulatory approval requirement. We currently envision that FDA approval would be required to trigger payment. Adding a new indication to a drug's label is shown to significantly increase adoption of the drug since it can support payer coverage decisions and promotion to providers. (See the appendix for a discussion of the pros and cons of this requirement.)

Sizing the reward

A funder should consider how large the reward must be to attract innovators. Reward sizes will vary based on the outcomes achieved, such as health impact or cost savings, but having an estimate helps the funder budget appropriately and the developer to weigh risks and opportunities of pursuing the pull fund. Our analysis suggests companies may be interested in repurposing generic drugs if rewards are around $1 billion in future cash flows, or about $350 million in today's terms. The exact amount will depend on

several factors, including the strength of existing evidence. For instance, if a drug has already completed Phase II testing, the reward could be smaller since developers can proceed directly to Phase III. Therefore, rewards should be tailored to the circumstances. Additional details are provided in the appendix.

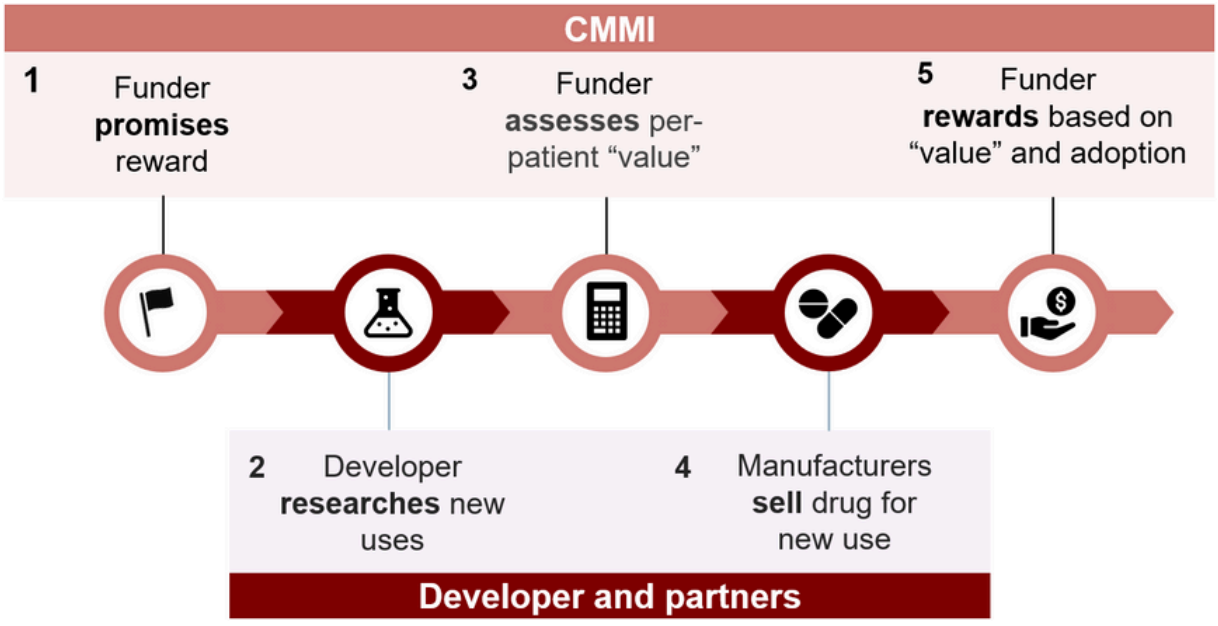
The proposal in practice

To ground this proposal, we present how the pull mechanism may operate if it were implemented by the Centers for Medicare and Medicaid Services (CMS).

While several organizations could implement such a mechanism, CMS is a particularly good candidate. CMS oversees health coverage for nearly 160 million Americans through Medicare, Medicaid, the Children's Health Insurance Program (CHIP), and the Health Insurance Marketplace, making it one of the most influential payers in the U.S. healthcare system. CMS is an ideal anchor funder of a generic drug repurposing pull mechanism because of its scale, financial incentive to reduce healthcare costs, and the authority of its Center for Medicare and Medicaid Innovation (CMMI).

