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BETWEEN PATENTS AND PATIENTS: WHY INTELLECTUAL PROPERTY ALONE CANNOT SUSTAIN DRUG REPURPOSING

Abstract

This paper explores why Europe's current intellectual property (IP) architecture provides insufficient support for the repurposing of older medicines. Focusing on second medical use patents and the 8+2(+1) regulatory exclusivity model, it shows how these mechanisms often fail to justify the cost of rigorous clinical trials once a drug's primary patents expire. The analysis then turns to Article 84 of the proposed EU Pharma Package, a measure that would grant a dedicated four-year data exclusivity for repurposed indications demonstrating substantial clinical benefit. While this legislative initiative marks an important step toward incentivizing further research into known compounds, the paper argues that IP-based solutions alone cannot overcome systematic obstacles. Chief among these are national reimbursement policies that rarely differentiate repurposed therapies from generics, conservative health technology assessments that require extensive clinical evidence, and widespread off-label prescribing that undercuts the economic rationale for formal authorization. The discussion concludes by suggesting a suite of complementary reforms—such as lifecycle-driven HTA, adjusted reimbursement models, and enhanced collaboration between academic institutions and industry—that together could create a more supportive environment for drug repurposing. By addressing both the regulatory and systemic impediments, the European Union may ultimately unlock greater value from existing compounds while preserving affordability and ensuring patient access.

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[1] PhD Candidate at the Institute of Law Studies of the Polish Academy of Sciences. This essay is part of a broader research project conducted as a component of my PhD thesis, prepared under the supervision of Dr Żaneta Zemła-Pacud at the Institute of Law Studies of the Polish Academy of Sciences.

Chapter 1 – Introduction

This opening chapter lays the groundwork for understanding the transformative potential of drug repurposing—revisiting older or off-patent compounds for new clinical indications. It highlights key examples, from thalidomide to sildenafil, demonstrating why "repurposing" can reduce the spiraling costs and high attrition rates of traditional drug discovery. The chapter also outlines the current European legal and regulatory backdrop, clarifying how intellectual property protections and reimbursement frameworks shape incentives for further research on known substances.

This paper will argue that while second medical use patents and EU regulatory exclusivity extensions theoretically encourage drug repurposing, real-world prescribing behaviors, reimbursement frameworks, and national HTA structures often undercut these incentives.

1.1 Background

Drug repurposing—revisiting older or off-patent compounds for new therapeutic uses—has gained significant traction as a cost-effective and time-saving strategy in pharmaceutical research. High-profile cases such as thalidomide (redeployed from a notorious sedative to a myeloma treatment) and sildenafil (initially developed for angina and later approved for erectile dysfunction) highlight the transformative potential of this approach.[2],[3],[4] By reducing development timelines and leveraging existing safety data, repurposing can mitigate the growing cost of drug discovery, often estimated in the billions of euros per successful new entity[5].

The European Medicines Agency (EMA) and the Safe and Timely Access to Medicines for Patients (STAMP) expert group[6] define it as "the process of identifying a new use for an existing medicinal/active substance in an indication outside the scope of the original

[2] Historical examples of talidomide and sildenafil are frequently cited in repurposing literature; see Rehman, W., Arfons, L. M., & Lazarus, H. M. (2011). The rise, fall and subsequent triumph of thalidomide: Lessons learned in drug development. Therapeutic Advances in Hematology, 2(5), 291–308. https://doi.org/10.1177/2040620711413165

[3] Rajkumar, S. V. (2004). Thalidomide: Tragic past and promising future. Mayo Clinic Proceedings, 79, 899–903.

[4] Cruz-Burgos, M., Losada-Garcia, A., Cruz-Hernández, C. D., Cortés-Ramírez, S. A., Camacho-Arroyo, I., Gonzalez-Covarrubias, V., Morales-Pacheco, M., Trujillo-Bornios, S. I., & Rodríguez-Dorantes, M. (2021). New approaches in oncology for repositioning drugs: The case of PDE5 inhibitor sildenafil. Frontiers in Oncology, 11. https://doi.org/10.3389/fonc.2021.627229

[5] Nosengo, N. (2016). Can you teach old drugs new tricks? Nature, 534(7607), 314–316. Retrieved from https://www.nature.com/news/polopoly_fs/1.20091%21/menu/main/topColumns/topLeftColumn/pdf/534314a.pdf

[6] European Commission. (2021). Commission expert group on safe and timely access to medicines for patients (STAMP). Retrieved from https://health.ec.europa.eu/medicinal-products/pharmaceutical-committee-veterinary-pharmaceutical-committee-and-expert-groups/commission-expert-group-safe-and-timely-access-medicines-patients-stamp_en; The Safe and Timely Access to Medicines for Patients (STAMP) expert group was established by the European Commission to provide guidance on policies aimed at improving access to medicines. One of its key areas of focus has been facilitating drug repurposing initiatives, particularly for non-commercial stakeholders such as academia and non-profit organizations. In collaboration with the European Medicines Agency (EMA) and other stakeholders, STAMP launched a pilot project in 2021 to support regulatory pathways for repurposed medicines;

indication[7]". With as many as 90% of clinical trials failing and costs for a single investigational compound often exceeding two billion dollars over 8 to 15 years, there is an urgent need for faster, more affordable strategies[8]. In this context, drug repurposing stands out by potentially reducing development time and investment risk.

Beyond economic and regulatory considerations, drug repurposing aligns with broader sustainability goals. By making use of existing compounds rather than developing new ones from scratch, this approach supports responsible resource management and reduces environmental impact, resonating with current environmental, social, and governance (ESG) priorities[9].

Estimates suggest as many as 75% of known drugs might have additional therapeutic uses beyond their originally approved indications[10]. In practice, though, few of these potential repurposing pathways attract sufficient investment. This gap arises not solely from scientific or clinical uncertainty—plenty of older compounds demonstrate interesting off-label efficacy—but also from regulatory, legal, and economic misalignments. Once patents and regulatory exclusivities expire, pharmaceutical companies lack the same commercial incentives to finance rigorous clinical trials in new indications. Even second medical use patents, while conceptually supportive of innovation, are notoriously difficult to enforce, in part because physicians may legally prescribe cheaper generic alternatives off-label[11].

The European Union has historically relied on an 8+2(+1) data and market exclusivity framework to incentivize pharmaceutical innovation[12]. The 8+2(+1) exclusivity framework is established under Article 14(11) of Regulation (EC) No 726/2004[13] and Article 10(1) of Directive 2001/83/EC[14], which govern the protection periods for medicinal products in the European Union. According to these provisions, a reference[15] drug benefits from eight years

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[7] European Commission. (2018). Repurposing established medicines: Background. Retrieved from https://health.ec.europa.eu/system/files/2018-11/stamp_8_repurposing_established_medicines_background_0.pdf

[8] Kulkarni, V. S., Alagarsamy, V., Solomon, V. R., Jose, P. A., & Murugesan, S. (2023). Drug repurposing: An effective tool in modern drug discovery. Russian Journal of Bioorganic Chemistry, 49(2), 157–166. https://doi.org/10.1134/S1068162023020139

[9] Bhar, S. (2023). Role of drug repurposing in sustainable drug discovery. IntechOpen. https://doi.org/10.5772/intechopen.110621

[10] Srivastava, K., & Singh, M. K. (2021). Drug repurposing in COVID-19: A review with past, present and future. Metabolism Open, 12, Article 100121. https://doi.org/10.1016/j.metop.2021.100121

[11] Roin, B. (2016). Solving the problem of new uses by creating incentives for private industry to repurpose off-patent drugs. Availabe at: https://www.bu.edu/law/files/2016/10/Solving-the-Problem-of-New-Uses-Ben-n.-Roin.pdf

[12] Regulatory exclusivity mechanisms are provided for under Regulation (EC) No 726/2004 (see Articles 8 and 10) and Directive 2001/83/EC (see Article 12(3)); further specific provisions are contained in Regulation (EC) No 1901/2006. Regulatory exclusivity guarantees a temporary period of market exclusivity and data exclusivity, enabling innovators to recoup their investments before competition is introduced.

[13] Art. 14(11), Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, OJ L 136, 30.4.2004, p. 1–33, EUR-Lex.

