

ON-PATENT DRUG REPURPOSING

Key Issues Report

Pan Pantziarka, Patricia Vandamme, Gauthier Bouche, Lydie Meheus,
Karolina Werynska, Paola Atzei, Alexandre Alencar,



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Executive Summary

The issues around financial and regulatory obstacles to the repurposing of off-patent/generic medicines are well characterised in the academic literature and are familiar to policymakers and funders. However, the repurposing of on-patent medicines is less well-characterised, including funding and regulatory obstacles that may occur in these cases. The Rising Tide Foundation for Clinical Cancer Research and the Anticancer Fund have, in recent years, been faced with clinical trial proposals involving on-patent medicines. In this report we have explored the commercial, regulatory, and social factors involved in on-patent drug repurposing, with particular emphasis on issues most relevant to research funders.

We begin by defining terms given that 'off-label', 'off-patent' and 'generic' are often used interchangeably - we define these terms and outline the regulatory paths available for adding approvals for new medical indications to drugs. In particular, the tension between market exclusivity and the arrival of competitor products is shown to be a major factor in the decision-making process of commercial drug developers. The prevalence of on-

patent drug repurposing in oncology is also touched upon, using both data derived from a repurposing clinical trial database and case studies.

The label extension pathways are outlined, showing both the central role of data generation via clinical trials and the role of the marketing authorisation holder, particularly when the data is generated by academic or not-for-profit sponsors. The importance of label extension is also emphasised, contrasting this with the use of drugs 'off-label', which is possible but is not an optimal solution to the problem of access to repurposed medicines for patients. In contrast to generic medicines repurposing, on-patent repurposing may include the possibility that not-for-profit organisations can contract with the commercial owners of a drug to get a return on their philanthropic investment. This 'revenue sharing' approach is discussed in the report.

Finally, the report includes the philanthropic approach that has been adopted by RTFCCR as a policy when dealing with future on-patent drug repurposing proposals.

Foreword

Many rare and ultra-rare cancer types remain without good treatment options. These high unmet needs may be addressed by repurposing existing licensed drugs into new indications and/or patient populations. Drug repurposing is most often viewed as involving older generations of drugs, typically off-patent or generic medicines. However, repurposing may also encompass newly licensed drugs still within the patent protection period. Many pharmaceutical companies are not interested in funding on-patent drug repurposing clinical trials. For many companies, the trajectory of development for a drug is decided even before the first approval and the development of repurposing opportunities outside of those plans is often not supported.

While the financial and regulatory hurdles involved in repurposing generic medicines are well characterised, the issues for on-patent medicines are less well known and have not been as comprehensively explored. However, the issues have assumed more importance as the number of examples of stalled on-patent repurposing has grown. Therefore, the Rising Tide Foundation for Clinical Cancer Research (RTFCCR) and the Anticancer Fund (ACF) have conducted a joint landscape analysis looking at on-patent drug repurposing to identify any unmet needs for philanthropic support.

This report outlines our findings.

1. Background

1.1 Introduction

In recent years there have been significant advances in a range of cancers, leading to improvements in overall survival in cancers that were previously viewed as fit for palliative treatment only. A notable example is metastatic melanoma – the development of immune checkpoint inhibitors (ICIs) has transformed the treatment of the disease [1]. However, for many other cancers, particularly rare and pediatric cancers, the outlook has not changed to any great extent in decades [2]. While it may be the case that some of the ICIs or other new classes of drug may be active in these diseases, the focus of commercial development remains on the more common cancers. This is where the patient numbers are highest and where clinical development may proceed more quickly. With lower patient numbers the financial incentives for developing novel treatments are often much lower. Alternatively, some companies are developing new drugs for orphan indications where they can exploit their monopoly position to charge very high prices, making these novel medicines unaffordable for many patients, particularly in resource-constrained health systems.

One consequence of these trends is an increased interest in drug repurposing – that is reusing drugs developed for other diseases to treat these rare cancers [3]. While much repurposing activity is focused on ‘older’ drugs, often available as generics, there is now increasing attention being paid to repurposing some of the more recently approved drugs to treat cancers for which the drugs have not been approved. A distinction is sometimes made between ‘soft’ drug repurposing and ‘hard’ drug repurposing [4]. Broadly, ‘soft’ repurposing refers to taking a drug used in one disease and reusing it for another disease in the same area of medicine. For example, taking a drug used in one cancer and repurposing it for a different cancer, or moving a drug from one infectious disease to another. ‘Hard’ drug repurposing takes a drug used in one disease area and using it to treat a disease in a very different medical area, for example taking a psychiatric drug and using it in oncology. This is referred to as ‘hard’ drug repurposing because there are many more challenges involved in such a repurposing exercise. In practice, repurposing exists on a spectrum; even with ‘soft’ repurposing some cases are more challenging than others – for

example a drug used for haematological cancers is challenging to move to solid tumours [3]. It should be noted that the issues outlined in this report apply to both ‘soft’ and ‘hard’ repurposing cases.

The background to this report arises from a number of cases where promising examples of drug repurposing exist, involving drugs that are still within their market-exclusivity period (i.e. ‘on-patent’ in common usage), but where the producer of the drug is not interested in investing in the repurposed use. This seems counter-intuitive as the producer of the drug would be assumed to benefit from the new use, should it be approved and consequently reimbursed by health providers/insurers. This outcome is due to commercial decision-making by the company – and key factors that contribute to such decision-making are based on potential returns on investment, which in turn relate to market exclusivity, regulatory incentives, projected drug sales, pricing and other commercial considerations. Regulation, for example in incentives to extend the period of market exclusivity, are therefore of major importance.

This report outlines the current regulatory framework for drug licensing and the key issues that impact the decision-making of commercial drug developers (pharmaceutical companies) when assessing the potential of repurposing their products to treat medical conditions (referred to as medical indications) that they are not approved for. As the focus is on repurposing, we are looking at drugs which have an approval to treat one or more indications. Drugs which have not been approved to treat an indication are called unlicensed medicines, even if they are in use in clinical trials or are available to patients via compassionate use or similar programs. Repurposing is also sometimes used to refer to the new development of ‘shelved’ compounds – that is drugs which were being developed at some point but which the original developer has ceased further work on, often because the drugs have not produced positive clinical trial results. In some cases, such compounds can be brought back into development, often by new commercial developers who buy the assets from the original developer, and some people call this repurposing. However, these compounds have not been approved and are therefore unlicensed medicines outside our scope. Similarly,

reformulation of an existing licensed medicine in order to gain intellectual property (IP) protection is also sometimes referred to as repurposing – but again, in this case the market mechanisms are very different to those where a drug is reused “as-is” for a new indication. Reformulation is also therefore out of scope of this report. Similarly, reformulation of an existing licensed medicine in order to gain intellectual property (IP) protection is also sometimes referred to as repurposing – but again, in this case the market mechanisms are very different to those where a drug is reused as-is for a new indication. Reformulation is also therefore out of scope of this report.