CMMI has the authority to test models that lower costs, improve patient care, and align payment systems. CMMI could test this proposal through a prescription drug model. While it is not clear that CMS has a pathway for direct payments to developers, CMMI's legal authority allows it to experiment with new approaches such as our proposal. A pull mechanism for repurposing generic drugs could operate through either a cost-savings or health-impact approach, following five steps: promise, research, assess, sell, and reward (see Figure 2).

Figure 2: Five steps in proposed pull mechanism



Below is a description of how this mechanism could work in practice:

Step 1. Funder promises reward

CMMI would publish clear guidelines for generic drug repurposing: any company that secures FDA approval for a new indication of a generic drug is eligible for *X* number of years (e.g., 10 years) of value-based payments. Payments could be based on either cost-savings or health impact (see Table 1):

- **Cost-savings:** A percentage of Medicare savings generated by the drug, such as 70% of the reduced hospital expenditures associated with fewer relapse episodes.

- **Health impact:** A fixed amount for each unit of health improvement, such as $10,000 per Disability-Adjusted Life Year (DALY) averted. DALYs are a common health metric that combines years of life lost due to premature death and years lived with disability.

Upon model launch, CMMI would publish preliminary "conversion factors," which could offer guidance for how clinical trial data might be converted to cost-savings or health impact estimates. For example, they could publish information about the average cost and/or disability weights of specific conditions (e.g., type 2 diabetes without complications has an average cost of ~$3,000 per year). These conversion factors would serve as guidelines for how clinical outcomes (like lowered incidence or fewer relapses) translate into Medicare cost savings or DALYs averted estimates.

CMMI would also establish a process for companies to declare interest, undergo an initial screening, and schedule low-fee consultations with CMMI to clarify conversion factors before investing in costly clinical trials.

Table 1: Payment multiplier

Payment approach	Example payment multiplier
Cost savings	70% of savings
Health impact	$10,000 per DALY

Step 2. Developer researches new uses

Suppose "Company X" sees promise in existing studies suggesting metformin, a generic diabetes drug, could help patients with multiple sclerosis (MS). Before starting a Phase III trial, Company X consults with CMMI to confirm which outcomes will determine payment. Satisfied, they officially declare interest and undergo a screening by CMMI staff. Once aligned and assured no other developers are currently pursuing this opportunity, Company X proceeds with the trial.

Step 3. Funder assesses per-patient "value"

Five years later, Company X's trial shows that metformin cuts the annual relapse risk by roughly half for MS patients, and the FDA grants approval for the new indication. Medicare staff apply the pre-agreed conversion factors to the trial results. They estimate the following annual benefits per patient (see Table 2).

Step 4. Manufacturers sell drug for new use

Following the approval of the new use, manufacturers sell the drug for the new use. Third-party health analytics companies analyze annual claims and prescription data to assess the adoption of metformin for the new use. In the first year after approval, data show that 45,000 Medicare beneficiaries (about 20% of Medicare MS patients) are using metformin to treat MS.

Step 5. Funder pays based on "value" and adoption

CMMI calculates Company X's annual payment and distributes the annual payment each year for the 10-year period. Payments are the product of the payment multiplier, estimated benefit per patient, and number of patients treated (see Table 3).

In this example, assuming a gradual increase in adoption, CMMI would pay Company X roughly $1 billion in reward payments over the 10-year period. This is sufficient to justify running the trials from the developer's perspective and enables Medicare to realize net-savings of roughly $500 million and/or a health impact of over 100,000 DALYs (see Table 4).

Table 2: Annual benefit per patient examples

Model	Annual benefit per patient
Cost savings	~$3,500 per patient (avoided hospitalizations and specialist care)
Health impact	0.24 DALYs averted per patient (fewer relapses and slower progression)

Table 3: Payment calculation example

Payment approach	Payment multiplier	Est. benefit per patient	Patients treated	Annual payment
Cost savings	70% of savings	$3,500	45,000	**~$110 million**
Health impact	$10,000 per DALY	0.24 DALYs	45,000	**~$110 million**
Data source	*Funder choice*	*Funder assessment*	*Independent analytics companies*	*N/A*

Notes: Values rounded. DALYs refers to disability-adjusted life years, a measure of overall disease burden. CMMI would recalculate payments each year, adjusting for the number of patients treated. See the appendix for more details.

