Title: New drug-development paradigms? Opportunities and uncertainties with new government drug repurposing programs

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One Sentence Summary: New government drug repurposing programs in the US and Europe present new opportunities for stakeholders, with three constituting novel development models

Abstract

Drug repurposing, the idea of finding new uses for authorized drugs, can be cheaper and faster than developing new compounds. Yet, repurposing remains underutilized, partially due to regulatory and intellectual property challenges. Over the past few years, US, UK, and EU policymakers have created seven drug development programs aiming to overcome these challenges. While each program seeks to accelerate repurposing, they do so via different strategies. This paper presents the first comparison of these programs, showing they offer new opportunities for organizations in drug development, including academics, physicians, and companies. Moreover, this paper shows that at least three programs feature new drug-development models. These models rely less on (i) patents and (ii) industry and more on (a) governments and (b) clinical trials conducted by hospitals and universities. However, the effectiveness of the programs is uncertain, and this paper begins the conversation about studying and improving them.

Keywords: drug repurposing; drug-development models; patent law; policy; government programs.

Main Text:

Drug Repurposing: The Benefits and Challenges

Drug repurposing, the concept of finding new uses for authorized drugs, holds great promise for medical care. A major advantage is that repurposing is generally less expensive and faster than the traditional process of developing treatments based on new chemical compounds. Estimates suggest repurposing can be 40-90 per cent cheaper than new compounds.[1–3] Furthermore, clinical trials designed to test repurposed drugs are generally safer than new drugs because initial safety studies have already been conducted in humans.

Despite the benefits, organizations repurposing drugs often face a distinctive set of legal and regulatory challenges that threaten the financial viability of the projects. The *first* challenge concerns patents. Patents are typically needed to secure a return on investment for drug developers. However, patents must relate to an invention that is novel (not publicly available) and inventive (not obvious based on prior knowledge).[4] While repurposed drugs meeting these requirements are principally patentable, patents are not granted (or if granted, they can be revoked) if the new use has been described in the literature or is obvious compared to prior uses (e.g. if a drug is authorized for pain and then found to treat another type of pain in a similar pathway). Commentators have previously stressed this challenge.[5] However, recent studies on patent filing data suggest that obtaining patent protection for new medical uses does not appear to be a major challenge. Notably, the number of patents granted has increased over the past 10 years, and the grant rate of these patents is above the average for all technologies.[6–7] Thus, this challenge may not curtail as much repurposing as previously thought. Nevertheless, some companies still mention it as a limiting factor.

The second and third challenges are probably more profound, concerning prices and sales. The second challenge is that the authorization of a new use for an established drug may trigger a re-evaluation of the drug's price, which typically erodes the profit the originators (the companies that developed the new use) hope to make.[8] The *third* challenge is known as 'cross-label' use. This is a version of off-label use that occurs when a generic drug is available but not authorized for the new use (often due to patent monopolies), and, therefore, the new use is omitted from the generic's label. The crux of the issue is that the generic is often still dispensed for the new use (typically for cost savings and based on knowledge of the originator's uses), thereby depriving the originator of a sale.[9] In the longer term, this erodes the incentive to identify, trial, and authorize new uses.

The government programs: diversity and opportunities

Seven government-run programs have recently been established, some temporarily or as pilots, that respond to these challenges in diverse ways, helping organizations reduce costs or mitigate one or more of the challenges. Other government-funded programs exist, but this paper only focuses on those run wholly or partially by governments. The programs are summarized in Figure 1, which is organized according to the themes discussed below.

The UK Innovative Licensing and Access Pathway supports any type of organization via an application process. The pathway calls for repurposing projects but is not limited to them. The program selects repurposing projects based on patient needs and whether the drug has the potential to offer patient benefits.[10] The pathway is open to pre-clinical and early-phase clinical projects, and successful applicants have access to a team of experts who will address various regulatory and development issues, including tailored advice and decentralized clinical trial design. However, the program does not fund clinical trials.

The second program, the US National Institute for Health's (NIH's) Discovering New Therapeutic Uses for Existing Molecules, began in January 2021 and is in the process of concluding, with the final Advisory Council Review in January 2024. Though, some of the funded project will run after this date. The program is run by the National Center for Advancing Translational Studies (NCATS). Applications are now closed, but previously, interested parties proposed a project that included conducting clinical trials.[11] Any organization could apply, and an initial aim of a project must have been to obtain approval for an investigational new drug (IND) application, which is required before clinical trials can begin. NCATS selected projects based on, amongst other things, the therapeutic potential of a drug. Successful applicants have been benefiting from assistance with various pre-clinical work, such as optimizing formulations and conducting pre-clinical studies. Once the IND is approved, the program funds phase I and II studies but not phase III, unless it is for a rare or neglected disease.