Reference will be made to differences between scenarios involving drugs at different ends of the

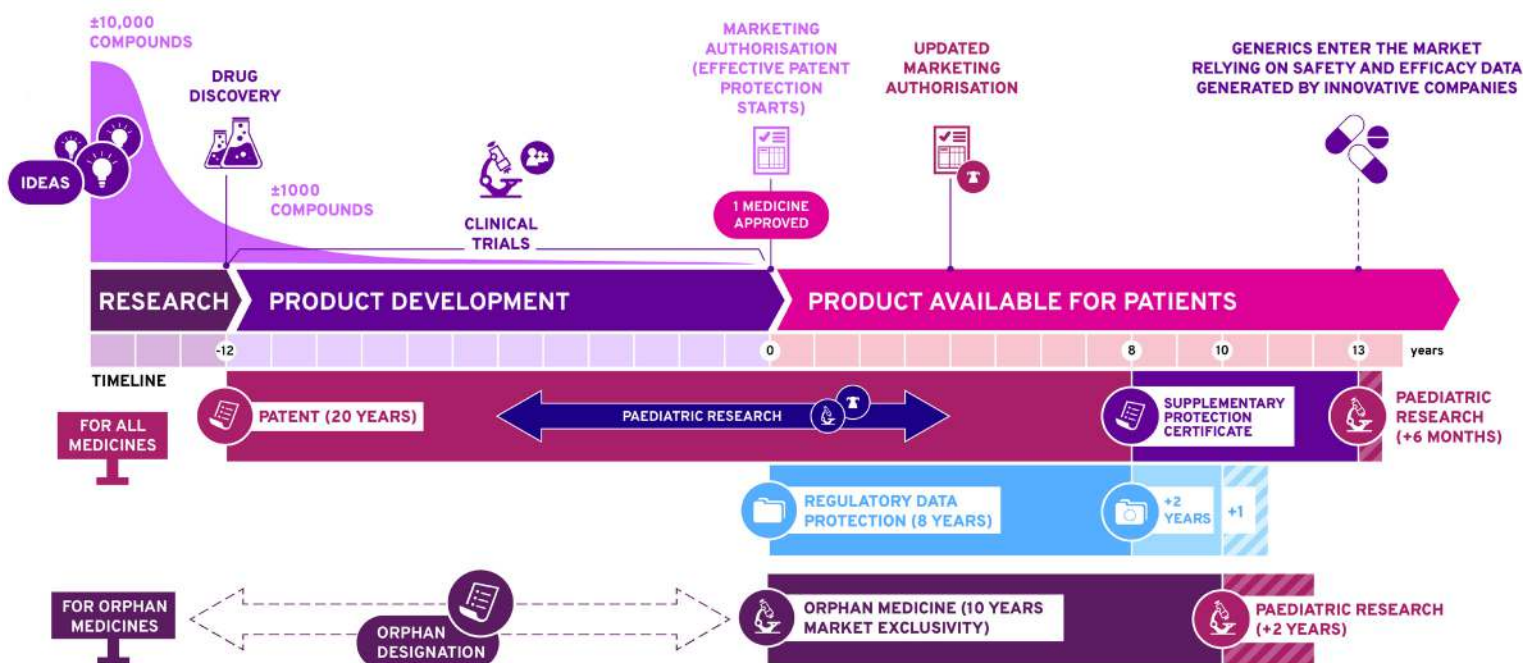
development spectrum – from drugs that are still within the market exclusivity period (often called ‘on-patent’ drugs), and those outside of that period (often called ‘off-patent’ or generic drugs). Many of these factors are related to the regulatory regimes for licensing medicines, with variations in different markets. **This report will focus on the EU (EMA), UK (MHRA) and USA (FDA).** While there are variations across these markets/regulatory regimes, there is also much commonality in how they approach the task of balancing the financial imperatives of drug developers and broader societal needs. Much discourse around drug development, particularly for drug repurposing, often lacks a degree of rigour when discussing incentives issues – for example, the terms off-patent and generic are used interchangeably.

1.2 Patents and Market Exclusivity

Patents are a form of intellectual property which grant the owners of an invention the right to control who may use that invention for a defined period of time. In return the inventor must publish the details of the invention; for the inventor that is the cost of being granted the patent. After that

period the exclusivity right expires, and others may exploit the invention. The normal lifetime of a patent is 20 years, and this applies to medicines and medical devices as much as it does to other patentable products or processes.

Figure 1. European Pharmaceutical Incentives Framework (adapted from efpia.eu)



However, in medicine 20 years is a relatively short timeframe given the lifecycle of drug development – which must progress from the discovery of the compound, through pre-clinical studies, safety studies in humans followed by larger and more costly clinical trials, finally culminating in regulatory approval and then, following health technology assessment (HTA), to the drug being reimbursed and implemented clinically. This is a long and risky process and given that the patent is applied for early in the discovery phase, it means that much of the 20-year patent lifetime may have expired before the drug can be manufactured and sold. For example, the European Federation of Pharmaceutical Industries and Associations (EFPIA), quotes an average of 10-years from the granting of a patent to drug approval. There are significant costs involved, estimates for the research and development (R&D) cost of bringing a drug to market range from US\$944m

to US\$2,826m [5], another study found that the median R&D cost associated with a new oncology drug was \$2,772m [6] (all costs in 2019 equivalent US dollars). This leaves a relatively short window of time during which the company has the exclusive right to manufacture and sell the drug to generate a return on that investment. See an overview of the process in the Figure 1.

Regulators recognise the fact that regulatory factors to do with safety, clinical trial conduct and other regulations contribute to the long development time and consequent shorter market exclusivity period. In order to incentivise drug developers, they have therefore created a number of mechanisms to extend the marketing exclusivity period beyond the 20-year lifetime of the patent. Together these are termed non-patent exclusivities and are listed in the table below:

Table 1. Non-patent exclusivities

	Name	Description
FDA regulated	New chemical entity (NCE) exclusivity	Automatically applied to newly approved compounds – grants protection of 5 years against competitor products. Applications for generics can be initiated when the 5 years ends, but applications take 2 years to process – so in practice this is 7-years of market exclusivity.
	Clinical investigation (CI) exclusivity	Automatically applied to approved drugs that are further developed by the originator – including new development for a different indication. The exclusivity is for a period of up to 3 years and protects against competitor products being developed in the same way. Note that this does not extend protection to the original drug in its original form or indication.
	Orphan drug exclusivity (ODE)	Applies to the development of an approved drug for a new indication in a rare disease. It applies 7 years of marketing exclusivity for the new indication but does not extend protection to the original drug in the original indication.
	Pediatric (PED) exclusivity	Applied when a company performs studies assessing the pediatric use of an approved drug at the request of the regulator. The PED adds 6-months of protection to all current protections for that drug, regardless of indications and regardless of the outcome of the pediatric studies.

Name	Description
Supplementary protection certificate (SPC)	Up to 5 years of marketing protection after the expiry of the patent protection period. This can be extended for an additional 6 months if pediatric studies are carried out. This is applied as a matter of course rather than being exceptional.
Data exclusivity “8+2+1”	This comprises of 8 years data exclusivity period, 2 years marketing exclusivity period and a one-year extension period. Data exclusivity means that the data of the originator company cannot be used by a generic manufacturer – hence it guarantees protection unless the generic manufacturer carries out registration studies in the original indication. The 2-years marketing exclusivity that follows means that competitors have access to the data and may apply for approval of generics (or biosimilars) – but no such products will be approved in that time. Finally, the one-year extension is granted if a new indication for the drug is developed by the originator and is approved within the exclusivity period.
Orphan drug designation (ODD)	Applies to a drug approved for an orphan disease when there is no existing treatment, or the drug is superior to the existing treatment. It provides 10 years of marketing exclusivity for that drug in that indication. This may be extended to 12 years for a pediatric orphan disease.
Pediatric Use Marketing Authorisations (PUMAs)	This can be applied to a drug that is already authorised for adult use and is outside of any marketing exclusivity periods (i.e. completed the SPC and other extensions) – it is used for drugs to be developed specifically for pediatric use and grants 10 years of marketing exclusivity.