Table 4: Outcomes example (cost-savings)

	Outcomes (10 years) (undiscounted)
Total savings	$1.6 billion
Payments to developer	$1.1 billion
Net-savings to CMS	**$500 million (112,500 DALYs)**

Note: Values rounded.

Additional example cost-savings estimates are available in the supplemental materials.

Implementing pull funding

Given the significant public health and economic benefits that generic drug repurposing can offer, the federal government is uniquely positioned to implement and support a sustainable mechanism. A well-designed pull mechanism could help unlock the full potential of repurposing by creating a predictable and attractive return for developers pursuing high-impact, low-cost generic therapies. We believe one federal agency should serve as the primary implementer, but collaboration and coordination with other agencies will be necessary.

As suggested in the scenario above, CMS is a leading contender to implement this mechanism. However, in this section, we explore all potential options for implementing agencies and supporting roles other agencies and stakeholders can play to ensure the mechanism successfully allows patients to reap the full benefit of our available drugs.

Public payers as implementers

Public healthcare payers – including CMS and the Department of Veterans Affairs (VA) – are ideally positioned to implement a generic drug repurposing mechanism. These payers have the most to benefit in terms of cost savings and improved patient outcomes. Additionally, both CMS and the VA have established innovation hubs to test new payment models aimed at reducing costs and benefiting their unique patient populations.

CMMI remains, based on our evaluation, the leading option for an implementer of the mechanism because of its size, reach, flexibility, and experience testing drug models. They have a track record of running multi-year cost-savings and health-impact focused "models." Although there have been a limited number of drug models tested to date, past efforts, such as the Cell and Gene Therapy (CGT) Access Model, illustrate CMMI's willingness to explore alternative value-based payment strategies. These efforts could be adapted for repurposed generics.

The aims of this proposed mechanism also align with CMMI's 2025 strategic direction and could complement CMS's broader goals of improving population health while curbing spending growth. These objectives further reinforce CMMI as a highly compatible and influential platform to pilot and scale this mechanism. If the model proves valuable, then legislative action may be taken to implement the mechanism as a sustainable program within CMS to support cost-saving innovations.

The VA, however, could also run a mechanism through its Center for Care and Payment Innovation (CCPI). CCPI, like

CMMI, was launched to test new care and payment models that improve outcomes and reduce costs for veterans. Though it would be on a smaller scale, CCPI could operate a payment model, like the one described for CMMI, either in parallel or as an alternate home. One benefit CCPI offers in terms of prescription drug models is the authority to directly negotiate with manufacturers and implement custom payment arrangements within the VA system. This makes it more agile in executing novel reimbursement strategies. However, we suggest that a CCPI model would be best positioned as a supplement to a CMMI model due to its smaller scale. We've outlined the unique advantages and drawbacks of these options below (see Table 5).

Table 5: Comparing CMS and the VA as potential implementers

Category	CMS	VA
Beneficiaries	160 million beneficiaries (67 million Medicare beneficiaries)	9 million beneficiaries
Drug developers	Does not currently make direct payments to drug developers	Capable of paying drug developers directly
Drug models	CMMI has previously tested drug models	CCPI has not previously tested drug models
Off-label prescribing	May not be reimbursed without prior authorization	Reimbursed if included on VA drug formulary
Clinical trials	Does not run clinical trials	Regularly conducts large, multi-site clinical trials
Data	Fragmented data from various health systems and plans	Comprehensive EHR data on beneficiaries
Budget	FY2025: $1.6 trillion	FY2025: $464 billion
Disease priorities	Sepsis, osteoarthritis, heart disease, stroke, respiratory failure, renal failure, urinary tract infection (Medicare source)	PTSD, depression, diabetes, ischemic heart disease, viral hepatitis (VA source)

However, implementation of this mechanism does not need to be limited to only one federal agency – both CMS and the VA could each implement their own versions of the pull mechanism. Running a mechanism in parallel at both CMMI and CCPI could help to unlock more opportunities in generic drugs and yield greater interest and attention on research to identify new uses. Furthermore, each public payer can bring its own unique capabilities and strategic advantages to bear for the benefit of their unique populations. Coordination between CMS and the VA would be necessary to ensure program set-up efforts aren't duplicated and efficiencies can be gained, such as in evaluations of cost savings or health impact.