[14] Art. 10(1), (5), Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use, OJ L 311, 28.11.2001, p. 67–128, EUR-Lex.

[15] A reference drug (also called an originator or innovative drug) is a medicinal product authorized based on a full dossier of clinical and preclinical data, serving as the comparator for generics and biosimilars. Defined under Article 10(2)(a) of Directive 2001/83/EC, it benefits from patent protection and regulatory exclusivity (Directive 2001/83/EC, OJ L 311, 28.11.2001, p. 67–128, EUR-Lex).

of data exclusivity, during which generic drug[16] manufacturers cannot rely on the reference's data for regulatory approval, followed by two years of market exclusivity, preventing the marketing of generics even after data exclusivity expires (together in this essay referenced as "regulatory exclusivities"). An additional one-year extension may be granted if the marketing authorization holder demonstrates a significant clinical benefit through a newly approved therapeutic indication[17].

However, this "+1 year" extension was widely viewed as insufficient for repurposed drugs, where substantial clinical trials may still be required to demonstrate efficacy in a new indication. Empirical data suggests, that one extra year on the market did not justify the cost of new trials, particularly for compounds with existing generic competition[18].

Coupled with the difficulty of securing effective second medical use patents—and the risk of off-label prescribing[19]—this shortfall in exclusivity helped create a discouraging environment for genuine repurposing projects. Academic institutions or smaller biotech firms might identify a promising new therapeutic target for an older compound but struggle to fund or commercialize the subsequent clinical program, especially if it was unlikely to achieve reimbursement at a premium price[20].

The pricing and reimbursement environment in the European Union further complicates matters. National reimbursement regulations are typically designed for either breakthrough innovations—which justify high prices due to extensive R&D—or for generics, which benefit from competitive pricing[21]. Repurposed therapies often fall into a gray area: they may require significant investment for new clinical trials, yet lack the exclusivity periods enjoyed by novel drugs. A notable example is the reformulation of midazolam into repurposed drug for pediatric seizure management, which, despite its clear clinical benefits, faced health technology assesment challenges that did not fully reflect its improved profile[22].

Against this backdrop, the European Commission introduced in April 2023 a significant pharmaceutical reform package, sometimes referred to as the "EU Pharma Package[23]." It

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[16] A generic drug is a medicinal product with the same active substance, dosage form, and therapeutic effect as a reference (originator) drug, but without requiring a full clinical dossier. Approval is based on bioequivalence studies under Article 10(2)(b) of Directive 2001/83/EC, allowing market entry after the reference drug's exclusivity expires (Directive 2001/83/EC, OJ L 311, 28.11.2001, p. 67–128, EUR-Lex).

[17] Article 10(5) of Directive 2001/83/EC

[18] Liddicoat, J., Liddell, K., Aboy, M., & Wested, J. (2021). Has the EU incentive for drug repositioning been effective? An empirical analysis of the "+1" regulatory exclusivity. IIC – International Review of Intellectual Property and Competition Law, 52, 825–851. https://doi.org/10.1007/s40319-021-01088-0

[19] Żakowska-Henzler, H. (2017). Patenty na drugie medyczne zastosowanie – niekończąca się historia wątpliwości i kontrowersji.

[20] van der Pol, K. H., Aljofan, M., Blin, O., Cornel, J. H., Rongen, G. A., Woestelandt, A. G., & Spedding, M. (2023). Drug repurposing of generic drugs: Challenges and the potential role for government. Applied Health Economics and Health Policy, 21(6), 831–840. https://doi.org/10.1007/s40258-023-00816-6

[21] Medicines for Europe. (2022, March). Advancing medicines repurposing in the EU. Retrieved from https://www.medicinesforeurope.com/wp-content/uploads/2022/03/Advancing-medicines-repurposing-in-the-EU.pdf

[22] Lee, D., Gladwell, D., Batty, A. J., Brereton, N., & Tate, E. (2013). The cost effectiveness of licensed oromucosal midazolam (Buccolam®) for the treatment of children experiencing acute epileptic seizures: An approach when trial evidence is limited. Paediatric Drugs, 15(2), 151–162. https://doi.org/10.1007/s40272-013-0009-5

[23] European Commission. (2023). Reform of the EU pharmaceutical legislation. Health. Retrieved February 21, 2025, from https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en

includes a draft directive (2023/0132)[24] that proposes, among other things, a dedicated four-year period of data exclusivity under Article 84 for drugs that demonstrate substantial new clinical benefits in a repurposed indication. Advocates suggest this change could energize investment in older molecules by correcting the current misalignment between the risks of additional clinical research and the potential returns from marketing authorization in a new indication.

Yet, any such reform will be shaped by broader systemic realities, including conservative health technology assessments (HTA)[25], reimbursement structures that prioritize cost-minimization, and habits of off-label prescribing among physicians[26]. This essay contends that while Article 84 could address the core problem of insufficient regulatory exclusivity for repurposed drugs, its ultimate success depends on complementary adjustments in legal and policy frameworks. After exploring the background of repurposing in the EU and the shortcomings of existing IP tools, the text examines the proposed legislation and how identified systemic constraints may still stall large-scale adoption. It concludes by presenting a series of policy recommendations that, taken together, could transform repurposing from an occasional success story into a cost-effectve and sustainable strategy for pharmaceutical innovation.

1.2 Significance of the Study

The growing interest in drug repurposing is driven by both economic and clinical imperatives. On the one hand, the pharmaceutical industry faces pressures from increasing research and development expenditures, lengthy approval processes, and the high likelihood of clinical trial failures[27]. On the other hand, healthcare systems and patients are in urgent need of new treatment options, particularly in therapeutic areas characterized by unmet medical needs—such as rare diseases[28], oncology, and certain chronic conditions. The repurposing of drugs offers a compelling solution, yet its potential is stifled by regulatory, economic, and legal barriers that limit investment and innovation in this field[29].

Despite the benefits, the systemic obstacles remain: sponsor companies and academic institutions frequently cite weak IP protection, conservative health technology assessment

[24] European Commission. (2023). Proposal for a Directive of the European Parliament and of the Council on the Union Code Relating to Medicinal Products for Human Use, and Repealing Directive 2001/83/EC and Directive 2009/35/EC (2023/0132(COD)). EUR-Lex. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52023PC0192

[25] Health Technology Assessment (HTA) is a systematic evaluation of the clinical, economic, and societal value of medical technologies, including pharmaceuticals, to inform reimbursement and pricing decisions in the EU. It is governed by Regulation (EU) 2021/2282, which establishes a joint EU framework for assessing health technologies across Member States (Regulation (EU) 2021/2282, OJ L 458, 22.12.2021, p. 1–32, EUR-Lex).

[26] Żakowska-Henzler, H. (2017)

[27] Sun, D., Gao, W., Hu, H., & Zhou, S. (2022). Why 90% of clinical drug development fails and how to improve it? Acta Pharmaceutica Sinica B, 12(7), 3049–3062. https://doi.org/10.1016/j.apsb.2022.02.002

[28] The definition of rare diseases in the European Union is provided for under Regulation (EC) No 141/2000 on orphan medicinal products (see Article 2), which characterizes a rare disease as one affecting no more than 5 in 10,000 people in the EU.

[29] Pushpakom, S., Iorio, F., Eyers, P. A., Escott, K. J., Hopper, S., Wells, A., & Pirmohamed, M. (2019). Drug repurposing: Progress, challenges and recommendations. Nature Reviews Drug Discovery, 18(1), 41–58. https://doi.org/10.1038/nrd.2018.168

(HTA) criteria, and complex pricing negotiations as major reasons why promising repurposing projects never progress to formal marketing authorization[30].

This essay examines if the intellectual property remains a cornerstone of pharmaceutical innovation, or is it not sufficient in isolation when it comes to drug repurposing. The abovementioned reform of EU pharmaceutical legislation, commonly referred to as the "EU Pharma Package[31]" seeks to modernize the regulatory framework governing medicinal products for human use.

Ultimately, the significance of this essay lies in its critical examination of the interplay between intellectual property rights, regulatory incentives, and market dynamics within the context of drug repurposing.