EMA/MHRA regulated

These different programs and extensions to marketing exclusivity are designed to incentivise drug developers – both by ensuring that there is a ‘pay-off’ for the long process between drug discovery and marketing approval, but also by encouraging drug developers to target specific sectors – rare/orphan diseases and pediatric medicines. These different pathways are factored into the long-term development plans of new drugs – often years before the drugs are finally approved for a given indication.

As we have outlined above, the drug development pathway includes many different incentives and exceptions that protect a drug from competitor products. Included within these are incentives designed to encourage repurposing of products within the initial exclusivity period. The EU and MHRA both include an additional one year of marketing exclusivity, specifically:

“ during the first eight years of those ten years [of marketing exclusivity for a new drug], the marketing authorisation holder obtains an authorisation for one or more new therapeutic indications which, during the scientific evaluation prior to their authorisation, are held to bring a significant clinical benefit in comparison with existing therapies. ”

The intent of this regulation was to explicitly incentivise drug developers to seek repurposing opportunities for newly authorised medicines. However, empirical evidence suggests that this has not succeeded. Liddicoat and colleagues showed that the rate of repurposing of newly approved drugs did not differ significantly for drugs approved before or after the introduction of the +1 year incentive [7].

In addition to marketing exclusivity, there are other mechanisms available to developers seeking to protect potential repurposing candidates from competitor products. These include taking out additional patents, for example using ‘medical use’ patents. The European Patent Convention (EPC) allows for patent protection of medical uses of known products under Art. 54(4) and Art. 54(5) EPC, introduced in 1990. Effectively these are exceptions to the normal patent claims process which depends on a novel invention or product. However, the medical use patents only apply to the specific new use and must still satisfy inventiveness rules (i.e. the new use must not be obvious or have been previously patented).

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Detailed analysis of patent records from the European Patent Office showed that there is in fact a very active rate of medical use patents being granted, at around 200 per year [8]. Furthermore, 99.2% of these are also US patents, with oncology being the medical area with the highest number of patents protected worldwide. The authors also note that the number of medical use patents granted exceeds the number of EMA label extensions for new indications over the same period. Other data shows that while historically (i.e. since 1990) it is large pharmaceutical companies that have been most active in filing medical use patents, the academic sector has been increasingly active, for example in 2020 among the 20 most active groups being granted medical use patents around half were academic centres [9].



half of the most active groups in filing for medical use patents in 2020 are academic centers

However, while the empirical data clearly shows that it is possible to be granted patent protection for new medical uses of existing drugs, it is less clear on the economic value of such patents. A key issue remains the difficulty of enforcing such patents. Cross-label prescribing describes the situation where physicians and/or pharmacists prescribe or dispense cheaper drugs for a given indication, for example prescribing a generic version of a drug rather than a branded version even when the indication is only on the branded version of the drug and not the generic. In effect this means that a company that secures a new medical use patent and proceeds to create a new product based on this

may find that patients are prescribed the original product or a competitor product if it exists. The case of Lyrica (pregabalin) is an exemplar case. The drug had been developed as an anti-epileptic and Pfizer had licensed the original patents from the drug's developer. It added a second use patent covering neuropathic pain, which became the main use of the drug (with annual sales of \$5billion). When the original patent and marketing exclusivity expired in the UK generic versions appeared, and Pfizer went to court arguing that prescriptions for neuropathic pain should use its branded version (Lyrica) rather than the generic versions which were not approved for this indication. Although initially successful the case was appealed and finally the UK Supreme Court ruled that Pfizer's second use patent was not warranted.

It can also include cases where patients are treated with an alternative medicine in the same drug class or with a similar mechanism of action. The signature case demonstrating this is from the UK, where the Court of Appeal has ruled unanimously that a policy of the NHS offering patients with wet age-related macular degeneration (AMD) treatment with the VEGF-inhibitor bevacizumab, which is not approved for this indication, as an alternative to the much more expensive VEGF-inhibitors ranibizumab and aflibercept, which are approved for AMD, is lawful [10]. Other countries, such as the Netherlands, also now recommend bevacizumab as first-line treatment for AMD, despite it being off-label.

Another issue with patents is that they can be challenged and for medical use patents this is a particular risk. One consequence is that companies are increasingly including additional medical indications when taking out the original patent for the drug. By including other indications, even at a very early stage of development, companies seek to pre-empt others from securing medical use patents later. Although, as the Pfizer/Lyrica case has shown, this is also not without risks of challenge.

1.3 Competitor Products

A drug approval is a very specific licence that is granted to a company to manufacture and sell a medicine as a specific formulation, defined dose, to treat one or more conditions (medical indications) and in specified patient groups (i.e. suffering from the condition and meeting defined criteria – for example newly diagnosed or as second-line treatment). A company that is granted the licence is called a marketing authorisation holder (MAH) in Europe, or a new drug application (NDA) in the US. Other companies can apply for approval to produce the same drug in the same indication after exclusivity periods have ended – in such cases we differentiate between the Originator or Reference product and a generic, or biosimilar for biologics, also referred to as competitor products. Note also that these approvals are not perpetual and must be renewed after a period of five years – in the US the renewals occur every five years, in the EU after the first 5-year renewal no further renewals are required unless specifically requested by the EMA.

The existence of competitor products introduces an element of competition in the supply of a drug – which often leads to a reduction in the price,

particularly for products where there are multiple producers. This is the case with many commonly prescribed drugs such as statins, analgesics, anti-diabetic medicines, antihistamines etc. However, there are also many examples of drugs which have been outside of the marketing exclusivity periods for a number of years but with no competitor products – for example sirolimus/rapamycin (Pfizer).

The lack of competitor products has two important consequences. The first is that without price competition the system can be ‘gamed’ – for example the US entrepreneur Martin Shkreli became the MAH for the anti-parasitic drug daraprim and raised the price by over 5000%. While extreme, this is not the only such case. More pertinent to the repurposing field, this lack of competitor products means that the repurposing of drugs such as sirolimus is more akin to repurposing drugs that are within the marketing exclusivity period than to the repurposing of generic drugs that are outside of the marketing exclusivity. **In effect there are three classes of approved drugs from the oncological repurposing perspective:**

Table 2. Classes of drug by marketing exclusivity/competitor products in oncology

