

# REPURPOSING DRUGS FOR CANCER TREATMENT: UNLOCKING THE POTENTIAL

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- Repurposing: benefits and barriers
- Aiding market authorisation for repurposed drugs
- Supporting preclinical and clinical research
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## INTRODUCTION

Various drugs already widely used for non-cancer diseases have shown promise for the treatment of cancer. Repurposing these drugs could allow new cancer treatments to be introduced relatively quickly and at low cost, thereby meeting the unmet needs of patients and healthcare payers alike. Focusing on medicines that are off-patent or near to patent expiry, this paper explains the actions needed at policy level to adapt regulatory, research and funding systems to unlock the enormous potential benefits of repurposed medicines.

### RISING BURDEN AND COSTS

Cancer kills over 1.25 million people each year in the European Union (EU), representing around one in four deaths.<sup>1</sup> Improvements in our understanding of cancer have led to important therapeutic advances in recent years. However, ensuring that all patients have sustainable access to high-quality care is a major challenge, as the costs of care are rising in the context of fiscal constraints on healthcare systems.

The costs of cancer care are rising in part because more people are being diagnosed each year and because diagnosed patients are living longer and hence require more care. The high prices of new anticancer medicines also contribute to both the increasing care costs and disparities between EU Member States in patients' access to care.<sup>2</sup> According to one estimate from the UK, the costs of cancer medicines (as a proportion of gross domestic product per capita) have risen seven-fold over the last two decades.<sup>3</sup> Echoing the concerns of European cancer experts,<sup>2</sup> the European Council and Council of Europe have expressed concern regarding the "exorbitant" price of cancer medicines<sup>4</sup> and "an increasing number of examples of market failure in a number of Member States, where patients' access to effective and affordable essential medicines is endangered by very high and unsustainable price levels, market withdrawal of products that are out-of-patent, or when new products are not introduced to national markets for business economic strategies."<sup>5</sup>

Moreover, it is increasingly recognised that multiple anticancer therapies will need to be used in combination to achieve greater efficacy and to prevent cancers becoming 'resistant' to treatment.<sup>6</sup> The prospect of combining expensive treatments threatens to exacerbate the spiralling increase in the costs of care and threatens the sustainability of cancer care services.

### WHAT IS REPURPOSING?

Repurposing (or repositioning) medicines offers a rational, evidence-based approach to help address these challenges and to provide patients, prescribers and payers with sustainable access to additional, cost-effective therapeutic options for cancer.<sup>6</sup> Drug repurposing can take many forms. Some approaches, such as the reformulation of existing drugs and the commercialisation of previously shelved compounds, offer the potential for a return on investment that provides an incentive for industry. However, the repurposing of marketed, unmodified drugs that are off patent (i.e. generic), or near to patent expiry, presents unique financial disincentives and is particularly challenging. This policy paper focuses specifically on actions to overcome the challenges to non-commercial repurposing of established medicines, in the context of the substantial benefits that this could deliver to patients and healthcare systems in Europe.

## REPURPOSING: THE BENEFITS AND BARRIERS

### Addressing unmet medical needs

Although pharmaceutical industry pipelines have provided many innovative drugs in recent years, this pipeline has become increasingly inefficient and less productive. In the United States, the number of new drugs approved per billion US dollars spent on research has approximately halved every 9 years since 1950, falling around 80-fold in inflation-adjusted terms.<sup>7</sup> The European Medicines Agency (EMA) has previously drawn attention to a 'productivity gap' in the development of medicines generally, in particular in the development of treatments for rare diseases.<sup>8</sup> Rare cancers are a specific case in point and are generally not attractive for development by pharmaceutical companies. There are so many different rare cancers that collectively these account for around 22% of new cancer cases in Europe.<sup>9</sup> There is no standard treatment for many rare cancers and generally they are associated with worse outcomes than common cancers.<sup>9</sup> Important unmet needs also remain in metastatic cancers (those that have spread to multiple sites in the body) and those that have not responded to previous treatment. Repurposing could help address these needs, as research has revealed mechanisms that can be targeted with existing drugs already used for non-cancer indications.