The EU program, Repurposing of Authorised Medicines, also provides advisory support to organizations repurposing drugs, but their support is only available to not-for-profit organizations and academics. Applications to join the program are evaluated based on the scientific rationale for the compound, including real-world data and the potential benefits to patients and public health.[12] Researchers are offered scientific and regulatory advice on attaining regulatory authorization for the new use, and the program expects the researchers to fund their clinical trials. Participants in the program are also expected to obtain authorizations for the new uses in collaboration with industry partners, and the program will provide contacts to help achieve this.

Compared to the first three programs that are oriented towards aiding other organizations, the CURE Drug Repurposing Collaboratory (CDRC) takes a different approach. The Collaboratory is a US public-private partnership between the FDA, NCATS and the Critical Path Institute, and at the center of the program is the CURE ID platform. The platform offers an online tool where global healthcare providers can report and search for new uses of existing approved drugs.[13] The Collaboratory also collects data from electronic health records, disease registries and literature reviews. Initially, the program focused on novel repurposed treatments for COVID-19 but is expanding to other communicable and non-communicable diseases, such as sepsis. The program aims to use the information gathered on the platform to inform clinical practice and, possibly, run clinical trials if more data is needed.[14] The program will consider only updating treatment guidelines, as opposed to pursuing regulatory authorization. The CDRC will consider sponsoring clinical trials and pursuing authorizations but will need a partner (the drug sponsor, known as the Reference Listed Drug holder) to achieve these goals.

NHS (National Health Service) England's Medicines Repurposing Programme is the only one that aims to conduct clinical trials in-house with minimal help from third parties. The program hunts for drugs to repurpose by searching clinical trial registries and inviting suggestions from the clinical community, including companies, medical research groups, and clinicians. The program selects projects by evaluating the drug's efficacy, preferably based on phase II clinical trial data, and whether the drug could improve the standard of care in a life-threatening or debilitating disease. The program establishes working groups for each project, including clinicians, program staff, and industry representatives, if appropriate.[15] The working groups, amongst other things, design phase III clinical trials to fill any gaps in the evidence base. Once data sufficient for authorization is generated, the program will offer the data to the originator or generic companies willing to obtain the authorization.[16]

The last two programs are from the US and rely on clinical trials conducted by third parties. The FDA's Project Renewal focuses on oncology treatments. Expert teams are set up to evaluate published data on new uses of 'older' oncology drugs.[17] The program aims to obtain authorizations for the new uses; however, it does *not* conduct clinical trials. Instead, it relies entirely on published data of older generic drugs, which are produced mainly by universities and hospitals.[18] If sufficient data for the authorization of a new use is found, the FDA contacts organizations with authorization for the drug and asks them to apply to update the drug label. However, the authorization holders are *not* obliged to apply for the authorization.

The program known as the 'MODERN Labeling Act' was first proposed in the Making Objective Drug Evidence Revisions for New (MODERN) Labeling Act of 2020. The Act was passed by the US

Congress but not by the Senate. However, the text was incorporated into the Consolidated Appropriations Act of 2021, which passed both houses.[19] The program is still known as the MODERN Labeling Act, referring to its origins. The program operates in a similar manner to Project Renewal, with the Act empowering the FDA to search for new uses and ask for input from the public or via agreements with third parties. One difference to Project Renewal, though, is that the Act empowers the FDA to look for new uses in any disease area.[20] Ultimately, the FDA is searching for new uses with sufficient data for authorization, including data from published clinical studies or reviews of real-world data.

One limitation of the Act is that the FDA can only consider drugs in which the originator has withdrawn their authorization from the market (but generic providers remain) and that are not covered by patents or other forms of exclusivities.[21] That said, the Act also provides the FDA with a surprising power. Once the FDA decides enough data exists to authorize a new use, the FDA must inform the generic companies about the proposed change. If the companies oppose the authorization, they can explain why. However, if the FDA disagrees with the explanation, it can continue the process to authorize the additional indication. Moreover, once the new use is authorized, the generic companies are obliged to update their labels, failing which they can be liable for mislabeling their product.[22]

New drug-development models and the road ahead

The programs present a myriad of opportunities for organizations in drug repurposing. In addition, taking a higher-level perspective, something more profound might be occurring.

In 2011, Francis Collins, the former head of the Human Genome Project and Director of the NIH, argued that new drug-development models are needed. He admitted that the traditional roles of the public and private sectors have served us well. However, he stressed that new models of drug development are needed to address the 'long timelines, steep costs, and high failure rates' that obstruct translational science.[23] He explained that the traditional model of drug development typically features the public sector producing breakthroughs in basic science and the private sector translating the breakthroughs into new therapeutics, which includes conducting expensive phase III clinical trials. Collins pointed to repurposing as an area ripe for change but did *not* articulate any significant changes to the model. The new spate of programs might represent the new models he hoped for and, depending on the programs' successes, perhaps a paradigm shift in drug development. In this section, we briefly discuss key features of the programs and their road ahead.