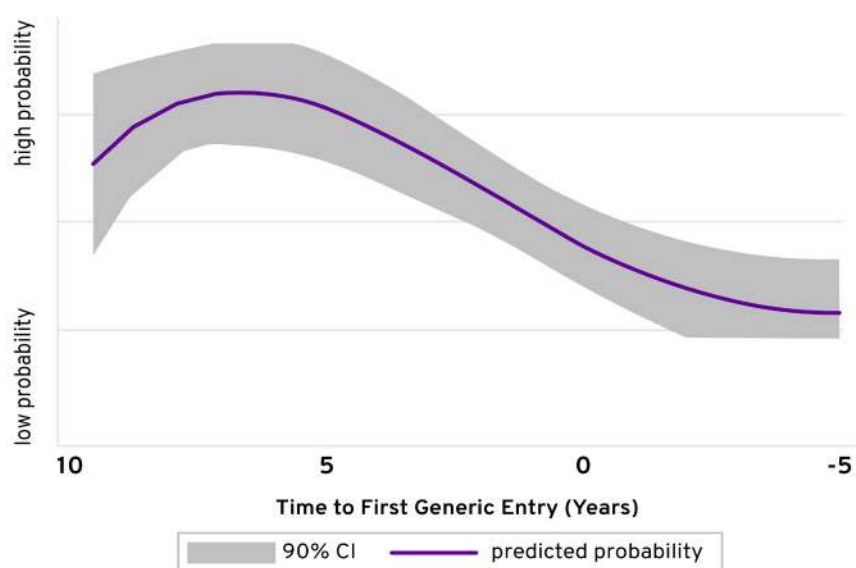
Class	Marketing Exclusivity	Competitor Products	Examples
1	Yes	No	Check-point inhibitors, newly approved targeted therapies
2	No	No	Auranofin, thalidomide
3	No	Yes	Most NSAIDs, ‘classical’ chemotherapy drugs

We will refer to these different classes of agents again later in this report.

The existence of competitor products also impacts drug repurposing activity by the originator company. Analysis of EMA-approved label extensions by Langedijk and colleagues found that the vast majority (92.5%) of approvals occurred within the marketing exclusivity period, and that

subsequent approvals declined rapidly after the granting of approval to the first competitor product [11] Sahragardjoonegani, and colleagues found a similar story based on FDA approvals [12], as shown in Figure 2. This does not mean that clinical investigation of repurposing opportunities ceased, but that the interests of the originator company in pursuing label extensions changed several years before competitor products arrived on the market.

Figure 2. Probability of approval for a new indication vs time of generic entry. From [12].



It should be noted that drugs which are often referred to as ‘me-too’ drugs are not competitor products. **‘Me-too’ drugs are defined as new drugs in an existing class of drug.** For example, new anti-PD(L)1 check-point inhibitors. This is a widely used class of anticancer onco-immunotherapy drugs with many products from different companies already approved for a range of cancer indications. However, companies are still attempting to bring new drugs in this class to market. A ‘me-too’ drug is

contrasted with a ‘first-in-class’ drug, which is a new drug using a novel mechanism of action that has not been previously used in an approved drug. As both ‘me-too’ and ‘first-in-class’ drugs are new drugs, they are not competitor products per se. From a repurposing perspective, ‘me-too’ drugs are often looking for novel indications as the other drugs in that class may already have the approvals in place for the more common cancers.

1.4 Current On-patent Repurposing Activity in Oncology

The ReDO_Trials DB is a database of active drug repurposing trials developed and maintained by the Anticancer Fund [13]. It records active, or recently active, clinical trials of non-cancer drugs which are being clinically investigated as potential cancer treatments rather than as cancer prevention agents or for symptomatic relief. The selection of drugs comes from another Anticancer Fund database, the repurposing drugs in oncology database (ReDO_DB) [14]. This database includes information on the patent status of the drugs included in it, therefore making it possible to select the subset of trials which include investigative agents which are on-patent/within marketing exclusivity.

As of the last release of the database (13/09/2023), the database contains 1,096 trials,

of which 947 are currently active (i.e. recruiting, preparing to recruit, no longer recruiting but in active follow-up). Of the 1,096 trials, only 73 (6.7%) have a company as sponsor, the vast majority are sponsored by academic or clinical institutions. Of the 371 drugs included in ReDO_DB, 190 (51.2%) are included in trials in the ReDO_Trials DB, and of these 190 drugs only 9 (4.7%) are within the marketing exclusivity period or do not have a competitor product. These 9 drugs are included in 49 trials, representing 4.5% of trials in the database.

For the repurposing of approved cancer medications for new indications, recently approved cancer drugs were selected from the CancerDrugs_DB, a global database of licensed cancer medicines developed

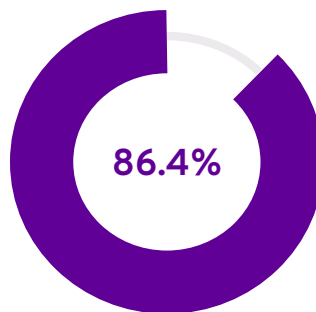
and curated by the Anticancer Fund [15]. Drugs which have been approved within the last eight years were selected as they would still be within the marketing exclusivity period in Europe and the US. Taking approvals from 2015 to 2023, 106

drugs were selected that are single API products approved for one or more cancer applications by the FDA, EMA or a national medicines regulator. The ClinicalTrials.gov was queried for active trials for each of these 106 drugs, producing a dataset



1096

number of all the **trials** included in the database

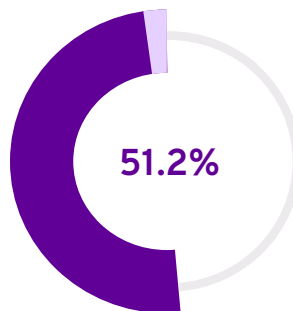


active trials (947) included in the ReDO database



371

number of all **drugs** included in the database



drugs included in trials database (190) of which only **4.7%** (9) are within the exclusivity period

therefore

9

drugs within the exclusivity period are included in

49

(4.5%) of all the trials in the database

of 5,250 trials that are currently active (open for recruitment, preparing to open, in follow-up). A preliminary analysis of these 5250 trials showed that 2151 (41%) did not list any industry funding.

Only 8 of the 106 drugs were not included in at least one non-industry funded trial. In terms of phases, of the non-industry funded trials, 226 were Phase 2/3 or Phase 3, covering 41 drugs.

1.5 Examples of ‘Blocked’ On-patent Repurposing

Below we present three examples of repurposing opportunities which are well-supported with evidence but where the existing MAH has chosen not to support or explore such development. The examples discussed include drugs in classes 1 and 2 of Table 2.

Alveolar soft-part sarcoma (ASPS)

ASPS is an ultra-rare soft tissue sarcoma, with an incidence of around 60 newly diagnosed patients in the EU annually. It mainly affects young people, with a peak incidence between 15 – 35 years, and has a high rate of metastases, with 43% of patients being metastatic at diagnosis [16]. The 5-year survival rate for patients with metastatic ASPS is 27%. Standard treatment of localised ASPS is surgery +/- radiotherapy, but for patients with advanced or metastatic disease systemic therapy is required. Currently there are no medicines in Europe specifically approved for ASPS and patients are most often treated with ‘classical’ chemotherapy approved for soft tissue sarcomas in general, despite a lack of activity in ASPS.

Two newer classes of drugs have shown evidence of activity in ASPS in recent year. The first are antiangiogenic multi-kinase inhibitors, with evidence from two small clinical trials, one of them randomised, showing convincing evidence that cediranib was active and associated with improved response rates and disease control rates [17,18]. Despite these positive signals AstraZeneca, which has yet to succeed in getting approval for cediranib in any indication, has not moved forward to seek approval for this indication. Instead, the company is continuing to explore other more common cancer indications.