Chapter 2 – The Rationale and Regulatory Context of Drug Repurposing in the European Union

This chapter analyse what exactly constitutes drug repurposing and how it is defined (or not defined) in various contexts—regulatory, industrial, and academic. It explores the different pathways by which an older compound can be repositioned, including “reprofiling” of shelved molecules. The analysis clarifies why the EU’s existing approval processes can either facilitate or hinder these efforts, setting the stage for a closer look at intellectual property challenges in the following chapter.

2.1 Unclear Boundaries in Definitions

The concept of drug repurposing may appear straightforward at first glance. Yet, in practice, there is no single, universally accepted definition[32]. Industry experts, regulators, and academic researchers often apply diffrent criteria to decide what counts as “repurposing,” as opposed to mere line extensions, brand expansion, or even entirely novel drug development.

A key factor in this differentiation lies in the regulatory framework governing market access. Any medicinal product intended for repurposing must adhere to the rules of Marketing Authorisation[33] (MA)—a legal prerequisite for placing a drug on the market. Depending on the regulatory pathway chosen, the entity responsible for the product, known as the Marketing Authorisation Holder[34] (MAH), may need to submit extensive registration data[35], including

[30] van der Pol et al. (2023)
[31] 2023/0132(COD). EUR-Lex (European Commission (2023)
[32] Langedijk, J., Mantel-Teeuwisse, A. K., Slijkerman, D. S., & Schutjens, M. H. (2015). Drug repositioning and repurposing: Terminology and definitions in literature. Drug Discovery Today, 20(8), 1027–1034. https://doi.org/10.1016/j.drudis.2015.05.001
[33] Art. 3(1), Regulation (EC) No 726/2004
[34] Art. 1(28), Regulation (EC) No 726/2004
[35] Art. 10(1), Directive 2001/83/EC; Registration data refers to the dossier of preclinical, clinical, and manufacturing information submitted for the approval of a medicinal product, which is also relevant in the context of generic applications relying on prior authorisations.

clinical and preclinical evidence, to justify the new therapeutic indication. These regulatory classifications not only influence the feasibility of repurposing but also shape incentives, intellectual property considerations, and the commercial viability of developing new uses for existing drugs.

In the most inclusive sense, drug repurposing can mean any newly discovered use of an existing compound[36]. However, narrower criteria should be applied. Repurposing definision should exclude instances in which a MAH simply finds an additional indication for a patented or newly patented product. In author's view, such discoveries represent deliberate market expansion rather than genuine repurposing. By contrast, if the relevant patents or data exclusivities have expired, or the compound is at least far enough along its lifecycle that exclusivity is weak, the process typically qualifies as repurposing in the classic sense—an attempt to revive a known substance by finding alternative therapeutic value.

In other words, the question of patent status frequently becomes the litmus test. Many authors cite off-patent, genericized molecules as the prime candidates for repurposing initiatives, especially when industry sponsors have lost interest in further development[37],[38]. Conversely, if a company still retains strong intellectual property rights, additional indications may be perceived more as strategic brand management or market expansion. As a result, repurposing is often tied in academic literature to older, off-patent drugs—ones whose original protections have lapsed, access to clinical and registration data is easy, but which remain pharmaceutically relevant and safe[39].

2.2 Multiple Pathways to Repurposing

A second layer of complexity arises from the variety of ways in which repurposing can occur. While some authors limit the term "drug repurposing" to exploring new clinical indications, others include modifications such as changing a drug's route of administration, reformulating its dosage form, or simply adjusting dosage levels[40]. The U.S. Food and Drug Administration (FDA) classification system for New Drug Applications illustrates this range of possibilities by distinguishing among new molecular entities (Type 1), new derivatives (Type 2), new formulations (Type 3), new combinations (Type 4), and so forth[41]. In that sense, adding a new indication is not the only scenario that can be labeled as repurposing. A product might be repositioned solely through a novel dosage regimen or a different route of administration, leading to a distinct regulatory category under the FDA's framework.

[36] Toumi, M., & Rémuzat, C. (2016). Value added medicines: What value repurposed medicines might bring to society? Journal of Market Access & Health Policy, 5. https://doi.org/10.1080/20016689.2017.1264717
[37] van der Pol et al. (2023)
[38] Roin (2014)
[39] Medicines for Europe. (n.d.). Value-added medicines. Retrieved from http://www.medicinesforeurope.com/value-added-medicines/
[40] Toumi & Rémuzat (2016)
[41] U.S. Food & Drug Administration. (n.d.). NDA Classification Codes. Retrieved from https://www.fda.gov/media/94381/download

2.3 "Reprofiling" Shelved Molecules

Yet another set of terms emerges when discussing substances that never reached the market in the first place. Some researchers and companies refer to "reprofiling" in cases where the compound was shelved early in development—perhaps failing in a particular clinical indication or for commercial reasons—and thus never proceeded to a full marketing authorization[42]. Unlike a typical off-patent scenario, these shelved molecules may still be patentable if they demonstrate new efficacy in an entirely different context. This scenario can allow for "clean slate" intellectual property, permitting the sponsor to file fresh patents on the newly discovered use, plus claim regulatory data protection if clinical trials are conducted.

Paradoxically, these "reprofiled" molecules often remain hidden in corporate pipelines. Companies may hesitate to share data from past failures, perceiving these as commercially sensitive or lacking in short-term profit potential[43]. That negative data—showing what does not work—may nonetheless contain valuable information for alternative targets[44]. Nevertheless, absent a robust incentive or data-sharing framework, sponsors frequently prefer to keep shelved molecules confidential, fearing that a competitor or external researcher might succeed where they failed and reap the rewards without the initial sponsor's involvement[45].

2.4 The Promise and Limitations of Academic-Driven Repurposing

When the pharmaceutical industry discontinues or de-emphasizes a compound—because patent protections are weak or the commercial prospects seem limited—academic institutions and non-commercial organizations frequently step in[46]. These entities often assume a more risk-tolerant stance, driven by public health objectives rather than profit margins[47]. Indeed, in many celebrated repurposing stories, universities or public research institutes have advanced a molecule into new indications long after industry sponsors walked away. As Liddicoat et al. (2022)[48] observe, loss of IP protection shifts research focus rather than ending it. As pharmaceutical companies deprioritize investment, academia and non-profits become more engaged in exploring new uses and public health applications.

Such activity, however, does not necessarily proceed smoothly. Publicly funded researchers often lack the resources or experience to navigate complex regulatory pathways, meaning that even if they identify a promising repurposing opportunity, they may struggle to conduct

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[42] Langedijk et al. (2015)
[43] Zemła-Pacud, Ż., & Lenarczyk, G. (2023). Clinical trial data transparency in the EU: Is the new clinical trials regulation a game-changer? IIC – International Review of Intellectual Property and Competition Law, 54, 732–763. https://doi.org/10.1007/s40319-023-01329-4
[44] Pushpakom et al. (2019)
[45] Rogawski, M. A., & Federoff, H. J. (2011). Disclosure of clinical trial results when product development is abandoned. Science Translational Medicine, 3(102), 102cm29.
[46] Bommer, M. (2020). The Role of Academia in Driving Post-Approval Innovation in Areas of Unmet Medical Need (Master's thesis, Rheinische Friedrich-Wilhelms-Universität Bonn).
[47] Liddicoat, J., Liddell, K., Darrow, J., Aboy, M., Jordan, M., Crespo, C., & Minssen, T. (2022). Repositioning Generic Drugs: Empirical Findings and Policy Implications. IIC – International Review of Intellectual Property and Competition Law, 53(5), 1287–1322. https://doi.org/10.1007/s40319-022-01241-3
[48] Liddicoat et al (2022)

confirmatory clinical trials or secure marketing approvals on their own[49]. In some cases, a public–private partnership emerges[50], with the university generating compelling preliminary data and then licensing the project to a smaller biotech or specialty pharma entity that has the operational capacity to run trials and register the drug. This model sometimes succeeds in bridging the gap left by the original sponsor, particularly if the initial patents have expired and new intellectual property is available to protect the repurposed indication[51].

