Urgent Need to Revisit Financial Incentives for Repurposed Medicinal Products

Off-Patent Drug Repurposing: Massive but Untapped Potential

Drug discovery is a complex, lengthy, and expensive process. Repurposing existing generic drugs to target new indications is less risky, as the behaviour of existing drugs in humans is already known, and research is much faster and cheaper.[1] **Repurposing generics can have groundbreaking effects for patients**: 35% of 'transformative' drugs approved by the US FDA are repurposed products.[2] Repurposing is especially relevant for rare or neglected diseases.[2]

Unfortunately, the pharmaceutical industry and venture capitalists have little incentive to invest in generic drug repurposing. As noted by pharmacologist Alasdair Breckenridge and Judge Robin Jacob, "If a generic version of a drug is available, developers have little or no opportunity to recoup their investment in the development of the drug for a new indication".[3] Therefore, the best examples of successful repurposed drugs have often been serendipitous discoveries. Generic drug repurposing efforts are currently underfunded and led mainly by universities and philanthropic organisations.[4] Promising candidates for repurposing include exenatide for Parkinson's disease, verapamil for Type 1 diabetes, ketamine for depression, and ambroxol for dementia with Lewy Bodies. With the advent of artificial intelligence and real-world evidence, the computational screening of existing drugs for new uses could scale the discovery of new therapies.[5]

The Commission's Proposal: Well-intentioned but Insufficient

The Commission's proposal of a 4-year data protection period for repurposed drugs in Article 84 of the proposed Directive is well-intentioned but will unfortunately prove insufficient based on the US experience. In the American market, drug developers obtain three years of protection if their product is authorised for a new indication. Despite these incentives, **the imminent threat of generic entries significantly deters companies from adding new indications**.[6]

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[1] Grabowski & Moe (2008). "Impact of economic, regulatory, and patent policies on innovation in cancer chemoprevention". *Cancer Prevention Research (Philadelphia, Pa.)*. **1** (2): 84–90; Drugs for Neglected Diseases Initiative. "15 Years of needs-driven innovation for access." (2019)
[2] Kesselheim et al. (2015). "The roles of academia, rare diseases, and repurposing in the development of the most transformative drugs". *Health Affairs (Project Hope)*. **34** (2): 286–293.
[3] Breckenridge, Alasdair, and Robin Jacob. "Overcoming the legal and regulatory barriers to drug repurposing." Nature reviews Drug discovery 18.1 (2019): 1-2.
[4] Krishnamurthy et al. (2022). "Drug repurposing: a systematic review on root causes, barriers and facilitators". *BMC Health Services Research*. **22**: 970.
[5] Paranjpe et al. (2019). "Insights into Computational Drug Repurposing for Neurodegenerative Disease". *Trends in pharmacological sciences*. **40** (8): 565–576.
[6] Sahragardjoonegani et al. (2021). "Repurposing existing drugs for new uses: a cohort study of the frequency of FDA-granted new indication exclusivities since 1997". *J. Pharm. Policy Pract*. **14** (1): 3.

The case of metformin, a diabetes medication under study as a possible treatment for multiple sclerosis (MS), illustrates this: Metformin is so cheap that even if a manufacturer secures four years of data protection and caters to all 1 million MS patients in the EU, they wouldn't be able to recoup their research investment. Besides these low profit margins, **the prevalence of off-label prescriptions and automatic substitutions by pharmacists to cheaper alternatives would make such a venture financially unattractive**.[7]

A Better "Pull" Mechanism for Generic Drug Repurposing

We believe that pay-for-success (PFS) contracts can leverage future cost savings to incentivise the repurposing of generic drugs without taxpayers taking on the financial risk of failed clinical trials.[8] **In addition to the 4-year data protection, it is necessary and complementary to mandate the Commission to establish a Union push and pull incentives scheme to promote the repurposing of generics, which could include market-entry rewards, 'play or pay' fees, or subscription payment mechanisms.** For instance, a €100m market-entry reward would strongly accelerate research for a cure for MS while being lower than the €40 billion yearly economic burden of MS in the EU.[9] The Rapporteur's Amendment 90, proposing the European Medicines Facility (EMF) in the revised Regulation under a new Article 40a, should also encompass generic drug repurposing.