The second class of drugs that has shown substantial activity in ASPS are anti-PD-(L)1 immune checkpoint inhibitors (ICI). The evidence comes from seven clinical trials, some including some mixed tumour type trials that recruited ASPS patients, and some from ASPS-only. Interventions

included single-agent ICIs or combinations that included an ICI (pembrolizumab, nivolumab, durvalumab, geptanolimab or atezolizumab). Summarising the data from the seven trials showed a response rate of 34% (48 of 142 patients). In December 2022, the anti-PD-L1 drug atezolizumab was approved by the FDA for the treatment of adult and paediatric patients 2 years of age and older with unresectable or metastatic ASPS. However, in Europe there is still no approved treatment. European investigators have approached MSD, owner of pembrolizumab, with a view to getting support for a registration trial but have been turned down, in part due to ‘strategic and business factors which are confidential and therefore would not be discussed outside the company’ (personal communication).

Angiosarcoma

Angiosarcoma is another rare soft-tissue sarcoma in need of new treatment options. Current systemic treatments are based on high-dose chemotherapy, either with anthracyclines or taxanes. A meta-analysis of results from 11 clinical trials showed that in advanced or metastatic angiosarcoma, treatment with anthracyclines had a 25% response rate, with median progression-free survival (PFS) of 4.9 months and median overall survival (OS) of 9.9 months [19].

A retrospective study of 25 angiosarcoma patients, 72% of them metastatic, treated with single agent pembrolizumab showed a response rate of 18%, with a median PFS of 6.2 months and median OS of 72.6 months [20]. This clearly warrants further clinical investigation. A proposal for a clinical study that combined pembrolizumab with another drug to treat angiosarcoma was made to MSD in 2021. But the company refused to support the trial, refusing even to supply the drug to the trial. Again, the repurposing of pembrolizumab for a rare cancer in which it has shown activity does not conform to the strategic plans of the company.



Example – outside market protection but no competitor product- Sirolimus for Epithelioid Hemangioendothelioma (EHE)

Another rare sarcoma, EHE is characterised by a tumour-specific fusion gene that uniquely identifies the disease. There are approximately 180 new cases in the EU per year, making this an ultra-rare sarcoma. More than 50% of patients present with metastatic disease, mostly involving lung, liver, and bone and in such cases palliative systemic treatment is the only option.

For reasons that are only now being elucidated, treatment with sirolimus (rapamycin) appears to be an effective treatment in slowing progression in the disease. Data comes from several retrospective studies which have shown that the drug is capable of producing enduring stable disease in patients who are progressing [21,22]. However, because the drug is not approved for EHE many patients continue to be treated with high-dose chemotherapy, the

standard treatment for soft-tissue sarcoma, despite these drugs having little evidence of efficacy [23]. The use of sirolimus is supported by an international consensus statement from clinicians, organised under the auspices of ESMO [24].

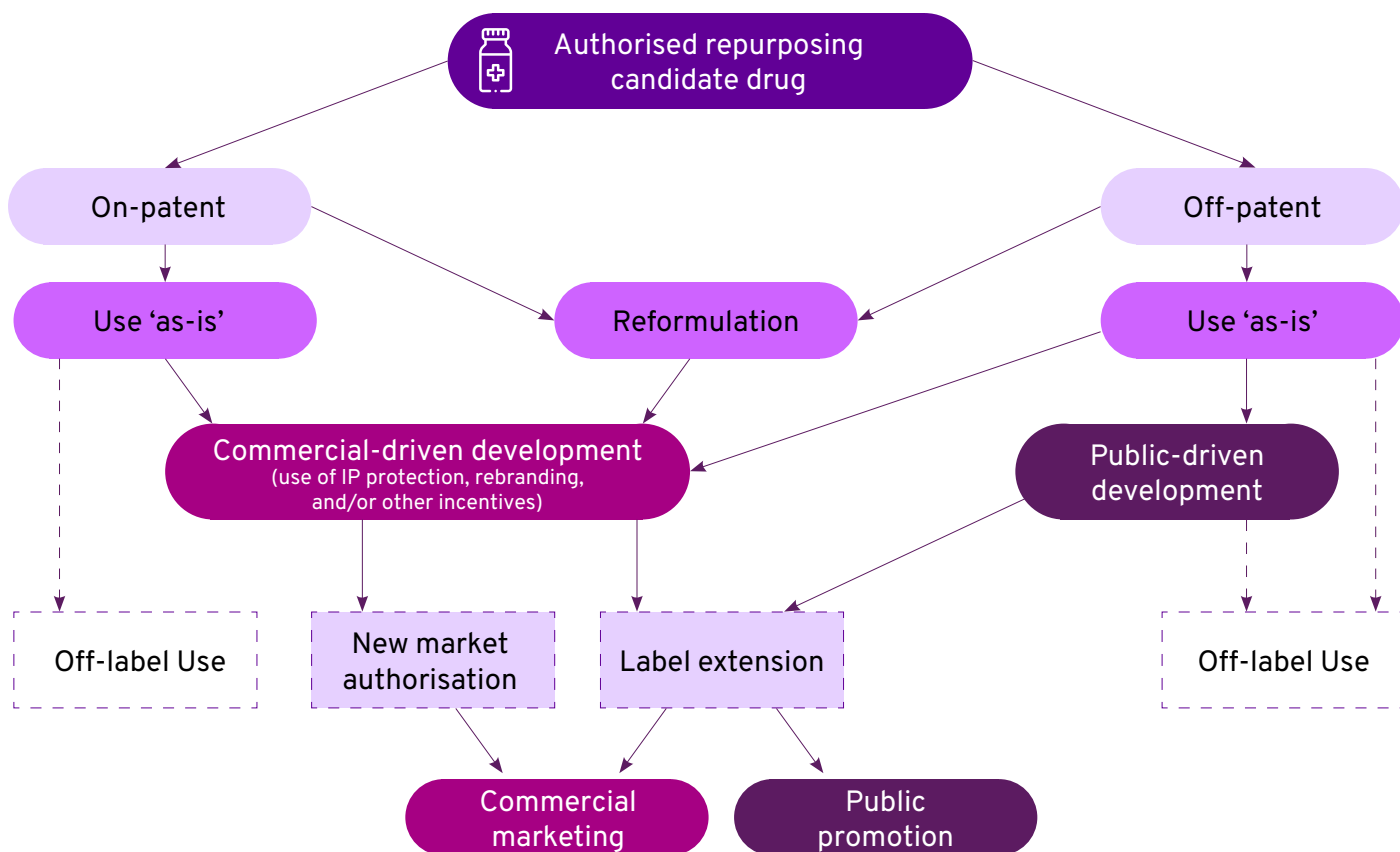
While sirolimus is outside of the marketing exclusivity and patent protection periods, the drug lacks competitor products, and although there are other drugs in the same class, Pfizer remains the sole MAH for sirolimus. Pfizer has also shown no interest in seeking marketing approval for EHE, despite the fact that there are currently no other drugs specifically approved for the disease. This means that access to the drug is via off-label prescribing only, leading to disparities of access across Europe and indeed even within countries.

2. Reaching Patients

There are a number of possible pathways available to follow for getting repurposed drugs to patients, as illustrated in [25]. In general, for drugs outside of the marketing exclusivity periods the path outlined

on the right-hand side in Figure 3 is normally operative, less well explored from a not-for-profit perspective is the path on the left-hand side. This is described further below.

Figure 3. Pathways for the development of repurposed drugs. Adapted from [25].



2.1 Label Extension Pathways

On-label use is the preferred route to getting drug treatments to patients. It avoids the issues previously listed, and therefore can help to equalise access to treatments for many patients. The process of adding a new indication to an approved drug is termed a label extension. This can include changes relating to safety issues, dosing instructions or the addition of a new medical indication for a drug.