Establishing a supportive environment

While a pull mechanism implemented by a public payer can provide a financial reward for generic drug repurposing, for the mechanism to be truly successful, there must be a supportive ecosystem to support developers and the implementer. There are several key roles that other government agencies and other groups, such as private payers and philanthropies, can play to support and maximize the impact of this pull mechanism.

Complementary and competitive push funding

Push and pull incentives are often used as complementary tools, particularly when used to address market failures related to drug development. Push funding can help drive success of the pull mechanism by supporting early research to identify opportunities and to de-risk investment in clinical trials.

Some push funding activities are already in place. For example, NIH has previously funded some drug repurposing studies, including for Alzheimer's disease. The Biomedical Advanced Research and Development Authority (BARDA) has also offered grants for repurposing as a tool for developing countermeasures for biological, chemical, and nuclear health threats. Recently, the Advanced Research Projects Agency for Health (ARPA-H) funded the nonprofit Every Cure to develop an AI platform for drug repurposing that can identify promising drug and disease matches. These are important complementary efforts that can help to uncover repurposing opportunities to be pursued for the pull mechanism.

More and better coordinated push funding could be made available through these and other government agencies, including the National Center for Advancing Translational Sciences (NCATS) and the Department of War (DoW). There may also be a role for the Immediate Office of the Secretary in the Department of Health and Human Services (HHS) to serve as a coordinator for various repurposing pull funding activities and "prime the pump" so to speak for the CMMI and/or VA-led pull mechanism.

The federal government does not need to be the only push funder in the market for drug repurposing. Creating a pull

mechanism that will reward repurposing opportunities can attract interest and investment from philanthropic and nonprofit organizations, too. Private payers may also be drawn to the opportunity and benefit of drug repurposing and be willing to invest in trials, especially if CMS implements a model to reward developers. Many private payers take cues from CMS when it comes to reimbursement decisions, and so it is conceivable that an interest from CMS in the value of repurposing could attract private payer interest as well.

In theory, private payers may be able to implement their own version of the pull mechanism. However, they face several disadvantages. First, commercial insurers would be unlikely to realize a significant portion of the cost savings due to high turnover among beneficiaries, with some studies showing up to 20% disenrollment each year. Medicare and Medicaid also experience some turnover but has a more consistent population to track cost savings across than private payers. Additionally, each company only captures a portion of the total private market. Medicare and Medicaid, on the other hand, account for nearly 43% of national health expenditure. Private payers may find advantages in pooling resources to share in the benefits of repurposed generic drugs. Some have proposed a model where private payers pool savings from repurposed drugs to fund additional repurposing trials.

Lowering developer risk

Drug development of any kind always comes with risks. While the risk of failure decreases as a drug advances to later stages of development, developers and investors still take on a high level of risk for their multimillion-dollar investments. In a pull mechanism, the risk still fully falls on the drug developers, though they know they will receive a suitable reward if their risk pays off. Developers must always weigh risks when making decisions on which drug candidates to invest in, and some may not find the risk of successfully obtaining FDA approval for a new indication worth the time and financial investment of trials and the regulatory review process. However, there may be actions that can help to lower the perceived risk for developers.

For example, the FDA could issue clear guidance on requirements and evidentiary standards for repurposing generic drugs and provide resources for developers who may be less familiar with the regulatory pathway (i.e., 505(b)(2)). FDA could also explore flexible approval pathways, without lowering the necessary evidentiary standards required to ensure drugs are safe and effective. These simple steps could help inform better trial designs, lower total development costs, and, therefore, reduce the necessary reward size.