2.5 Defining the Limits of Repurposing

All of these scenarios—adding new indications to off-patent drugs, modifying formulations or dosages, reprofiling shelved candidates, and academia-led development—underscore why the boundaries of "drug repurposing" remain fluid. Author assumes however that "true" repurposing involves older compounds that have lost market exclusivity and either no longer attract the original sponsor or were never commercialized to begin with. From this point, a brand-name company discovering another approved use for its still-patented product might not be "repurposing" in a strict sense but rather "extending the brand." Meanwhile, significantly adapting a formula for a new patient population might legitimately count as repurposing, especially in the eyes of regulators classifying the change as a separate, distinct clinical use case (FDA classification Types 2–6)[52].

Ultimately, the real significance of repurposing arises from its potential to accelerate innovation in areas of unmet need—whether that involves an older off-patent antibiotic deployed against novel-resistant pathogens, or a "shelved" oncological compound that resurfaces as a targeted therapy in a rare tumor type[53]. The lines can blur, however, given the overlaps among brand-extension strategies, incremental innovation, and truly novel repositioning.

Hence, clarity in terminology becomes crucial to avoid confusion and to define the policy instruments—patent incentives, regulatory exclusivity extensions, or public grants—best suited to each form of repurposing.

Chapter 3 – Shortcomings of Current Intellectual Property Tools

Building on the conceptual groundwork of Chapter 2, this chapter examines why Europe's traditional IP mechanisms—especially second medical use patents and the 8+2(+1) exclusivity regime—often fail to incentivize repurposing. It illustrates how off-label prescribing, patent enforceability issues, and a limited one-year extension frequently undercut the economic

[49] Pantziarka, P., Verbaanderd, C., Huys, I., Bouche, G., & Meheus, L. (2021). Repurposing drugs in oncology: From candidate selection to clinical adoption. Seminars in Cancer Biology, 68, 186–191. https://doi.org/10.1016/j.semcancer.2020.01.008
[50] Nosengo (2016)
[51] Pushpakom et al. (2019)
[52] U.S. Food & Drug Administration. (n.d.),
[53] Antoszczak, M., Markowska, A., Markowska, J., & Huczyński, A. (2019). Old wine in new bottles: Drug repurposing in oncology. European Journal of Pharmacology. https://doi.org/10.1016/j.ejphar.2019.172784

rationale for investing in new clinical data. By dissecting these shortcomings, the chapter establishes the need for more robust, repurposing-specific measures—an idea further explored in Chapter 4.

It is widely acknowledged that IP protection plays a crucial role in fostering innovation in de novo drug development by granting regulatory exclusivities. These rights create a temporary market monopoly, additionaly strengthening the negotiation position of pharmaceutical companies with national authorities, which often regulate the pricing of reimbursed medicines. Given the high-risk nature of drug development, these mechanisms aim to mitigate financial uncertainty and promote investment in research and clinical trials[54].

A fundamental question for any effort to repurpose an older medicinal product lies in how to secure intellectual property protection sufficient to recoup the costs of additional research and clinical trials[55].

Whereas de novo drug development begins with a novel chemical entity that typically attracts strong patent protection, repurposed therapies often involve compounds that have exhausted their primary patent life or never enjoyed robust patent coverage in the first place. Even if secondary patents—commonly referred to as "second medical use patents[56]"—are available in principle, real-world considerations such as off-label prescribing, weak enforceability, and uncertain reimbursement frequently erode whatever theoretical incentives they might offer. In parallel, the system of data exclusivities, most notably the "8+2(+1)" model set forth in Directive 2001/83/EC, has proven insufficient to address the needs of older molecules that have long since lost their original market exclusivity[57].

3.1 Second medical use patents

European patent law has evolved to recognize that discovering a new therapeutic application for a known substance can be as inventive and socially beneficial as discovering an entirely new chemical entity. The European Patent Convention (EPC) allows for patent protection not only for new chemical entities but also for new therapeutic applications of known substances, acknowledging their potential inventiveness and public health benefits.

Articles 54(4) and 54(5) of the EPC[58] permit the grant of patents covering these so-called second (or further) medical uses, provided the sponsor satisfies the usual requirements of novelty, inventive step, and industrial application. Conceptually, second medical use patents create a monopoly over the use of a known molecule in a particular new indication, thereby

[54] Boyer, B., & Carino, T. (2023). Drug repurposing for pandemic innovation: Establishing an effective and efficient ecosystem. Duke-Margolis Center for Health Policy.
[55] van der Pol et al. (2023)
[56] Stevens, P., & Ellis, J. (2023). Second medical uses for existing drugs. Geneva Network. Retrieved from https://geneva-network.com/
[57] Liddicoat et al. (2021)
[58] A Art. 54(4) and 54(5), Convention on the Grant of European Patents (European Patent Convention) of 5 October 1973, as revised by the Act revising the EPC of 29 November 2000, OJ EPO 2001.

incentivizing companies or research institutions to invest in clinical trials demonstrating efficacy in that new therapeutic context.

Notwithstanding their theoretical appeal, second medical use patents exhibit notable weaknesses in practice. A major challenge is enforcement: once a drug's active ingredient is off-patent for its original indication, generics can legally be sold at significantly lower prices[59]. Physicians who wish to treat a patient for the new indication need only prescribe the generic version off-label, bypassing the "on-label" brand that holds the second-use patent. Although patent holders can claim infringement if a generic manufacturer markets its product expressly for the patented use, the reality is that medical professionals are frequently at liberty to repurpose older products as they see fit, without necessarily violating any patent claims. This undermines the economic exclusivity that would otherwise motivate sponsors to invest in formal repurposing[60].

Identified empirical research has shown that, on paper, second medical use patents are granted more often than might be expected[61]. The European Patent Office (EPO) appears relatively open to well-substantiated claims[62]. This is evidenced by European Patent Office statistics, which show that the number of patents granted for new uses of known medicinal products significantly exceeds the actual number of authorizations for these indications by the European Medicines Agency (EMA) [63]. Yet the real question is whether these patents ever deliver a sufficient return on repurposing investments. The gap between patent grant and effective commercial exclusivity is aggravated by the difficulty of tracking and controlling prescribing practices in a fragmented healthcare environment. National payers and regulatory bodies often lack the tools or the mandate to ensure that doctors prescribe only the branded (on-label) version for the new indication. Consequently, companies may hold a patent right in name but see limited revenue in practice, leading to a situation where patent protection does not translate into meaningful market protection.

3.2 The "8+2(+1)" Exclusivity Regime

Aside from patent protection, the EU has long relied on a system of regulatory exclusivities to encourage pharmaceutical innovation. This system, codified in Directive 2001/83/EC and related regulations, grants new active substances a period of 8 years during which no generic company may rely on the originator's data to obtain its own marketing authorization (regulatory data protection, RDP), followed by 2 additional years of market exclusivity (making it a total of 10 years free from direct generic competition)[64]. An extra 1-year extension

[59] Pantziarka, P., et al. (2024). On-Patent Drug Repurposing: Key Issues Report. Rising Tide Foundation for Clinical Cancer Research.
[60] Bhagwat, M., Kaushik, G., & Shivpuje, V. (2016). Second Medical Use Patenting: A Review of Practices Across Different Jurisdictions. Journal of Intellectual Property Rights.
[61] Aboy, M., Liddell, K., Jordan, M., Crespo, C., & Liddicoat, J. (2022). European patent protection for medical uses of known products and drug repurposing. Nature Biotechnology, 40(4), 465–471. https://doi.org/10.1038/s41587-022-01269-3
[62] Aboy et al. (2022)
[63] Aboy et al. (2022)
[64] Art. 14(11), Regulation (EC) No 726/2004

is possible if, within the first 8 years, the sponsor demonstrates a significant clinical benefit by securing a new indication[65].

The exclusivity periods prevents the EMA and other European national regulatory agencies from approving generics and biosimilars, which can use the original drug's safety and efficacy data for faster approval[66]. In sum, these periods alows the MAH to maintain higher drug prices in given timeframe because there aren't any competitors. The extended market protection (+1) prevents above-mentioned regulatory agencies from authorizing generic and biosimilar alternatives, thereby enabling the MAH to sustain elevated prices over a longer period, ensuring time to recoup investments and finance further innovation.