In the EU/UK an extension of indication is technically called a type II variation of a marketing authorisation – and currently only an existing marketing authorisation holder is able to apply. In the case of medicines outside the marketing exclusivity period, then any of the MAHs for the drug may apply. When a drug is still within the marketing exclusivity period it is entirely the

decision of the originator of the drug to take it forward for a label extension. In the US there are two main routes to adding a new indication. Within the marketing exclusivity period the originator company is able to file a supplementary New Drug Application (sNDA). Outside the exclusivity period competitor companies can file for a 505(B)(2) NDA.

It should be noted that a label extension may be required even for a variation in the use of the drug in a disease for which it has already been approved. For example, a drug that is approved for 2nd line treatment of a particular cancer may require a label extension for it to be approved as a 1st line therapy in newly diagnosed patients.

In all cases, whether it is the originator or a competitor seeking approval for a new indication, the regulators require evidence of safety and efficacy for the target population in the new indication. Safety data may come from the original registration studies, though this may have to be supplemented with additional data in the new indication, particularly if the dosing differs from the originator studies.

Efficacy data would normally come from new clinical studies of a scale and type that would be used to show efficacy in a new drug for that indication – there is no relaxing of the rules because the drug has already been approved in a different disease.

A key question, therefore, is where this new data comes from. In many respects the simplest option is for the company to invest in new studies to answer the efficacy and safety questions that arise from using their medicine in a new disease. However, given the complex development lifecycle and the remaining period of marketing exclusivity and the market landscape in terms of competitor or potential competitor products, such a decision

is not necessarily straightforward. For each drug in its portfolio a company will have mapped out a development strategy that aims to maximise the return on investment, often including the gaining of approvals within the marketing exclusivity period. Typically, once a drug has been approved in one indication in oncology the development focus will shift to gaining other approvals in related cancers or in different settings within the same cancer. Factors that influence such decisions include existing results generated in those cancers prior to approval in the first indication, for example the drug may have been trialled in a range of cancers prior to approval in the first cancer indication. Other factors include disease prevalence, existing standard of care treatments, developments by other companies for that indication, specific marketing incentives that target the new indication and so on.

For other actors seeking to repurpose a drug for a new indication that is not included in the company's development strategy, cooperation with the company is one of the most important issues to resolve under current pharmaceutical legislation. From a company perspective, the new indication may not be attractive in terms of potential returns on investment. Even if a 3rd party actor, such as a not-for-profit foundation or academic/clinical institution, generates the data showing efficacy in the new indication, it is still the company who must file for the label extension. This means the company must incorporate the data from the 3rd party clinical studies with its own dataset and documentation, even when it has had no influence or involvement in the design or implementation of the new studies.

This is not an insurmountable obstacle, and a number of strategies have been used in the past to address the issue:



A

The company decides to run its own confirmatory trials in the new indication, effectively de-risking the development by waiting to see the results of the 3rd party studies first. For example, Roche, the MAH for rituximab performed a confirmatory trial for a new indication (for the treatment of adult patients with moderate to severe pemphigus vulgaris), following a successful trial by an independent academic group (led by Rouen University Hospital, France) [26].



B

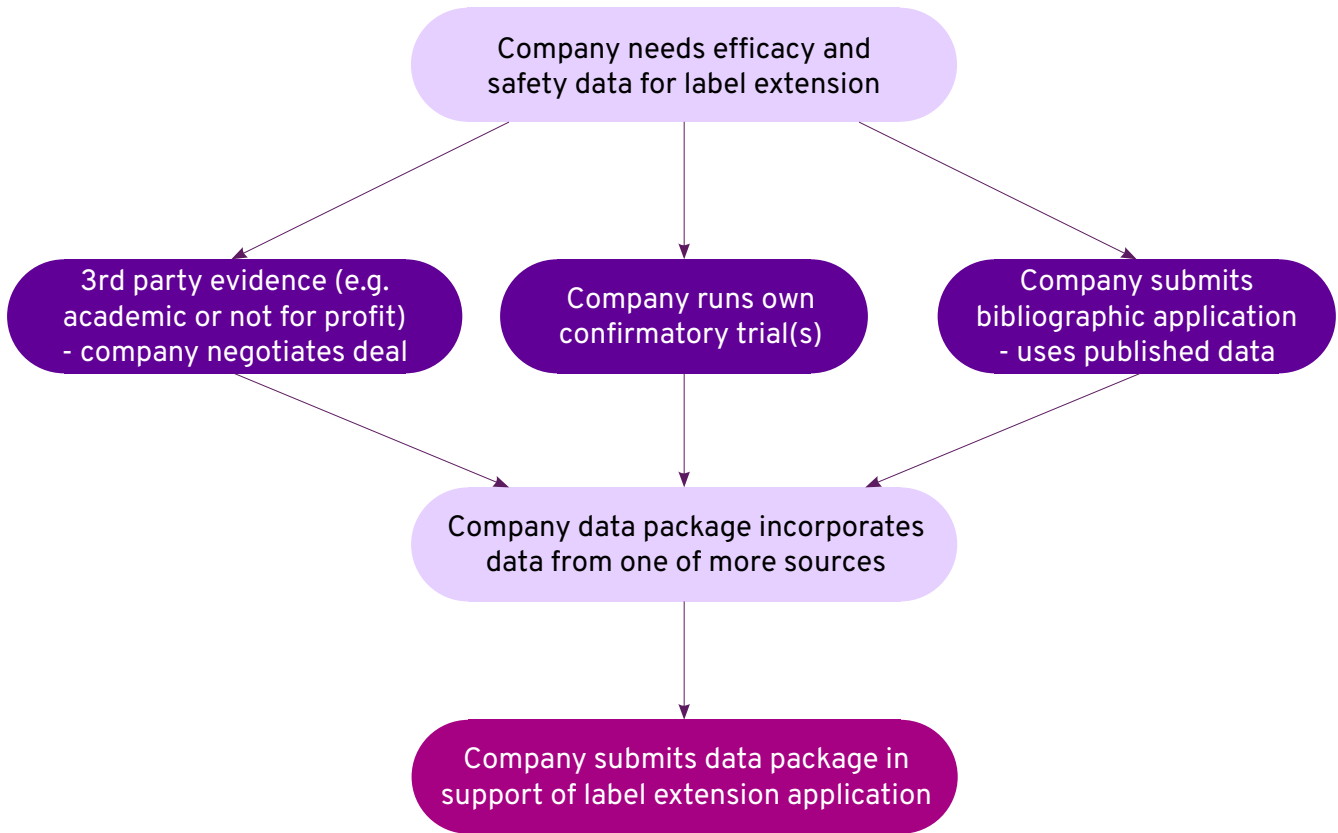
The company negotiates a deal prior to the 3rd party trial to incorporate the resulting data into the dossier for a future label extension application. For example, in the UK the National Institute of Health Research (NIHR), a major public funder, will only run Phase 3 randomised controlled trials using drugs still under marketing exclusivity if a deal is negotiated agreeing a price reduction of the drug for the NHS should the company succeed in gaining the new indication (confirmed in a personal communication with the NIHR, 29/03/23). In the case of the new indication for rituximab, mentioned previously, Roche used the data from the academic trial for the label extension application. The company had played no role in study design, study conduct, data collection, or publication of the results. The academic sponsor transferred all the database and supporting documents to Roche after the study had been completed and database lock had occurred [26].