### Faster, cheaper drug development

The typical drug development process for new drugs – involving preclinical laboratory tests followed by a phased programme of clinical studies in volunteers and patients – generally takes at least 10 years and costs up to US\$2.6 billion to capitalise.<sup>10</sup> Moreover, fewer than one in 10 cancer medicines that enters clinical testing achieves approval by drug regulators.<sup>11</sup> Drugs that are good candidates for repurposing have the advantage that preclinical, pharmacokinetic and safety data are already available. This allows them to be fast-tracked into clinical trials in patients with cancer, thereby greatly shortening the necessary development timeline.

### Improved cost-effectiveness

Drugs that are good candidates for repurposing are often available as generic (non-proprietary) formulations that are far less expensive than patented, branded products. Should these drugs turn out to be efficacious and well tolerated, they could prove highly cost-effective compared with novel therapies and could greatly improve the efficiency of healthcare spending on cancer.

### But barriers exist

Making optimal use of existing generic medicines is of obvious and intuitive benefit, especially given the unsustainable rise in the costs of new drugs, and there is no shortage of off-patent medicines that offer promise as cancer treatments.<sup>6</sup> An ongoing analysis of literature has identified over 130 drug candidates and more than 11,000 relevant papers published

between 1995 and 2015.<sup>12</sup> However, two key barriers restrict the repurposing of these medicines:

- 1. Lack of clear regulatory pathways:** Current pharmaceutical regulations principally focus on the development of new medicines, not new indications for existing medicines,<sup>13</sup> and there is a clear lack of EU and national pathways to facilitate drug repurposing.
- 2. Lack of financial incentives and research funding:** The pharmaceutical industry, including the generic sector, has little or no incentive to invest in the research necessary to gain regulatory approval for a cancer indication for a drug that is no longer under patent. This is because there is no return on investment anticipated, given the lack of intellectual property protection and the low prices of generic formulations. Drugs whose development is blocked in this way have been called 'financial orphans'.<sup>14</sup>

The following sections explain these barriers in more detail and offer actionable solutions.

## AIDING MARKET AUTHORISATION FOR REPURPOSED DRUGS

*Restrictions should be removed on the application for market authorisation (or 'label' extensions) in order to facilitate repurposing.*

All medicines sold in the EU require a market authorisation (MA). Depending on the circumstances, an MA may be granted on an EU-wide basis via the centralised procedure mediated by EMA (this is mandatory for novel cancer medicines) or it can be granted by Member States, and recognised by others, via the mutual recognition or decentralised procedures. The MA for off-patent, non-cancer medicines that are candidates for repurposing for cancer indications may be held by the original market holder or by generics manufacturers. Crucially, only an MA holder can apply for an MA extension to cover new indications, and yet companies have little or no incentive to invest in the necessary research because of a lack of return on the investment. Filing for label extension has not only an administrative cost but may also require one or more additional clinical trials to be sponsored by the MA holder. If the new indication is a rare cancer, the fact that this is a limited market compared with the main indication means there is no rationale for the pharma company to take action. A further disincentive exists where the existing MA holder no longer manufactures the drug, especially if it markets an alternative, patented product for the same indication.

Existing EU schemes aimed at promoting drug repurposing are limited to 1 year of data exclusivity granted for a new indication for a well-established medicine<sup>15</sup> and to provisions under the orphan designation scheme. Generics manufacturers are exploring repurposing in this latter context, where orphan

designation can allow a price increase that provides a return on investment. However, these schemes do not offer sufficient incentives for industry overall and are under-used.<sup>13,16</sup>

There is also an under-recognised lack of developmental and approval pathways for repurposed medicines at national level. A recent survey was conducted for the European Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP). It concluded that only six of 18 participating Member States considered that significant regulatory barriers exist to the addition of new indications to MAs of approved medicines, even though several raised the obstacle that only the MA holder can seek a new indication.<sup>17</sup> Only one Member State was exploring means of fostering collaboration between manufacturers of generic pharmaceuticals and academics with a view to repurposing off-patent medicines.