While the 8+2(+1) framework has effectively incentivized novel drug development, it operates poorly for repurposed products. First, repurposing typically arises at a point when the compound is already off-patent or near the end of its exclusivity life cycle, making it ineligible for the initial 8+2. The crucial option is thus the +1-year extension for a newly approved indication that offers a "significant clinical benefit." In theory, this extra year aims to reward the sponsor's additional R&D. In practice, however, one extra year rarely justifies the cost and risk of a fresh clinical development program—particularly if generic versions are freely available[67].

Indentified study[68] analyzed cases of drug repositioning both before and after the introduction of +1 and observed that the percentage of companies choosing to develop new indications for existing products remained nearly unchanged (42.2% and 42.4%, respectively)[69]. Such a minimal difference suggests that the introduced incentive, while intended to stimulate research, was insufficient to encourage widespread investment in costly clinical trials.

Moreover, the "significant clinical benefit" threshold has itself been criticized as vague and inconsistently applied across Member States[70]. Even if a sponsor believes its new indication meets this standard, the prospect of navigating national health technology assessment requirements and uncertain reimbursement negotiations further hinder the attractiveness of that one-year extension[71]. Thus, while 8+2(+1) was designed to balance the interests of originators and generics, the model creates a gap for older drugs that merit repurposing but do not receive adequate data protection to incentivize a full-scale development program.

In summary, while intellectual property tools such as second medical use patents and the "8+2(+1)" exclusivity regime have been effective in incentivizing de novo drug development,

[65] Art. 10(5), Directive 2001/83/EC
[66] Art. 10(1), Directive 2001/83/EC
[67] Liddicoat et al. (2021)
[68] Liddicoat et al. (2021)
[69] Liddicoat et al. (2021)
[70] Scholte, M., Bendicksen, L., Grimm, S. E., Abu-Zahra, T., Pauly, B., Joore, M., & Kesselheim, A. S. (2024). A Regulatory Roadmap for Repurposing: Comparing Pathways for Making Repurposed Drugs Available in the EU, UK, and US. Journal of Law, Medicine & Ethics, 52(4), 940–949
[71] Scholte, M., Grimm, S. E., Pauly, B., Verbeeck, F., Pasmooij, A. M. G., Bouma, B., van Duijn-Wiersma, J., Guney, E., Kesselheim, A. S., Schmidt, H. H. H. W., & Joore, M. A. (2025). Revising EU pharmaceutical legislation: Will it foster drug repurposing? Drug Discovery Today, 30(1), 104286. https://doi.org/10.1016/j.drudis.2024.104286

they fall short when it comes to repurposing older medicines. Both mechanisms struggle to provide robust economic incentives—second medical use patents due to enforcement challenges and the 8+2(+1) model due to its limited extension and stringent criteria—leaving a significant gap in the current framework for supporting the full potential of drug repurposing.

Chapter 4 – Article 84 of the EU Pharma Package

This chapter shifts from diagnosing existing failings to exploring a proposed legislative solution: Article 84 of the Draft Directive 2023/0132 (part of the EU Pharma Package). It details the introduction of a non-cumulative four-year data exclusivity period for certain repurposed medicines, highlighting how the EU aims to correct current gaps in economic incentives. Yet the chapter also questions whether this new provision alone can address persistent problems like payers' cost-focused policies or physicians' off-label habits, setting grounds for Chapter 5's broader discussion of systemic barriers.

4.1 Mechanisms and Implications of Article 84

The European Commission's Pharmaceutical Package Reform, proposed in April 2023, is the most significant revision of EU pharmaceutical legislation in over two decades. It aims to modernize market exclusivity, regulatory data protection, and incentives for drug development, balancing innovation with patient access[72].

Article 84 of the Draft Directive 2023/0132 introduces a non-cumulative four-year data protection period for medicinal products that have been authorized for at least 25 years or previously lacked data protection, upon identification of a new therapeutic use.

Paragraph 1 requires the submission of adequate non-clinical or clinical studies demonstrating a significant clinical benefit for the new indication, together with either the absence of any prior data protection for the product or the passage of 25 years since its initial marketing authorisation. Paragraph 2 clarifies that this protection may only be granted once per medicinal product, preventing a repeated extension. Under paragraph 3, the marketing authorisation issued during this four-year term must explicitly indicate that the product in question—already authorised in the European Union—has now been authorised for an additional therapeutic indication that triggers this new period of data protection.

By reshaping incentives for drug development and commercialization, Article 84 is set to impact investment strategies, generic competition, and repurposed medicines.

The Commission's explanatory memorandum[73] indicates that this provision complements broader efforts to address unmet medical needs and encourage drug repurposing, in line with

[72] EC (2023), 2023/0132(COD)
[73] EC (2023), 2023/0132(COD)

the EU's objectives of promoting innovation and ensuring patient access. Article 84 helps address unmet clinical needs through targeted incentives for "repurposing" older medicines or those never before covered by data protection. By offering a data exclusivity period contingent on genuine clinical significance, the provision supports ongoing innovation while aiming to ensure broad patient access. Consequently, it reflects a legislative strategy to balance incentives for pharmaceutical development with the overarching goals of affordability and public health across EU Member States[74].

However, Article 84 does not alter the core marketing authorization pathway: sponsors must still comply with EU procedures under Directive 2001/83/EC and relevant regulations (e.g., Regulation (EC) No 726/2004)

At the time of this proposal, Article 84 remains subject to the legislative process within the EU. Upon adoption, it would integrate into Directive 2001/83/EC as a specific measure addressing repurposing for off-patent drugs. Stakeholders—ranging from pharmaceutical companies to academic institutions—will need to assess whether their repurposed compound qualifies under the 25-year criterion and whether their additional data sufficiently meets the "significant clinical benefit" threshold for securing the new four-year exclusivity.

4.2 Challenges and Future Considerations

Despite the Commission's rationale for introducing a four-year data protection period under Article 84, this legislative change has drawn also scepticism. One view holds that offering an exclusive period proportionate to the degree of new clinical benefit is an important step toward encouraging investment in older substances, particularly when the newly discovered use pertains to a high-prevalence or otherwise commercially attractive condition. A different perspective, however, questions whether four years suffices to offset the substantial costs of conducting clinical trials, particularly if payers do not recognize the added value of the new indication by allowing higher reimbursement rates[75].

Critics also note that Article 84 does not tackle widespread off-label prescribing, which can undermine commercial incentives for obtaining a formal on-label indication[76]. Additionally, the requirement to demonstrate "significant clinical benefit" depends on how that term is interpreted by national authorities, raising the possibility of inconsistent or fragmented application throughout the Member States[77].

Nonetheless, Article 84 stands out as one of the most targeted legislative efforts yet to encourage genuine repurposing efforts. By highlighting older compounds that can demonstrate new benefits, the EU signals a willingness to adapt its regulatory framework to an era where

[74] EC (2023), 2023/0132(COD)
[75] Scholte et al. (2025)
[76] European Federation of Pharmaceutical Industries and Associations (EFPIA). (n.d.). Position Paper on Drug Repurposing. Retrieved from https://www.efpia.eu/media/2mlhtlac/position-paper-on-drug-repurposing.pdf
[77] Medicines for Europe. (2024, April). Medicines for Europe Position Paper – Repurposing v2. Retrieved from https://www.medicinesforeurope.com/wp-content/uploads/2024/04/Medicines-for-Europe-Position-Paper-Repurposing-v2.pdf

not all pharmaceutical breakthroughs need to originate with novel chemical entities. Whether this alone is sufficient to overcome the systemic constraints discussed in subsequent chapters is an open question. Still, the introduction of a dedicated repurposing incentive in a major EU directive reflects a growing consensus that the existing system is inadequate to unlock the full potential of older molecules.

The table below compares the 8+2(+1) system with the new Article 84 four-year exclusivity, highlighting key differences, potential improvements, and remaining challenges in drug repurposing incentives.

Table 1. Own work.