These "pull" incentives allow governments to only pay for success and save money by identifying cheap treatments using existing generics. It will also foster investments in artificial intelligence startups for drug repurposing in the EU.

Conclusion

We appreciate the Commission's efforts to incentivise drug repurposing. We firmly believe that implementing "pull" incentives, complemented by a 4-year data protection period, would **catalyse drug repurposing, foster innovation, and potentially unlock untapped, cost-effective therapies**. We strongly urge the Parliament to reassess Articles 84 of Directive and 40a of the Regulation per our proposed amendments below.

[7] Lietzan (2018). "Paper Promises for Drug Innovation". *George Mason Law Review*. **26**(1):207. See also Warner-Lambert v Generics [2018] UKSC 56

[8] Kerdemelidis & Fiorenza (2023) "Leveraging Pharmacoeconomics and Advance Market Commitments to Reduce Healthcare Expenditures". *Federation of American Scientists*.

[9] Paz-Zulueta et al. (2020). "A literature review of cost-of-illness studies on the economic burden of multiple sclerosis". *Multiple Sclerosis and Related Disorders*. **4**.

About the Signatories

- Savvas Kerdemelidis, LLM, BSc, Patent and Trade Mark Attorney, Founder & CEO of the drug repurposing charity Crowd Funded Cures. Citizen of the Hellenic Republic.
- Antoine Dusséaux, French open data activist and founder of the legal AI platform Doctrine.
- Every Cure is a nonprofit organization dedicated to unlocking the full potential of every existing medicine to treat every disease possible.
- Dr. Bruce Bloom founded Cures Within Reach which developed more than a dozen repurposed generic therapies. Chief Science Officer for the Kabuki Syndrome Foundation.
- REPO4EU, EU-funded initiative building a platform for drug repurposing with 28 partners from 10 countries.
- Vikas P. Sukhatme MD ScD and Vidula Sukhatme MS, co-founders of the Emory Morningside Center for Innovative and Affordable Medicine and GlobalCures, a non-profit focused on the clinical development of financial orphans, including generic drugs.
- Arthur Grenier, PharmD, Chief of Strategy at MedInsights, the drug repurposing accelerator.

Recommendation for Article 84 of the Directive

~~Data protection~~ Incentives for repurposed medicinal products

1. A regulatory data protection period of four years shall be granted for a medicinal product with respect to a new therapeutic indication not previously authorised in the Union, provided that:
    a. adequate non-clinical or clinical studies were carried out in relation to the therapeutic indication demonstrating that it is of significant clinical benefit, and
    b. the medicinal product is authorised in accordance with Articles 9 to 12 and has not previously benefitted from data protection, or 25 years have passed since the granting of the initial marketing authorisation of the medicinal product concerned.
2. The data protection period referred to in paragraph 1 may only be granted once for any given medicinal product.
3. During the data protection period referred to in paragraph 1, the marketing authorisation shall indicate that the medicinal product is an existing medicinal product authorised in the Union that has been authorized with an additional therapeutic indication.
4. The Commission shall furthermore establish a Union push and pull incentive scheme to promote and accelerate the repurposing of generic medicinal products. Member States shall be encouraged to participate in the Union level scheme.[10]

Recommendation for Article 40a of the Regulation

Insert after (iii):

(iv) the repurposing of generic medicinal products.

[10] This language could alternatively be inserted into Article 40a of the revised Regulation based on the draft report of the Committee on the Environment, Public Health and Food Safety on the proposed Regulation 2023/0131(COD), under the title *"Additional measures to incentivise the repurposing of medicinal products"*.