**ACTION ITEM 1: Remove restrictions on the entities eligible to apply for market authorisation (label) extensions to facilitate repurposing.**

As industry has no incentive to repurpose off-patent medicines, regulatory frameworks should be amended to allow this to be done by not-for-profit organisations and other non-commercial actors. Various not-for-profit organisations, including academic centres, patient organisations and medical research charities and foundations (such as the Anticancer Fund), are ready and able to undertake this work. One approach would be to eliminate the restrictions on who can apply for an MA extension for off-patent medicines. This would be facilitated by measures to promote the sharing of relevant data by industry to support MA extension applications by third parties.<sup>13</sup>

More fundamentally, policymakers should consider how drug repurposing could be uncoupled from the existing MA in order to overcome the current obstacle whereby only the MA holder can apply for an extension. The fact that new approaches have been developed to address other unmet needs (e.g. adaptive pathways, PRiority MEdicines [PRIME] scheme, conditional market authorisation and orphan diseases regulation) shows that other ways of thinking are possible.

## SUPPORTING PRECLINICAL AND CLINICAL RESEARCH

*Policymakers can help in drug repurposing by supporting translational research that bridges the gap between preclinical laboratory tests and clinical trials.*

The Anticancer Fund is among the organisations funding early clinical trials to test whether the promising results from preclinical laboratory tests translate into benefits for patients with cancer. For example, studies currently funded by the Anticancer Fund include PIONEER, a multicentre, randomised clinical trial underway in the UK. PIONEER will

determine whether a drug called megestrol acetate (Megace®) reduces the proliferation of cancer cells in women with oestrogen-receptor positive breast cancer, as has been shown in laboratory tests.<sup>18</sup> If the drug does reduce proliferation, a second, larger clinical trial will test whether it improves progression-free survival and quality of life.

Although current initiatives are promising, they are limited in terms of scope and resources and this important field of research remains largely untapped. The main barrier is a lack of funding, as the pharmaceutical industry has little interest in this work and public funding is limited.

Given the public health impact of cancer and the potential value of repurposed drugs, the commitment of a far greater proportion of EU and national funding to repurposing is warranted, especially where treatment options are currently lacking. The European Commission has recently affirmed the value of innovation in existing drugs.<sup>19</sup> In our experience, only a few, highly specific research projects on repurposing drugs for certain rare diseases and other conditions are currently funded through the Horizon 2020 programme and these show a bias toward projects driven by intellectual property and commercialisation considerations. Publicly funded research should be oriented towards patient outcomes and public health benefits, rather than being indirectly supportive of commercial goals. Needs can be prioritised and the risks of failure can be limited by careful selection of candidate cancer medicines, for example via the Repurposing Drugs in Oncology (ReDO) project.<sup>20</sup> European collaboration could help avoid duplication of effort, for example by a European 'Network of Experts' as has been proposed for the assessment of off-label indications.<sup>13</sup>

Other barriers to research include a lack of clear communication channels between preclinical scientists and clinicians and a lack of incentives for scientists because the successful translation of preclinical results into new treatments is not a key performance indicator for academia. Policymakers could further promote clinically relevant research by academic institutions by supporting the establishment of centres of excellence.

We urge policymakers to help address these barriers by supporting research and collaboration.

