Unleashing Therapeutic Innovation for Patients

By Overcoming Hurdles to New Uses of Authorized drugs

Anticancer Fund

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Summary

The repurposing of authorized drugs by non-traditional developers that demonstrate new uses for existing medicines through non-commercial research offers a promising complementary path for generating patient benefit and public health impact. It can lead to faster and more cost-effective medical innovation compared to traditional drug development and potentially deliver more affordable treatments. This approach is especially useful for addressing important health needs such as those of patients with rare diseases or paediatric cancers, as these areas often lack commercial interest. It also allows for the exploration of diverse research avenues that were previously overlooked due to a lack of profit incentives. Realizing this potential requires a supportive policy and regulatory framework. The proposed EU Pharmaceutical Regulation, especially Article 48, could be transformative to this effect. It allows non-profit organizations to submit non-clinical and clinical evidence for new uses of authorized drugs to national or European regulators for assessment and provides a pathway to label change. This in turn will facilitate integration of the new use into medical guidelines and reimbursement schemes, enhancing and accelerating the adoption of innovative treatments with clear patient benefit into clinical practice.

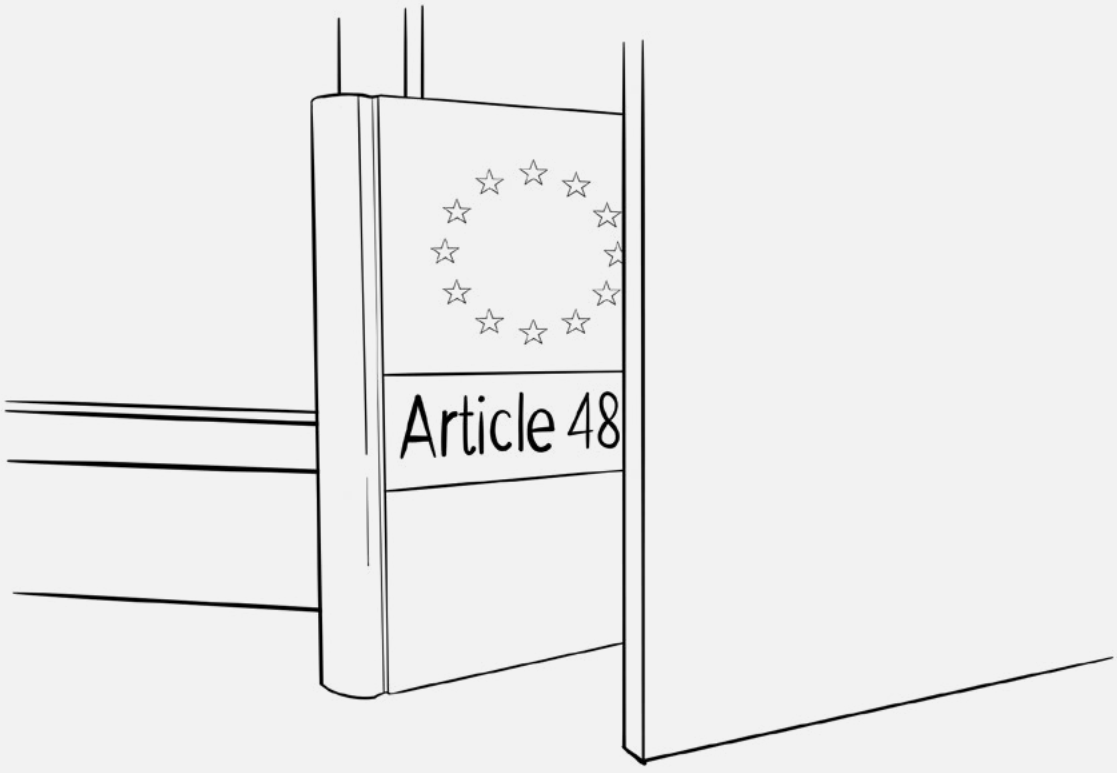


Illustration 1. *Article 48 (of the draft regulation) is our "foot in the door" towards repurposing of already approved medicines by non-traditional developers*