Three of the programs depart significantly from traditional drug development models: namely, the NHS England's Medicines Repurposing Programme, the FDA's Project Renewal, and the Modern

Labeling Act. A common feature among these initiatives is that companies remain involved in drug development, but the public sector is responsible for conducting clinical trials. Additionally, there is limited private involvement in selecting drugs for repurposing. The MODERN Labeling Act stands out in particular for the public sector's increased influence on the labelling of the drug. Indeed, companies cannot even choose what goes on their labels!

One possible criticism of NHS England's Medicines Repurposing Programme is that it takes on too much risk, especially if it sponsors phase III clinical trials. However, studies have shown that repurposing has a much higher authorization rate than new molecular entities.[24] Thus, the risk-reward ratio might favor the government undertaking this role. Project Renewal and the MODERN Labeling Act take a different approach to this risk, relying on pre-existing data only. However, the value of these programs may be called into question: are there sufficient new uses that can be authorized based on available data? And, if abundant data already exists on a drug's new use, what benefits does society gain from authorizing its use?

But not all the programs constitute new models of drug development. The UK's Innovative Licensing and Access Pathway, for example, provides helpful services to a range of organizations in drug development, but it is *not* orientated towards changing the roles played by public and private organizations. The EU program might represent a change in the standard model of drug development. So far, however, it is unclear how much of the clinical work academics will conduct. If academics (or other public sector organizations) consistently fund and conduct phase III clinical trials sufficient for authorization, this would mark a departure from the model where these are conventionally conducted by private industry.[25] The CRDC program might be a new model, too; however, this also depends on who conducts the trials. The CDRC program's strategies of using real-world data and working towards improving treatment guidelines are not enough to make it a new model, as other organizations frequently adopt these strategies.

All seven of the programs are relatively new, and questions surround their success and longevity. The NIH's Discovery New Therapeutic Uses for Existing Molecules is a case in point, with no news of renewal announced. One key question is: will the programs with new models (i.e. the NHS England's Medicines Repurposing Programme, the FDA's Project Renewal, and the Modern Labeling Act) herald new paradigms of drug development? Some early results are encouraging; for example, NHS England's project has obtained one new authorization,[26] and the FDA's Project Renewal has obtained two.[27] Yet, it is too early to tell whether these are isolated instances or the first of many impactful new uses. Nevertheless, steps can be taken to maximize their chances of success. An initial step is to optimize the processes for selecting drug candidates. For this, it will be helpful for the programs to share information and experiences. Such an exchange is already underway, with the CRDC holding a

meeting open to all programs last year. Ideally, this is only the start, and the programs will continue to collaborate on key issues; such as sharing data on analyses that show a drug is inferior to existing standards of care, which would save other programs the effort of considering the compound.

Indicators of success will help evaluate whether the models should be pursued as new paradigms. In theory, the programs could be emulated in various countries around the globe. At least five criteria could be used to determine success: (i) the number of authorizations granted; (ii) their clinical impact; (iii) the number of patients treated in accordance with the new use; (iv) savings in public healthcare; and (v) reductions in off-label use, especially if the earlier use was based on inadequate data. An issue, however, with these indicators is their subjectivity. For example, there are numerous ways to measure clinical impact. The evaluations will also involve trade-offs. For instance, public healthcare savings might not support better patient outcomes. While these programs will likely produce reports describing their success, a broader range of voices and analyses will be necessary to determine which models to retain, if any. Input will be needed from patient groups, academics, clinicians, companies and advocacy groups, just to name a few. These inputs will be vital as society continues to seek new approaches for rapid and cost-effective production of new treatments.

Table 1. **Program's Functions and Aims** summarizes the programs' aims and functions. The boxes in grey highlight the functions or aims of the programs. The spread of grey boxes illustrates the diversity of aims and functions.

		Programs' Functions and Aims						
Programs (Country)	**Agencies**	Will run clinical trials and provide data to companies to obtain authorizations	Provide regulatory and scientific advice to businesses	Sponsor or provide funding for clinical research	Provide support for academics and not-for-profit researchers	Provide evidence of unauthorized uses to clinicians or advisory bodies	Advise authorization holders of new uses that can be obtained without more trials	Can oblige generic companies to update labels based on published evidence
CURE Drug Repurposing Collaboratory (CDRC) (US)	C-Path, FDA and NIH	Possibly	N	N	N	Y	N	N
Discovering New Therapeutic Uses for Existing Molecules (US)	NIH	N	Y	Y	Y	N	N	N
Innovative Licensing and Access Pathway (UK)	Consortium of UK Health Agencies	N	Y	N	Y	N	N	N
Medicines Repurposing Programme (England)	Led by the UK NHS and supported by multiple agencies	Y	N	Y	N	Y	N	N
MODERN Labeling Act (US)	FDA	N	N	N	N	N	Y	Y
Project Renewal (US)	FDA	N	N	N	N	N	Y	N

Repurposing of Authorized Medicines (EU)	EMA & the Heads of Medicines Agencies	N	N	N	Y	N	N	N

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