**ACTION ITEM 2: The EU, national governments and philanthropic organisations should fund research calls specifically including drug repurposing for cancer on a non-commercial, public health-driven basis.**

**ACTION ITEM 3: All stakeholders (including policymakers, experts, payers, patient organisations and not-for-profit organisations) should collaborate on the establishment of centres of excellence for horizon scanning and to share knowledge; they should also establish a common and up-to-date understanding of drugs that show promise for repurposing.**

## NEW DEVELOPMENT AND FUNDING PATHWAYS

*New drug development pathways and funding schemes are needed to facilitate drug development by not-for-profit bodies.*

### Non-commercial development pathway

EU Member States could strongly foster the repurposing of medicines by establishing a parallel, non-commercial drug development track independent of the pharmaceutical and biotechnological industries. This approach was among those resulting from a recent consultation project conducted by the Belgian Healthcare Knowledge Centre (KCE) and Dutch Health Care Institute (Zorginstituut Nederland; ZIN) in order to construct creative new scenarios to help ensure patient access to safe and effective drugs, while incentivising innovation focused on public health needs.<sup>21,22</sup>

In this scenario, coalitions of not-for-profit research institutes, payers, authorities and patient organisations could develop treatments that the pharmaceutical industry has no incentive to invest in, including repurposed cancer medicines. The research and development costs could be covered by public funding, crowdfunding or social bonds or other innovative financial approaches, as discussed below.

A non-commercial pathway would not require industry to change its operations, but instead offer health systems an alternative means of developing repurposed cancer medicines and other medicines addressing key unmet needs.<sup>21</sup> The clinical research already funded by the Anticancer Fund, and other non-profit organisations, demonstrates the feasibility of this approach.<sup>6,20</sup> Clinical trial networks, such as the European Clinical Research Infrastructure Network ([www.ecri.org](http://www.ecri.org)) and the European Organisation for Research and Treatment of Cancer (<http://www.eortc.org>) could be valuable in facilitating multicentre and international non-commercial clinical studies. However, additional national and international initiatives will be required to make independent clinical research happen.

Patient organisations and philanthropic organisations should be involved in initiating clinical trials with repurposed drugs and raising awareness of their value among patients and stakeholders to promote participation. Unfortunately, not-for-profit organisations sometimes have problems recruiting patients into trials because of competition from industry-sponsored trials that are significantly more financially rewarding for investigators and clinics. Policymakers need to address this barrier if recruitment into non-commercial trials is to proceed.

***ACTION ITEM 4: Policymakers need to facilitate recruitment of patients into non-commercial clinical trials by addressing the financial disincentives faced by investigators and clinics.***

### Novel funding approaches

As industry is not expected to fund non-commercial drug repurposing, at least alone, and governments are anticipated to have limited public funding for clinical trials, creative funding models are required. Funding models for repurposing could be based on partnerships between public funders, health insurers, academic investigators and philanthropic supporters. Potential models include social impact bonds, whereby investors in a public interest initiative receive a return on investment according to its success. In the case of generic drug repurposing research, the return on investment could come from healthcare savings generated by the use of approved repurposed drugs.<sup>23</sup> Such savings could incentivise investment in repurposing studies by governments and health insurers.<sup>6</sup>

***ACTION ITEM 5: Policymakers must establish novel funding systems for non-commercial drug-repurposing that are based on a comprehensive assessment of the potential socioeconomic benefits to patients, healthcare systems and society at large.***

## CONCLUSION

*Innovative policy actions in the current medicines regulatory sphere are needed to unlock the enormous potential of drug repurposing for patients, health systems and societies at large. We urge health policymakers at EU and national level to engage with all relevant stakeholders, including not-for-profit foundations, researchers, patient organisations, regulators, health technology assessment (HTA) authorities and payers to act collaboratively on these actions.*



The Anticancer Fund is a non-profit foundation with an international reach dedicated to expanding the range of treatment options available to patients, regardless of their commercial value.