The Growing Cancer Challenge

Among other growing health challenges such are rare diseases, the cancer burden is expected to increase both at European Union (EU) and global level. Globally, over 35 million new cancer cases are predicted by 2050, a 77% increase from the estimated 20 million cases in 2022.[1]

35 million

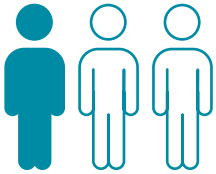
new cancer cases *globally before 2050*

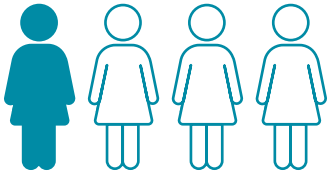
→

77%

increase *from the estimated 20 million in 2022[1]*

In the EU, 31% of men and 25% of women are expected to be diagnosed with cancer before reaching the age of 75 years[2] while cancer deaths are expected to increase by more than 24% by 2035 and become the leading cause of death.[1]





31% ***men*** **&** **25%** ***women***

diagnosed with cancer *before reaching the age of 75*

→

↑24%

increase in cancer deaths and by 2035 cancer will become the ***leading cause of death***

The estimated economic impact of cancer in the EU exceeds €100 billion annually.[3] Medical innovation that generates effective products and interventions is expected to contribute to curbing the health and socio-economic impacts of cancer.

100 billion

estimated ***economic impact of cancer*** *in the EU[3] (in €)*

→

effective ***medical innovation*** *expected to curb the impact of cancer*

To deliver upon that promise, it is important to maximize the opportunities for useful medical innovation, with a focus on both patient and societal benefit, and including under-served populations that suffer from rare diseases and cancers, paediatric illnesses, and neglected infectious conditions.

Introduction

Pharmaceutical company research and development (R&D) efforts are an important source of medical innovation in, yet largely focus on developing new (bio)pharmaceuticals that can bring substantial financial returns.[4] Meanwhile, there are many other opportunities to bring evidence-based therapeutic innovation and benefit to patients outside the commercial realm that are currently overlooked. This includes exploring new indications for approved medicinal products, both within and outside the primary therapeutic area. To fill this gap and broaden the scope of research that can deliver critically needed improvements in cancer care based on high evidentiary standards, well-designed policy and regulatory incentives are needed to enable non-traditional developers like universities and non-profits to step up and deliver on this untapped potential.

Expanding the Scope of Therapeutic Innovation

Therapeutic innovation encompasses any novelty in therapeutic strategy and interventions that improves a patient's quality of life and health outcomes. Ideally, it also improves the quality of overall health care and public health in cost-effective ways. Therapeutic innovation is usually incremental and relies on carefully designed studies and a build-up of evidence and experience to show the benefit of the innovation, which may or may not involve a novel product. In the cancer field, there are many opportunities to improve and accelerate therapeutic innovation, both through new drug R&D efforts as is typically done by pharmaceutical companies, and through making better and different uses of approved or investigational medicines outside the original indication, a strategy known as drug repurposing.[5] For the purpose of this paper, **drug repurposing** by non-profit organizations **encompasses the use of a marketed drug for a new indication**, regardless of whether the product is still under patent protection as unfulfilled therapeutic opportunities exist for both generic and patented products.[6]

Drug repurposing involves conducting additional research to **build the evidence base for extending the indication** (label change) of a drug originally developed for a primary use, often by actors other than the marketing authorization holder (MAH). There are numerous examples of successful drug repurposing with significant health impact, such as the well-known analgesic aspirin, now used for prevention of cardiovascular disease and thalidomide, once notorious for causing severe developmental defects when given to pregnant women, which was later repurposed as a safe and effective treatment for leprosy and, subsequently, multiple myeloma.[7]