Additionally, FDA could collaborate with NIH or other agencies offering push funding for repurposing trials to support the development of research protocols that would meet requirements for FDA reviewers. This aligns with the "Make America Health Again Commission" (MAHA) Strategy Report's call for FDA and NIH to "jointly investigate opportunities to

strengthen the use of repurposed drugs." Research funded by NIH could be targeted towards generating data that would boost the confidence of developers to run Phase II and/or III trials and ensure study designs would support label expansion.

Additional implementation opportunities

Although a public payer offers a strong option to implement the pull mechanism, other health agencies may also be considered as implementers. One advantage of operating the incentive program in a non-payer agency is the opportunity to reward repurposing efforts based on broader health system impact rather than just cost savings.

Already mentioned for its role as a push funder, ARPA-H might also play a role as an implementer of a pull mechanism. ARPA-H could offer initial funding to reward the first few generic drug repurposing opportunities to demonstrate the value of having a pull mechanism to unlock more uses of existing drugs. This would serve as a pilot, which could give another agency the confidence to implement the model or even inspire legislative action to establish a dedicated program within HHS to reward generic drug repurposing.

NIH may also be a potential implementer of a pull mechanism for generic drug repurposing. While NIH primarily funds innovation in the form of grants (push funding), it also has authority to conduct challenges and prize competitions (pull funding). This authority, along with the directive to NIH in the MAHA Strategy Report, could be leveraged to implement a pull mechanism that rewards developers based on health impact on a repurposed generic drug. One advantage of NIH as a home for the pull mechanism is the opportunity for better coordination among push and pull funding to improve efficiency in federal government spending.

Areas for continued exploration

Here we have presented a proposal for how a pull mechanism can incentivize generic drug repurposing and how it can be implemented by public payers in the US. We have carefully considered a range of design features and potential alternatives, but recognize that some elements may still require additional refinement and stakeholder feedback as the proposal evolves. These include:

1. How large should the pull mechanism be? Determining the right size and structure of the reward will be critical to attracting developer interest without overspending public resources. Greater insight on the estimated costs and risks can inform appropriate sizing of the reward. To address variability in trial costs, different reward amounts may be considered for different therapeutic areas or another relevant factor. Our preliminary model, informed by available cost and probability of success data, provides an estimate of the necessary reward size (an abstracted version is described in the "pull sizing" blog). Additional data and more refined modeling would improve these estimates.

2. How can health impact and cost savings for specific opportunities be estimated in advance? Policymakers will need robust methods to project the potential value of repurposed drugs before committing to rewards. Determining which agency and what approach to use to estimate these value metrics in advance will require deeper engagement with potential implementers and organizations with the capabilities to conduct such analyses. CMMI and CCPI may have internal resources to estimate these values. Other organizations, such as the Agency for Healthcare Research and Quality and the Institute for Clinical and Economic Review, could play a supporting role as well.

3. How should adoption be tracked? Transparent tracking of provider prescribing and patient adoption is essential for triggering incentive payments and evaluating the success of a repurposed therapy. Preliminary exploration suggests health data analytics firms, such as IQVIA, may have the capability to retroactively track prescribing patterns for the new indication. Further engagement is needed to validate this approach and determine whether it provides sufficient accuracy and reliability for use within a pull mechanism framework.

Conclusion

The Trump Administration has demonstrated a clear interest in drug repurposing as a tool for achieving its core healthcare objectives, as indicated by the MAHA Strategy Report and efforts to repurpose the drug leucovorin for cerebral folate deficiency. Additionally, the Administration has expressed interest in innovative approaches to advancing innovations, including the use of pull funding (i.e., prizes and advance market commitments). This proposal for a pull funding mechanism aligns strongly with both of these aims and offers a timely opportunity to overcome the market-based barriers that have hindered exploration into the full potential value of generic drugs.