Aspect	8+2(+1) Regime	Article 84 Four-Year Exclusivity
Scope	Typically applies to new active substances upon initial authorization	Specifically targets older medicines (25+ years since first authorization) or those never previously granted data protection
Duration of Exclusivity	- 8 years data exclusivity - 2 years market exclusivity - Possible +1 year extension (for proven significant benefit)	A single, non-cumulative 4-year data exclusivity period (cannot be extended or granted more than once per product)
Eligibility Trigger	Granted automatically for novel drugs, with the extra +1 year requiring evidence of new benefit within the first 8 years	Requires sponsor to show a "significant clinical benefit" in a newly authorized indication for a product lacking current data protection or 25+ years old
Effect on Generics/Biosimilars	Blocks generic/biosimilar applications for up to 10–11 years total	Prevents generics from relying on the new clinical data for 4 years
Off-Label Prescribing Issue	Not directly addressed; prescribers can still use cheaper generics off-label	Also not addressed; risk remains that clinicians prescribe older generic versions off-label instead of the on-label product
Primary Goal	Incentivize first-to-market novel drugs to recoup high R&D costs	Stimulate repurposing of older or off-patent medicines by providing a meaningful data exclusivity window
Main Critiques	+1 year extension is often insufficient to justify large new clinical trials for off-patent drugs	4-year term may still be inadequate if payers do not grant higher reimbursement or if off-

Aspect	8+2(+1) Regime	Article 84 Four-Year Exclusivity
		label use undermines market potential.

Chapter 5 – Systemic Constraints beyond IP

This chapter explores that real-world adoption depends on more than just IP adjustments. It outlines how health technology assessments, complex reimbursement schemes, and off-label prescribing norms often overshadow formal marketing authorization efforts. By detailing these structural impediments, the chapter prepares the ground for the policy recommendations proposed in Chapter 6, emphasizing why a holistic approach is crucial.

While Article 84 clearly attempts to resolve the deficit in IP-based incentives for repurposed drugs, the real-world viability of any such measure depends on factors that extend well beyond IP regime. Health technology assessments, pricing and reimbursement structures, prescribing behaviors, and various enforcement challenges each shape how (and whether) a newly approved repurposed indication achieves commercial success[78]. Even if a sponsor has four years of data exclusivity, there is no guarantee that European public payers will endorse the drug at a price that justifies the underlying R&D expenses, nor that clinicians will prefer the newly authorized version over cheaper generics.

5.1 Off-label Prescribing

One of the most salient obstacles is above-mentioned the practice of off-label prescribing. Many EU jurisdictions give physicians considerable discretion to prescribe clinically accepted therapies outside the label, particularly in areas like pediatrics or oncology, where clinical guidelines can evolve faster than formal marketing authorizations. If an older molecule is available in generic form, nothing stops a prescriber from using it off-label for a new indication—even if that indication has recently been recognized on-label for a sponsor's reintroduced product. From the sponsor's viewpoint, this dynamic severely weakens the commercial advantage of going through the formal authorization process[79].

5.2 HTA Challenges

Within the European Union, Health Technology Assessment is a structured process used to asses the clinical, societal and economic benefits of healthcare interventions. Although there is

[78] Scholte et al. (2025)
[79] Verbaanderd, C., Rooman, I., Meheus, L., & Huys, I. (2020). On-label or off-label? Overcoming regulatory and financial barriers to bring repurposed medicines to cancer patients. Frontiers in Pharmacology, 10, Article 1664. https://doi.org/10.3389/fphar.2019.01664

an evolving common framework under Regulation (EU) 2021/2282[80], different Member States may still interpret results differently. Because HTA informs reimbursement and pricing decisions, it is a crucial determinant of the commercial prospects for drug repurposing.

HTA provides a structured approach to appraising the clinical, economic, and societal value of repurposed drugs, ensuring their potential benefits are recognized and integrated into healthcare systems.[81] Traditionally, HTA has been use-focused—predominantly guiding reimbursement decisions once a technology reaches the market.[82] However, an emerging concept called development-focused HTA (df-HTA) shifts the assessment earlier in the drug lifecycle, enabling stakeholders to identify promising repurposing candidates, address evidence gaps, and refine research designs before final approval[83].

Despite these advances, challenges persist, particularly in generating robust clinical data for off-patent therapies, securing funding for large-scale trials, and establishing fair pricing frameworks that balance affordability with sufficient incentives for developers[84]. Recent EU legislative proposals, including Article 48[85] (facilitating scientific opinion submissions by not-for-profits) and Article 84 (offering additional data protection for clinically beneficial repurposed indications), seek to alleviate these barriers.[86] Combining df-HTA methodologies with such policy measures could further streamline repurposed drug development by promoting a participatory, iterative process—one that employs real-world evidence, anticipates regulatory hurdles, and encourages collaborative funding models.[87] To solidify these gains, policymakers should continue refining HTA processes to ensure early and continuous evaluation, strengthen incentives for high-quality evidence generation, and foster transparent pricing mechanisms, thereby maximizing both the clinical and societal impact of repurposed medicines.[88]

5.3 Pricing Considerations for Successful Repurposing

Determining a viable pricing strategy is crucial to ensure that drug repurposing initiatives can both attract investments and maintain affordability for patients and publicly funded healthcare systems. Evidence indicates that repurposing can drive price increases compared to the original generic substance, particularly when the drug's category of availability changes (for instance, from ''pharmacy'' to ''hospital'' use) or when it addresses significant unmet medical needs.[89]

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[80] European Parliament and Council of the European Union. (2021). Regulation (EU) 2021/2282 on health technology assessment and amending Directive 2011/24/EU. Official Journal of the European Union, L 458, 1–32.
[81] Scholte et al. (2025)
[82] Joore, M., Grimm, S., Kimman, M., et al. (2022). Health Technology Assessment Will Make Drug Repurposing More Successful. https://doi.org/10.14293/S2199-rexpo22013.v1
[83] Joore et al. (2022)
[84] Joore et al. (2022)
[85] European Commission(2023) 2023/0132, Art. 48
[86] Scholte at al. (2025)
[87] Joore et al. (2022)
[88] Scholte et al. (2025)
[89] Murteira, S., Millier, A., & Toumi, M. (2014). Drug Repurposing in Pharmaceutical Industry and Its Impact on Market Access: Market Access Implications. Journal of Market Access & Health Policy, 2. https://doi.org/10.3402/jmahp.v2.22814

In an analysis of 144 repurposing cases, shifting the availability category to a hospital setting resulted in a 374% price rise, while targeting an unmet medical need correlated with a 69% price increase.[90] These findings underscore the necessity of coherent pricing policies that recognize the unique cost structures of repurposed drugs—particularly when higher prices reflect meaningful clinical improvements. Aligning such pricing approaches with early and continuous HTA input can help balance equitable patient access against the commercial incentives needed to spur investment in promising repurposed therapies.

5.4 Regulatory Barriers

Although drug repurposing offers significant potential for accelerating innovation, academic institutions and small sponsors often face formidable regulatory hurdles in bringing repurposed therapies to market. In recent years, the European Union has introduced pilot initiatives to lighten the burden on these smaller sponsors. The STAMP (Safe and Timely Access to Medicines for Patients) Repurposing Observatory Group (RePoG) is one such program, providing channels for knowledge-sharing and early scientific advice.[91]

Recent Belgian regulatory discussions underscore the resource-intensive nature of navigating formal marketing authorization—particularly for smaller sponsors such as academic units or not-for-profit organizations.[92] These sponsors often lack the specialized expertise, funding, and administrative capabilities needed to align with requirements on clinical trial design, good manufacturing practice (GMP), and post-approval pharmacovigilance. Recognizing these gaps, the European Commission's STAMP Repurposing Observatory Group (RePoG) pilot has introduced new pathways for early scientific and regulatory advice, aiming to refine clinical protocols and identify key data requirements before launching formal approval processes.[93],[94]

While early engagement under the RePoG pilot reduces entry barriers by clarifying evidence-generation standards and regulatory expectations, it does not independently resolve the broader structural issues inhibiting repurposing. [95],[96]

Ultimately, success still hinges on the availability of streamlined authorization pathways, transparent HTA and reimbursement mechanisms, and partnerships with existing marketing authorization holders—areas in which smaller sponsors traditionally struggle.[2] Consequently, despite these supportive efforts, many repurposed therapies risk being lost in the final stages of market access unless more cohesive reforms are enacted to facilitate the entire journey from scientific discovery to patient access. [97]

[90] Murteira et al. (2014)
[91] Lahorte, C. (2024). Drug Repurposing: The Point of View from the Regulator in Belgium. KCE Trials Symposium.
[92] Lahorte (2024)
[93] European Commission. (2021). Proposal for a Framework to Support Not-for-Profit Organisations and Academia in Repurposing Authorised Medicines: Question and Answers on the Repurposing Pilot Project.
[94] European Commission. (2019). Proposal for a Framework to Support Not-for-Profit Organisations and Academia (Institutions and Individuals) in Drug Repurposing
[95] European Commission (2021)
[96] European Commission (2019)
[97] European Commission (2019)

Chapter 6 – Toward an Effective Repurposing Ecosystem: Policy Recommendations

In response to the multiple barriers identified in earlier chapters, this Chapter 6 provides a recommendation for how policymakers, industry stakeholders, and academia can collectively bolster repurposing.