Pharmaceutical companies, driven by financial market pressures, select R&D priorities and design drug life-cycle management strategies including extending the indication of their drugs beyond the primary approved use, with a focus on maximizing profits. Unless there's a strong business case, companies typically have little interest in exploring additional uses of the medicines beyond those priority indications. However, patients and doctors have long pointed out, and the medical community has actively explored, the **untapped potential to increase health impact with marketed medicinal products, and the opportunities to accelerate access to therapeutic innovation**, often at only a fraction of the cost of novel drug development.[8]

From a patient perspective, **the safety and efficacy of a product in treating their condition**, ideally validated through a regulatory authority, matters more than the source of therapeutic innovation—whether from a new product or a new use of an existing product. What also matters is **reliable, predictable and affordable access to the drug**. This means it should be recommended in professional treatment guidelines, available in the healthcare system, and covered by the (social) health insurance.

Unleashing Innovation through Drug Repurposing, and the Critical Role of Non-Profit Organizations

Commercial drug development is currently the main pathway to bring new health technologies and products to the market and to patients and constitutes an important source of therapeutic innovation. This has led to a supply-driven medical innovation ecosystem in which pharmaceutical companies (on behalf of investors and shareholders) determine which products are being developed for which indication, even if that is not necessarily guided by patient needs.[9,10] In fact, a significant proportion of novel drugs coming out of the commercial pipeline show limited patient benefit compared to already approved treatments,[11] despite efforts to incentivize companies to focus R&D efforts towards that, such as the ESMO Magnitude of Clinical Benefit Scale.[12] Meanwhile, there are many opportunities to deliver meaningful therapeutic innovation in response to patient needs that are currently being missed and underexplored because they do not fit into the market model.[5,10,13]

In this context, **repurposing by non-traditional developers of already approved medicines** to identify new ways in which those products can deliver patient benefit (in addition to the indications and dose regimes pursued commercially) has enormous potential. Not only can it **maximize the medical benefit to be gained from a given medicinal product, but it can accelerate and broaden the scope of therapeutic innovation** in a cost-effective way and deliver much needed health value for society, including for lower-resource settings. Compared to commercial drug development, non-profit actors can also explore different avenues and practices that have remained sidelined for lack of profit prospect and bring therapeutic innovation at lower cost and risk. This potential has been recognized by the WHO,[7] in the UK and in the USA,[14] and also the European Union, where a legislative proposal[15] and pilot activities[16,17] are underway to build a conducive environment for drug repurposing. It recognizes the **critical role of non-traditional developers such as not-for-profit organizations, research institutions and the medical and patient community in generating the evidence, and translation of this evidence** into improved cancer care with adequate assistance and oversight by regulatory authorities.

To ensure the public health community can maximize the opportunities presented by drug repurposing, critical legal and policy changes are required **to empower not-for-profit actors as equal partners** in the medical innovation ecosystem. Alongside new drug development, drug repurposing must be recognized **as an equally valuable approach to increase patient benefit** that deserves adequate financing, legal protections, and cooperation from regulatory authorities to advise on methodologies and protocols, evaluate the data, and as appropriate validate the positive benefit-risk of repurposing efforts. It is also important to ensure that such improvements are equitably accessible to patients, which requires marketing authorization, reimbursement, and integration in guidelines and clinical practice.

Overcoming a critical barrier to patient benefit: regulatory approval and label change

Currently, non-traditional developers are driving repurposing efforts by conducting and/or financing clinical trials in areas of promise. In relation to repurposing efforts using approved pharmaceutical dosage forms, these include: treatment optimization through dose-regimen adaptation (typically dose-reduction also known as de-escalation) to improve the tolerability and effectiveness, combination treatments (possibly with dose-adaptations), optimizing the use of adjuvant and neoadjuvant treatments, exploring the activity of a given cancer drug in other types of cancers (soft repurposing), or testing the efficacy of a non-cancer drug in cancer (hard repurposing).[18]

While building the evidence base for patient benefit of repurposed drugs faces many challenges, including access to the drugs and adequate funding for clinical studies, the most important hurdle to patient access is **translating the evidence into regulatory approval and a label change**. In cases where the MAH is not interested in pursuing an extension of indication, there is currently no mechanism that allows other stakeholders to collect and submit evidence for evaluation of benefit-risks by regulatory authorities. Moreover, where such regulatory review would support the finding that patients could benefit from this new use of an existing drug, without label change by the MAH it remains challenging to ensure this advance translates into patient access. In many European countries, regulatory approval is a pre-condition to reimbursement. Similarly, professional treatment guidelines tend to focus mainly on formally approved indications rather than off-label use, which has liability implications that prescribing doctors may be unwilling to take on.