C

The company can use a bibliographic approach and submit published data in support of a new indication. The data must be of a sufficient depth and breadth to satisfy the evidentiary demands of the regulator, but from the perspective of the MAH this is an approach that does not necessarily involve direct contact with the 3rd parties who have generated the data. For example, Teva, MAH for arsenic trioxide, used a bibliographic approach for the extension of the indication for arsenic trioxide in combination with all trans-retinoic acid for first line treatment of acute promyelocytic leukaemia [27].

Figure 4. Data sources in support of label extension.



Note that the above, illustrated in Figure 4, are not mutually exclusive, and a company may adopt more than one of the options when pursuing a label extension.

From the perspective of a drug repurposing funder the issues around data apply regardless of whether the drug is within the marketing exclusivity period or not. The data showing efficacy has to be produced in either case. However, in terms of seeking a financial return for the investment a repurposing funder may find that there is greater potential to negotiate a deal when there is only

one marketing authorisation holder in place (i.e. for drugs in class 1 or 2, as defined previously).

Another factor that may influence commercial considerations when a company assesses a possible repurposing application is the cost associated with the label extension process. While these costs are lower than the costs associated with generating new data supporting a label extension – particularly compared to the costs of clinical trials – the costs may still be significant. The costs are both direct and indirect:



Direct **costs for the application to the regulator**. For example, the application cost in the EMA is €103,800, with an annual maintenance fee of €123,900. Renewal fees are €17,000 per medicinal form (e.g. strength of tablet) included in the renewal. (All fees as of 01/04/23)



Costs with any associated **scientific advice (SA) sessions**. These costs include the direct costs of the SA application to the regulator and the associated indirect costs. These indirect costs include the personnel costs associated with producing the briefing documents for the advice session. The briefing document is a scientific document summarising data related to a set of scientific and/or regulatory questions. In the context of a label extension such questions could relate to questions on the design of supporting trials, potential end-points, assessment of safety data or the use of pre-clinical data. The direct cost of the SA application at the EMA is €51,800 to €103,800 (01/04/23). Medicines for Europe, a trade body for the generics industry in Europe, quotes costs in the range of €90,000 to €180,000, and further note that 50% of such meetings require a follow-up meeting [28].



A major part of the costs associated with a label extension application is the preparation of the **data dossier**. The creation of these supporting documents is not a trivial task and requires regulatory expertise, scientific training, and will involve multiple authors. Medicines for Europe quotes costs of €30,000 to €120,000 [28].



Additional **pharmacovigilance costs**. These include costs incurred by the company internally, and in direct fees to the regulator. Pharmacovigilance costs to the EMA are complex and depend on the number of forms of the product (i.e. number of different strengths and type of format [tablet, syrup, injectable etc]), the number of different countries in which the drug is marketed and the number of different active ingredients (drugs) in the product. Medicines for Europe lists costs in the range €20,000 to €100,000, and additional costs for the development of educational and other materials of up to €100,000.



Costs for the update of **product information leaflet** and other product documentation of €20,000 to €90,000, with additional costs of €12,000 per translation needed.



Additional **consultancy costs** incurred in pursuit of the above activities.



Current public initiatives to address label extension obstacles.

England/NHS Drug Repurposing Program: the program is looking for repurposed use outside current license (new indication, dose, formulation), evidence of safety & efficacy (ideally phase II trial), as good or better than standard care, support from patients or clinicians, not already widely used and has UK or GB license for human use. If an unmet need is addressed, a clinical benefit is covered and has value for money then the proposed candidate gets prioritized and can enter the program. The drug candidates may be proposed by stakeholders, including patient and not-for-profit organisations, or NHS England clinical advice networks or could be identified internally when searching clinical trials nearing completion. [SOURCE: Opportunities to repurpose medicines in the NHS in England, recommendations of the medicines repurposing program board 2019/20 and proposed forward work program 2020/21-2022/23]

US/ FDA Project Renewal: this is a pilot program of the FDA Oncology Center of Excellence and leverages expertise from the clinical and scientific oncology communities to review published literature and generate a drug-specific product report summarizing data that may support updates to FDA-approved product labelling. The intent is to standardize this strategy to result in a transparent and consistent approach to update the product labelling of older marketed, off-patent drug products based on current scientific knowledge. Project Renewal has released an updated label for capecitabine that includes new and revised indications. [SOURCE: Kluetz et al., Clin Cancer Res 2021;27:916-21]

EU/ STAMP-RepOG Drug Repurposing pilot: Following the discussions at the EU Commission Expert Group on Safe and Timely Access to Medicines for Patients (STAMP) a Repurposing Observatory Group (RepOG) was established to define and test the practical aspects of a pilot project thought to provide support to not-for-profit organizations generating or gathering data for a new therapeutic use for an authorized medicine. The projects that meet the entry criteria will be able to ask for scientific advice (SA) from the Agency, after which they can assemble advised data and reach out to MAH, assuring them that the data quality is in compliance with the SA obtained, allowing the MAH to submit a type II variation in order to add the additional indication on the product label. The Anticancer Fund is working with clinicians on two of the selected projects in the pilot program. The pilot is limited to medicines out of intellectual property, data or marketing protection. [SOURCE: Asker-Hagelberg et al., Front. Med. 2022; 8:817663]

Ongoing assessment of EU Pharma Package (EU Commission's proposal REG & DIR dated 26 Apr 2023) including art 48 in REG: Scientific submission on data submitted from not-for-profit entities for repurposing of authorized medicinal products. This article allows not-for-profit entities to submit, to the Agency (EMA) or to a Competent Authority of a Member State, (non-)clinical evidence for a new therapeutic indication that is expected to fulfil an unmet medical need. The Agency may make a scientific evaluation, based on all available evidence, of the benefit/risk of the use of a medicinal product with a new indication. The Agency's opinion shall be made publicly available and the MAH shall, if the opinion is favourable, submit a variation to update the Product Information Leaflet (PiL). It remains to be seen if this article, which currently does not limit itself to off-patent medicines, will be adopted as such in the final pharma legislation or whether it will be changed/deleted during the negotiations at EU Parliament & Council level. Nevertheless, it is the first step in the direction of allowing 3rd parties to proceed with label extension without MAHs' involvement. [SOURCE: draft EU pharmaceutical legislation dated 26 Apr 2023]

2.2 Off-label Usage

The drug label describes which medical indications a drug has been approved for, as well as dosing instructions, safety notices and other information relevant to the use of the drug. When a drug is used according to the label it is said to be an 'on-label' use. However, many drugs are also used outside of the labelled use – most notably when a drug is used to treat a condition that is not listed on the label, i.e. 'off-label' use.

Some degree of off-label use is legal in most jurisdictions – generally a doctor is allowed to prescribe whatever treatment he or she believes will benefit the patient. However, there are a number of issues relating to off-label use such that regulators and others tend to discourage this route for getting medicines to patients. Specific issues include:

1

Increased legal liability for the prescribing physician – often it is a personal decision by a physician to prescribe off-label.

2

Lack of data collection – much off-label prescribing is opaque and data collection on outcomes (positive and negative) is not collected.

3

Disparities in patient access to off-label prescriptions – because physicians vary in their use of off-label drugs, some patients who might benefit are not able to access treatment from their doctors.