Building upon the new incentive structure under Article 84, any meaningful strategy to foster drug repurposing must extend beyond intellectual property reforms and tackle the deeper, system-wide hurdles that stall development.

First, HTA frameworks should adopt a more lifecycle-based approach, wherein incremental benefits from older compounds are recognized through accelerated or conditional pathways. Rather than demanding the same randomized clinical trial data expected of novel drugs, HTA bodies could accept real-world evidence and intermediate endpoints, as is increasingly common in orphan or oncology settings. This approach would reduce the financial burden on repurposing sponsors, particularly smaller academic or not-for-profit institutions, and better reflect the fact that much of the compound's safety profile is already known.[98]

Second, pricing and reimbursement systems in the European Union needs recalibration. While Article 84 aims to solve the exclusivity gap, it cannot by itself offset the risk of minimal commercial returns if national payers continue to treat newly authorized repurposed therapies as if they were commoditized generics.[99] Under a reformed model, drugs that earn a repurposed indication and demonstrate "significant clinical benefit" could be granted a premium price or a time-limited reimbursement uplift.[100] In parallel, outcome-based agreements—where payers adjust compensation based on post-launch performance—can mitigate payer concerns that sponsors are overcharging for minimal therapeutic gains.[101]

Third, to discourage off-label prescribing in circumstances where an authorized, repurposed product exists, national clinical guidelines could explicitly promote the on-label version. Payers might also restrict reimbursement for off-label use if a formally approved repurposed option is available, so long as patient safety and continuity of care remain protected.[102]

Fourth, supportive academic–industry partnerships could be incentivized by public grants or co-funding models. For instance, academic groups might access dedicated funds to advance a promising off-patent compound up to "proof-of-concept," after which industry partners would take on pivotal trials under the new four-year exclusivity window.[103]

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[98] Nosengo (2016)
[99] Roin (2014)
[100] European Commission (2023), 2023/0132(COD)
[101] Scholte et al. (2024)
[102] Liddicoat et al. (2022)
[103] Joore et al. (2022)

Lastly, creating a pan-European consortium to coordinate repurposing efforts—building on the STAMP RePoG pilot—would help consolidate fragmented national initiatives and accelerate mutual recognition of new indications, thus maximizing the return on research investment.[104]

Chapter 7 – Conclusion

Drug repurposing offers a powerful mechanism to reduce research costs and bring new treatments to patients more efficiently, especially in areas where therapeutic gaps remain. In the European Union, however, existing intellectual property frameworks—primarily second medical use patents and regulatory exclusivities—have struggled to encourage the widespread development of new indications for older compounds. Although these mechanisms function well for novel molecules, they rarely provide sufficient return on investment in repurposing contexts, where off-label prescribing and conservative pricing policies can render an approved new indication commercially nonviable[105].

Article 84 of the EU Pharma Package recognizes this gap. By granting a four-year data exclusivity period for certain repurposed medicines that demonstrate significant clinical benefit, it marks a long-overdue attempt to align incentives with the unique requirements of older compounds. Yet, as discussed, the measure's ultimate success depends on complementary reforms. Lifecycle-based health technology assessment, pricing frameworks that reward clinically meaningful improvements, and more stringent reimbursement guidelines for off-label use would all help ensure that this new legislative tool reaches its potential.[106] Fostering partnerships between academic researchers and commercial sponsors through public grants or early regulatory advice can further reduce the resource barriers that small entities often face.[107]

In essence, the future of EU drug repurposing depends on a balanced approach. If Article 84 is integrated within a broader policy environment that recognizes the distinct challenges of repositioning older drugs, it can help transform a patchwork of sporadic successes into a consistently viable strategy. By doing so, Europe may not only unlock significant therapeutic value from well-known compounds but also mitigate the vast costs and attrition rates associated with traditional drug discovery. This shift could ultimately benefit both industry stakeholders, public payers and patients, encouraging innovation in therapeutic areas that have long been overlooked under the traditional patent-based model.[108]

[104] European Commission (2021)
[105] Roin (2014)
[106] Scholte et al. (2025)
[107] Bommer (2020)
[108] Liddicoat et al. (2022)

Bibliography

1. Aboy, M., Liddell, K., Jordan, M., Crespo, C., & Liddicoat, J. (2022). European patent protection for medical uses of known products and drug repurposing. *Nature Biotechnology, 40*(4), 465–471. https://doi.org/10.1038/s41587-022-01269-3
2. Antoszczak, M., Markowska, A., Markowska, J., & Huczyński, A. (2019). Old wine in new bottles: Drug repurposing in oncology. *European Journal of Pharmacology.* https://doi.org/10.1016/j.ejphar.2019.172784
3. Bhagwat, M., Kaushik, G., & Shivpuje, V. (2016). Second medical use patenting: A review of practices across different jurisdictions. *Journal of Intellectual Property Rights.*
4. Bhar, S. (2023). *Role of drug repurposing in sustainable drug discovery.* IntechOpen. https://doi.org/10.5772/intechopen.110621
5. Bommer, M. (2020). *The role of academia in driving post-approval innovation in areas of unmet medical need* (Master's thesis, Rheinische Friedrich-Wilhelms-Universität Bonn).
6. Boyer, B., & Carino, T. (2023). *Drug repurposing for pandemic innovation: Establishing an effective and efficient ecosystem.* Duke-Margolis Center for Health Policy.
7. Convention on the Grant of European Patents (European Patent Convention). (1973, revised 2000). Articles 54(4) and 54(5). Munich: European Patent Office.
8. Cruz-Burgos, M., Losada-Garcia, A., Cruz-Hernández, C. D., Cortés-Ramírez, S. A., Camacho-Arroyo, I., Gonzalez-Covarrubias, V., Morales-Pacheco, M., Trujillo-Bornios, S. I., & Rodríguez-Dorantes, M. (2021). New approaches in oncology for repositioning drugs: The case of PDE5 inhibitor sildenafil. *Frontiers in Oncology, 11*. https://doi.org/10.3389/fonc.2021.627229
9. European Commission. (2018). *Repurposing established medicines: Background.* [STAMP document]. https://health.ec.europa.eu/system/files/2018-11/stamp_8_repurposing_established_medicines_background_0.pdf
10. European Commission. (2019). *Proposal for a framework to support not-for-profit organisations and academia (institutions and individuals) in drug repurposing*
11. European Commission. (2021a). *Commission expert group on safe and timely access to medicines for patients (STAMP).* https://health.ec.europa.eu/medicinal-products/pharmaceutical-committee-veterinary-pharmaceutical-committee-and-expert-groups/commission-expert-group-safe-and-timely-access-medicines-patients-stamp_en

12. European Commission. (2021b). *Proposal for a framework to support not-for-profit organisations and academia in repurposing authorised medicines: Question and answers on the repurposing pilot project.*

13. European Commission. (2023a). *Proposal for a Directive of the European Parliament and of the Council on the Union Code Relating to Medicinal Products for Human Use, and repealing Directive 2001/83/EC and Directive 2009/35/EC (2023/0132(COD)).*

14. European Commission. (2023b). *Proposal for a Regulation of the European Parliament and of the Council on the authorization and supervision of medicinal products for human use, repealing Regulation (EC) No 726/2004.* COM(2023) 192 final, 26 April 2023.

15. European Federation of Pharmaceutical Industries and Associations (EFPIA). (n.d.). *Position paper on drug repurposing.* https://www.efpia.eu/media/2mlhtlac/position-paper-on-drug-repurposing.pdf

16. European Parliament and Council. (2000). *Regulation (EC) No 141/2000 on orphan medicinal products.* OJ L 18, 22.1.2000, p. 1–5.