Proposed Solution: A Complementary Regulatory Pathway for Non-traditional Developers

To maximize patient benefit, it is critical to **establish a complementary pathway for regulatory approval of therapeutic innovations** based on evidence submitted by non-traditional developers. Supplementing traditional industry-led innovation, it will ensure that all potentially impactful cancer research, including by not-for-profit organizations and the medical community, get equal attention and conducive routes to marketing authorization and patient access.

To this end, the currently **proposed EU Pharmaceutical Regulation, in particular Article 48 titled "Scientific opinion on data submitted from not-for-profit entities for repurposing of authorised medicinal products", could be a gamechanger.**[19]
If adopted, Art 48 would provide key adjustments to boost drug repurposing for both on-patent and off-patent drugs. First, it would allow not-for-profit entities to submit non-clinical or clinical evidence for a new therapeutic indication of an authorised medicinal product to a regulatory authority (EMA or at member state level) for regulatory assessment. Second, upon review of all available evidence, the regulatory authority will provide a scientific evaluation of the benefit-risk for such a new therapeutic indication, which will be made publicly available. Third, if the opinion is favourable, MAHs of the medicinal product concerned must submit a variation to the regulatory authorities to bring the new therapeutic indication on-label and update the product information with the new indication.

These legal changes are expected to overcome one of the critical barriers that currently stands in the way for drug repurposing, which is formal marketing approval, and thus smoothen the path to bring therapeutic innovation into clinical practice. Article 164 of the proposed Regulation further offers support schemes to facilitate the engagement of not-for-profit entities with EMA, including scientific advice and possible fee waivers.

It is important that these policy changes are not restricted to repurposing efforts that are defined in the context of "unmet medical needs" as initially proposed but instead focus on delivering benefit for all. Currently, there is no agreed definition of "unmet medical need", while opportunities for therapeutic and societal benefit through repurposing are much broader, including innovation towards safer, more practical and more cost-effective treatments. The European Parliament supports this approach,[20] and the final legislation must maintain this broader scope to maximize patient benefit.

While the first 2 points of article 48 are mostly procedural and concern a broadening of EMA's mandate, the obligation of MAHs to update the product label comes with cost, pharmacovigilance responsibilities and liability implications that must be satisfactorily addressed to ensure MAH endorsement and facilitate implementation. For instance, in the case of products that did not use the centralised

authorization procedure, repurposing may provide an opportunity for label harmonization across the EU through EMA. Similarly, it can be explored whether EMA can play a more proactive role in delivering public health benefit from existing medicines, as it has been empowered to do in the context of health emergencies.[21]

Article 48: Scientific opinion on data submitted from non-for-profit entities for repurposing of authorized medicinal products

May submit non-clinical or clinical evidence for a new therapeutic indication of an authorized medicinal product to a regulatory authority

Will provide a scientific evaluation of the benefit - risk for such a new therapeutic indication

Shall submit a variation to the regulatory authorities to bring the new therapeutic indication on-label and update the product information with the new indication.