[www.anticancerfund.org](http://www.anticancerfund.org)

# REPURPOSING DRUGS FOR CANCER: UNLOCKING THE POTENTIAL

## WHY REPURPOSE DRUGS FOR CANCER?

### REDUCE COSTS

Cancer medicines prices rose 7-fold over the last 20 years<sup>a</sup>

7-fold  
PRICE INCREASE

### NEW ANTICANCER AGENTS

>€100,000  
vs €10–1000

New anticancer agents cost >€100,000 per year of treatment<sup>b</sup> vs €10–1000 per year for repurposed drugs

### CHEAPER DEVELOPMENT



Conventional drug development takes 10+ years, costing ~US\$2.6 billion<sup>c</sup> while repurposing may take only ~6 years, costing ~US\$300 million<sup>d</sup>

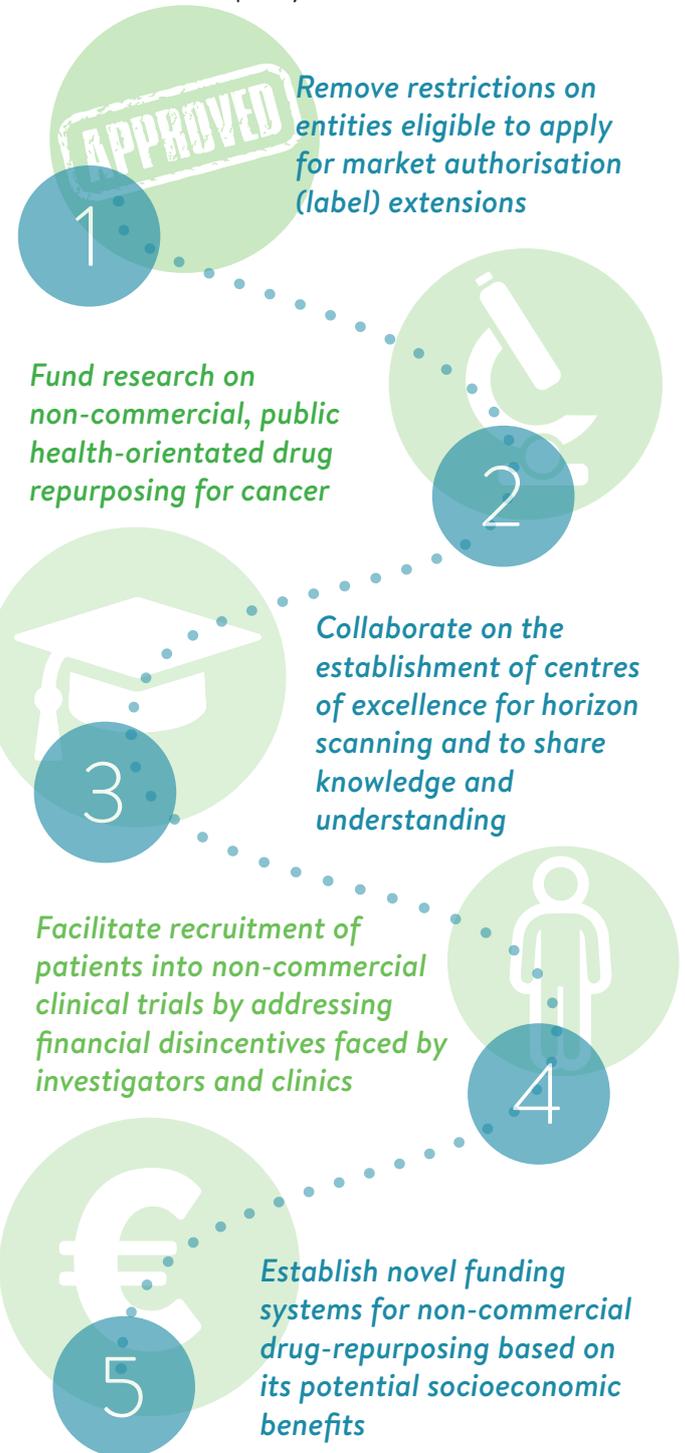
>130  
CANDIDATES  
FOR REPURPOSING



>11,000  
PAPERS PUBLISHED<sup>e,f</sup>

## POLICY ACTIONS

Non-commercial drug repurposing by third parties is impeded by current European regulations. Anticancer Fund recommends policymakers to:



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