17. European Parliament and Council. (2001). *Directive 2001/83/EC of 6 November 2001 on the Community code relating to medicinal products for human use.* OJ L 311, 28.11.2001, p. 67–128.

18. European Parliament and Council. (2004). *Regulation (EC) No 726/2004 of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.* OJ L 136, 30.4.2004, p. 1–33.

19. European Parliament and Council. (2006). *Regulation (EC) No 1901/2006 on medicinal products for paediatric use.* OJ L 378, 27.12.2006, p. 1–19.

20. European Parliament and Council. (2021). *Regulation (EU) 2021/2282 on health technology assessment.* OJ L 458, 22.12.2021, p. 1–32.

21. Joore, M., Grimm, S., Kimman, M., et al. (2022). Health technology assessment will make drug repurposing more successful. https://doi.org/10.14293/S2199-rexpo22013.v1

22. Kulkarni, V. S., Alagarsamy, V., Solomon, V. R., Jose, P. A., & Murugesan, S. (2023). Drug repurposing: An effective tool in modern drug discovery. *Russian Journal of Bioorganic Chemistry, 49*(2), 157–166. https://doi.org/10.1134/S1068162023020139

23. Lahorte, C. (2024). Drug repurposing: The point of view from the regulator in Belgium. *KCE Trials Symposium*.

24. Lee, D., Gladwell, D., Batty, A. J., Brereton, N., & Tate, E. (2013). The cost effectiveness of licensed oromucosal midazolam (Buccolam®) for the treatment of children experiencing acute epileptic seizures: An approach when trial evidence is

limited. *Paediatric Drugs, 15*(2), 151–162. https://doi.org/10.1007/s40272-013-0009-5

25. Liddicoat, J., Liddell, K., Aboy, M., & Wested, J. (2021). Has the EU incentive for drug repositioning been effective? An empirical analysis of the "+1" regulatory exclusivity. *IIC – International Review of Intellectual Property and Competition Law, 52*, 825–851. https://doi.org/10.1007/s40319-021-01088-0
26. Liddicoat, J., Liddell, K., Darrow, J., Aboy, M., Jordan, M., Crespo, C., & Minssen, T. (2022). Repositioning generic drugs: Empirical findings and policy implications. *IIC – International Review of Intellectual Property and Competition Law, 53*(5), 1287–1322. https://doi.org/10.1007/s40319-022-01241-3
27. Langedijk, J., Mantel-Teeuwisse, A. K., Slijkerman, D. S., & Schutjens, M. H. (2015). Drug repositioning and repurposing: Terminology and definitions in literature. *Drug Discovery Today, 20*(8), 1027–1034. https://doi.org/10.1016/j.drudis.2015.05.001
28. Medicines for Europe. (n.d.). *Value-added medicines.* Retrieved from http://www.medicinesforeurope.com/value-added-medicines/
29. Medicines for Europe. (2022, March). *Advancing medicines repurposing in the EU.* https://www.medicinesforeurope.com/wp-content/uploads/2022/03/Advancing-medicines-repurposing-in-the-EU.pdf
30. Medicines for Europe. (2024, April). *Medicines for Europe position paper – Repurposing v2.* https://www.medicinesforeurope.com/wp-content/uploads/2024/04/Medicines-for-Europe-Position-Paper-Repurposing-v2.pdf
31. Murteira, S., Millier, A., & Toumi, M. (2014). Drug repurposing in pharmaceutical industry and its impact on market access: Market access implications. *Journal of Market Access & Health Policy, 2.* https://doi.org/10.3402/jmahp.v2.22814
32. Nosengo, N. (2016). Can you teach old drugs new tricks? *Nature, 534*(7607), 314–316. https://www.nature.com/articles/534314a
33. Pantziarka, P., Verbaanderd, C., Huys, I., Bouche, G., & Meheus, L. (2021). Repurposing drugs in oncology: From candidate selection to clinical adoption. *Seminars in Cancer Biology, 68*, 186–191. https://doi.org/10.1016/j.semcancer.2020.01.008
34. Pantziarka, P., et al. (2024). *On-patent drug repurposing: Key issues report.* Rising Tide Foundation for Clinical Cancer Research.
35. Pushpakom, S., Iorio, F., Eyers, P. A., Escott, K. J., Hopper, S., Wells, A., & Pirmohamed, M. (2019). Drug repurposing: Progress, challenges and recommendations. *Nature Reviews Drug Discovery, 18*(1), 41–58. https://doi.org/10.1038/nrd.2018.168
36. Rajkumar, S. V. (2004). Thalidomide: Tragic past and promising future. *Mayo Clinic Proceedings, 79*, 899–903.

37. Rehman, W., Arfons, L. M., & Lazarus, H. M. (2011). The rise, fall and subsequent triumph of thalidomide: Lessons learned in drug development. *Therapeutic Advances in Hematology, 2*(5), 291–308. https://doi.org/10.1177/2040620711413165

38. Roin, B. (2014). *Solving the problem of new uses by creating incentives for private industry to repurpose off-patent drugs.* [Working paper or final citation if published.]

39. Rogawski, M. A., & Federoff, H. J. (2011). Disclosure of clinical trial results when product development is abandoned. *Science Translational Medicine, 3*(102), 102cm29.

40. Scholte, M., Bendicksen, L., Grimm, S. E., Abu-Zahra, T., Pauly, B., Joore, M., & Kesselheim, A. S. (2024). A regulatory roadmap for repurposing: Comparing pathways for making repurposed drugs available in the EU, UK, and US. *Journal of Law, Medicine & Ethics, 52*(4), 940–949.

41. Scholte, M., Grimm, S. E., Pauly, B., Verbeeck, F., Pasmooij, A. M. G., Bouma, B., van Duijn-Wiersma, J., Guney, E., Kesselheim, A. S., Schmidt, H. H. H. W., & Joore, M. A. (2025). Revising EU pharmaceutical legislation: Will it foster drug repurposing? *Drug Discovery Today, 30*(1), 104286. https://doi.org/10.1016/j.drudis.2024.104286

42. Scholte, M. (2025). Key points on HTA assessment for drug repurposing.

43. Srivastava, K., & Singh, M. K. (2021). Drug repurposing in COVID-19: A review with past, present and future. *Metabolism Open, 12*, 100121. https://doi.org/10.1016/j.metop.2021.100121

44. Stevens, P., & Ellis, J. (2023). Second medical uses for existing drugs. Geneva Network. https://geneva-network.com/

45. Sun, D., Gao, W., Hu, H., & Zhou, S. (2022). Why 90% of clinical drug development fails and how to improve it? *Acta Pharmaceutica Sinica B, 12*(7), 3049–3062. https://doi.org/10.1016/j.apsb.2022.02.002

46. Toumi, M., & Rémuzat, C. (2016). Value added medicines: What value repurposed medicines might bring to society? *Journal of Market Access & Health Policy, 5.* https://doi.org/10.1080/20016689.2017.1264717

47. U.S. Food and Drug Administration. (n.d.). *NDA classification codes.* Retrieved from https://www.fda.gov/media/94381/download

48. van der Pol, K. H., Aljofan, M., Blin, O., Cornel, J. H., Rongen, G. A., Woestelandt, A. G., & Spedding, M. (2023). Drug repurposing of generic drugs: Challenges and the potential role for government. *Applied Health Economics and Health Policy, 21*(6), 831–840. https://doi.org/10.1007/s40258-023-00816-6

49. Verbaanderd, C., Rooman, I., Meheus, L., & Huys, I. (2020). On-label or off-label? Overcoming regulatory and financial barriers to bring repurposed medicines to cancer patients. *Frontiers in Pharmacology, 10*, 1664. https://doi.org/10.3389/fphar.2019.01664

50. Zemła-Pacud, Ż., & Lenarczyk, G. (2023). Clinical trial data transparency in the EU: Is the new clinical trials regulation a game-changer? *IIC – International Review of Intellectual Property and Competition Law, 54*, 732–763. https://doi.org/10.1007/s40319-023-01329-4

51. Żakowska-Henzler, H. (2017). Patenty na drugie medyczne zastosowanie – niekończąca się historia wątpliwości i kontrowersji.