Illustration 2. *Drug repurposing for on and off-patent drugs.*

Fostering a Conductive Environment for Successful Repurposing

Once this legal change is established, to ensure that patients and the health community can benefit, it is essential to **facilitate, accelerate and boost high quality evidence generation for therapeutic innovation outside of the commercial realm.** To this end, it is critical to establish, at the European level, the needed **clinical trial infrastructure, adequate funding, and efficient regulatory oversight** to support EU-wide trials to generate evidence of clinical benefit for both adults and children, as relevant. Such pre-positioned clinical trial platforms can host well-designed pragmatic trials that focus on establishing safety, efficacy, quality of life and overall survival benefits of repurposing drug candidates for submission to regulatory authorities (if positive). These can be complemented with European registries for research and quality real-world evidence (RWE), the collection of which can also be supported by not-for-profit entities. An additional proposal to help evidence generation would be for EMA to establish a "Drug Evidence Watch", in which it would not only monitor safety evidence for new and unexpected signals as it does today, but also collect information on new and unexpected efficacy signals when drugs are used off-label.[21] In the United Kingdom and the United States of America, several programs already exist that monitor and collect data to inform possible repurposing opportunities, some including incentives or policies to facilitate subsequent label change.[14]

Essential towards generating clinical evidence is to have **(affordable) access to the drugs for research purposes,** which can be a challenge in the case of expensive (on-patent) drugs. Today, MAHs can be reluctant to make products available for research, especially if they see no commercial interests in the outcome of the research. Additionally, adequate financing must be made available for non-commercial research to build the evidence base for new indications, accepting the fact that such research will not deliver financial return on investment.

Another important question to resolve is clarifying data ownership and governance, in particular how to ensure that establishing new uses of existing drugs does not result in additional intellectual property monopolies or unwarranted price increases, while at the same time ensuring sustainable availability in the market at an affordable price. Here, research funders could play a critical role, for instance by adding conditionalities about affordability and equitable access to their funding agreements, as is sometimes done today for global health R&D, and proposed in the context of the pandemic treaty.[22]

Overall, it will be important to minimize the risk of unintended consequences, including that companies would become even more reluctant to make available product for research if they become obliged to pursue a label update in case of positive EMA opinion.

Towards a sustainable "public health purpose value proposition" (aka business model)

To establish a sustainable public health value proposition, it is crucial **to ensure both the availability of, and equitable access to, essential treatments.** This requires revisiting overall economic and financing models for pharmaceutical development to secure adequate funding for non-commercial, health needs-driven and patient-centred research and development, in order to balance innovation incentives with health system sustainability. Additionally, strategies must be implemented to prevent free-riding, ensuring that all stakeholders contribute fairly and transparently to the costs associated with developing and delivering these treatments, and no-one disproportionally benefits. This will be particularly important for patented medicines, where safeguards need to be incorporated to avoid the misuse of non-commercial research for profit-making purposes through excessive pricing or evergreening practices. By building a robust case for non-commercial R&D, we can **create an ecosystem that is driven by beneficial public health outcomes, in addition to economic drivers including competitiveness.**

Conclusion

With a projected growth of the cancer burden in Europe in a chronically budget-constrained healthcare environment, maximizing the patient and societal benefits of medical innovation is a priority for patients, the medical community, and policy makers. Drug repurposing is a promising avenue to that effect that requires establishing a complementary regulatory pathway for non-traditional developers, as proposed under article 48 of the EU Pharmaceutical Regulation. Ensuring its adoption as outlined in this paper is a critical step toward unleashing medical innovation for maximal public health impact.

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Financial Contributors

Supported by KWF

Kom op tegen Kanker

BARNCANCER FONDEN

Content Contributors

AIM Healthcare anc social benefits for all

ALAN Acute Leukaemia Advocates Network

Fondation pour la recherche sur le cancer arc

asociación española contra el cáncer

BIG Breast International Group

CANCER PATIENTS EUROPE

Childhood Cancer International EUROPE

DIGESTIVE CANCERS EUROPE

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Visual Communication & Document Design

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About the Anticancer Fund

The Anticancer Fund is a Belgian non-for-profit organisation with an international scope. We are dedicated to expanding the range of treatment options available to cancer patients, regardless of commercial value. Our goal is to extend lives, increase quality of life and provide cures for cancer patients by complementing the commercial drivers of cancer care with exclusive patient-first thinking and a focus on evidence-based potential for new treatments.

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