We propose a public payer, such as CMS, is best suited to implement such a mechanism. However, a coordinated approach that brings together the power of multiple agencies is also needed to ensure generic drug repurposing is systematically explored as a solution to provide affordable, accessible treatments for patients, especially those with limited or no treatment options. We encourage policymakers to consider pull funding as a way to unlock this underexplored opportunity.

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Appendix

Frequently asked questions

1. How does one appropriately size the pull fund (i.e., avoid over or under-paying)? What if the pull fund size is insufficient?

We have developed a preliminary model to estimate appropriate reward sizes. A simplified version is described in the pull sizing blog (updated version coming soon). This model used available clinical trial cost and probability of success data as inputs. To appropriately incentivize sponsors to invest in costly trials, the mechanism will use tiered reward structures to calibrate payments based on actual costs. For example, if Phase II trials have already been run, a smaller reward will be offered. To safeguard from overpromising rewards that could lead to windfall profits or wasteful entry by low-value competitors, the mechanism will cap total rewards or tie payments to value (e.g., cost savings or DALYs) using the tiered reward structure mentioned above.

2. Could this be done at ARPA-H or BARDA?

While both ARPA-H and BARDA have previous or current engagements in generic drug repurposing work, we believe they are better suited to complement a pull mechanism by funding early research through grant or push funding. Not only does CMS have a much larger budget than these organizations, making CMS a more capable funder, but payers also have the most stake in the game with the savings that repurposing offers.

3. Why are we requiring FDA approval?

We propose requiring FDA approval to access the pull fund because it is the clearest path to ensure safety, efficacy, and broad adoption of a repurposed generic drug. Research shows FDA approval raises adoption by about 40 percent overall and up to 65 percent for new disease areas. It also allows companies to educate physicians, which increases prescriptions by 8 percent. Trial data alone can sometimes drive use, but it is often hard to interpret without FDA review. Furthermore, expert summaries are not always current. Insurers also strongly prefer FDA-approved uses, making coverage and patient access more dependable. For these reasons, FDA approval remains the clearest and most

trusted path for patients, providers, and payers.

4. Why not pay directly for trials using grant funding?

There are several reasons not to pay directly for trials. Paying for trials, essentially push funding, does not guarantee developers follow through to FDA approval, which, as previously discussed, promotes the adoption and broadens access to the drug. Tying the reward to the adoption of a new use ensures payers would see cost savings or health impact down the line. It also encourages sponsors with the most useful private information to invest in trials, rather than rewarding sponsors who are less suited, therefore increasing the chances of success. Instead of relying on limited philanthropic or government funding that doesn't guarantee results, waiting to pay until a drug is successfully repurposed and approved will drive a sustainable market solution. It also enables firms to explore drug-use combinations that might not have otherwise occurred to grant funders.

5. What companies are we targeting?

The mechanism would be open to any sponsor interested in repurposing generic drugs. As we see it, small to mid-size pharmaceutical companies or generic manufacturers with R&D capabilities are most likely to be interested in pursuing the pull funding for generic drug repurposing. Where large, multinational pharmaceutical companies may be more interested in pursuing de novo drug development with the potential for large profit margins (i.e., chasing the next blockbuster drug), small to mid-size companies may be more likely to pursue opportunities with moderate profit margins in the range of this pull mechanism. Generic sponsors, particularly those with a research and development arm, would have a vested interest as they're already engaged in the generics market and are capable of doing the research. While the current regulatory framework limits academia and nonprofits from pursuing regulatory approval (i.e., label expansion) at the moment, these groups will still play a crucial role in the early stages of identification and research to support repurposing efforts.

Generic drug repurposing examples

Established examples

(Late-stage trial data)

1. Metformin for diabetes prevention
2. Aspirin for heart disease prevention
3. Acetazolamide for fluid retention caused by heart failure
4. Spironolactone for resistant hypertension
5. Colchicine for coronary artery disease

Promising opportunities

(Early-stage trial data and/or RWE)

1. Metformin for multiple sclerosis
2. Fenofibrate for diabetic retinopathy
3. Bumetanide for Alzheimer's prevention
4. Fenofibrate for primary biliary cholangitis
5. NRTIs for Alzheimer's disease