4

Some older drugs disappear from the market as newer medicines are used for the original indication – which means the drugs also disappear as potential off-label treatments.

5

Problems with reimbursements – payers may not be willing to pay for drugs that are used off-label.

Off-label use can be attractive from a company perspective – it means that their products are used without having to incur the expense of registration clinical studies or engaging with regulators to seek approval for the new indication. To this end

regulators actively police this activity, and there have been numerous cases of pharmaceutical companies receiving heavy fines for promoting the off-label use of their products [29].



Other Routes to Implementation

In general, we have focused on the licensing route as the optimal path to providing access to drugs in repurposed indications. However, there are also some alternative routes that can be viewed as ‘official’ off-label implementation. These routes do not involve label extension and are often specific to one health system or country rather than being accessible at a European level. Two case studies illustrate the potential of these routes, and also the limitations.

Sorafenib for FLT3-ITD AML

Bayer is the originator for sorafenib (Nexavar), which has marketing authorisation for a number of cancer indications including advanced renal cell carcinoma, hepatocellular carcinoma and advanced thyroid cancer. While it is available as a generic in some countries it has been the subject of patent litigation in the US (Bayer vs Mylan). Data from two randomised controlled clinical trials, which were completed while the drug was still within the exclusivity period, have shown that the drug can reduce the risk of relapse and death in a molecularly defined subset of Acute Myeloid Leukemia patients.

The placebo-controlled Phase II SORMAIN trial, funded by Bayer, showed that in patients with FLT3-ITD-positive AML, in remission after stem cell transplant, and treated with sorafenib as maintenance for 24-months the hazard ratio for relapse or death in the sorafenib versus placebo group was 0.39 (95% confidence interval 0.18 to 0.85). The estimated probability of relapse-free survival to 24 months was 85.0% in the sorafenib group and 53.3% in the placebo group [30]. The open-label trial by Xuan and colleagues, NCT02474290, recruited people with FLT3-ITD-positive AML in ‘composite complete’ remission after allogeneic hematopoietic stem cell transplantation. Participants were randomly assigned to receive either sorafenib (n=100) or no sorafenib (n=102) until day 180 post-transplantation. The primary outcome was relapse. The 1-year cumulative incidence of relapse was 7.0% (95% CI 3.1–13.1) in the sorafenib group and 24.5% (16.6–33.2) in the control group (hazard ratio 0.25, 95% CI 0.11–0.57) [31].

Despite these positive results, confirmed in long-term follow-up [32], in a cancer with poor prognosis following post-transplant relapse, the new indication has not been added to sorafenib and Bayer, despite supporting the SORMAIN trial, has not been supportive of label extension.

However, the US National Comprehensive Cancer Network (NCCN) guidelines have an open policy which allows third parties, including not-for-profit organisations outside of the US, to apply to have new treatments added to the guidelines. The Anticancer Fund applied to have sorafenib maintenance added to the AML guidelines. After review by the NCCN AML panel sorafenib was added to the guidelines, thereby unlocking access to the drug for many FLT3-ITD-positive AML patients in the US. It has also been added to German national treatment guidelines and therefore been made available to patients in Germany, but unfortunately the drug remains off-label and in many parts of Europe this means the drug is not accessible to patients who may benefit from it.

Pembrolizumab for drug resistant gestational trophoblastic neoplasia

Gestational Trophoblastic Neoplasia (GTN) is a rare group of pregnancy-related cancers that derive from the placenta. Standard treatment is single-agent chemotherapy, and most patients respond, however, there are a small number of patients with resistance disease who



require high-dose multi-agent chemotherapy with consequent toxicity and safety issues. Because placental tissue carries DNA from the father it should be attacked by the mother's immune system, but during pregnancy the immune response is disarmed by an immune checkpoint called PD-L1 that binds to an immune cell receptor called PD-1. This is the same mechanism that some cancers use to evade the immune system and which is blocked by immune checkpoint inhibitors.

A small number of cases have shown that pembrolizumab can induce prolonged remissions in patients with GTN otherwise expected to die. This is an ultra-rare population and there is no prospect of Merck seeking a label extension. There is a current small clinical trial assessing the treatment prospectively, but this is not supported by the company.

Given the dismal prognosis the NHS England implemented an 'Urgent Clinical Commissioning Policy Statement' on the issue. This is a mechanism that authorises the use, and reimbursement, of a medicine by specialist services within the NHS for patients and meeting strictly defined clinical criteria. In this case as third line treatment following standard regimes for GTN patients assessed as high risk. This is effectively an officially sanctioned off-label use of a drug in a rare disease setting.

Conclusion

These illustrative examples show that there are mechanisms which can be used to implement repurposed medicines into clinical use outside of the terms of the marketing authorisation, the label and indeed without the support of the marketing authorisation holder. However, these mechanisms are specific to one country and/or health system, apply to well-defined patient populations and are difficult to build into a drug development plan.

While off-label use is not an optimal solution, there are circumstances when it is a good option for repurposing. Specifically, in the cases of ultra-rare diseases where patients are treated in a specialist reference centre by a relatively small number of expert clinicians, then off-label use is a good solution if there is consensus amongst the experts. In such cases all patients will be able to access the drug. In paediatric oncology, many standard of care drugs that are in routine use are off-label as the drugs do not have paediatric approvals [33]. However, while this is a pragmatic solution to the problem of accessing treatments for paediatric patients, ultimately more steps need to be taken to develop drugs or drug formulations that are age-appropriate [34].

In the US, off-label use of drugs in oncology may also be a good compromise solution if the drug is included in NCCN treatment guidelines. In such

cases inclusion in the guidelines is sufficient for many insurance companies to agree to reimburse the drug – again, with the consequence that patients are able to access the drug.

However, in Europe the status of treatment guidelines, including the European Society for Medical Oncology (ESMO) guidelines, is not enough to unlock access to treatments in most cases. For example, a panel of ESMO experts assessed the use of 17 generic cancer medicines that are widely used off-label [35]. In addition to confirming the high-level evidence supporting the use of these drugs off-label, 51% of the panel had to implement a time-consuming process associated with additional workload, in the presence of litigation risks and patient anxiety. Therefore, for the majority of oncological diseases in Europe off-label use is not an optimal solution for drug repurposing.

3. RTFCCR Philanthropic Approach

This landscape analysis has highlighted the lack of funding in the on-patent drug repurposing field. Therefore, philanthropic funds are needed to help close the gap in this space. RTFCCR has decided to consider applications in this area for patient populations with high unmet need. Proposals will be assessed case-by-case, taking into consideration the likelihood of the trial to establish new standards of care.

Clinical trials on both off-patent and on-patent drugs are eligible for RTFCCR funding. In addition to the thorough grant review process, on-patent drug project Letter of Intent (LOI)s will be categorised according to their potential to establish

new standard of care. The RTFCCR team will then utilize decision trees to select applications for next steps. For more information, see: <https://www.risingtide-foundation.org/clinical-cancer-research-therapy-optimization-drug-repurposing/>

The data generated during the trials most likely will be used to support off-label use (evidence for clinicians to prescribe in a new indication) or in a less likely scenario for label extension (if the company is willing to file) – on-label use. RTFCCR believes that the impact it can create, in order to improve patient outcomes, can be highly increased from new treatment options generated through this approach.

4. Summary / Conclusions

This report has outlined the processes governing the licensing of drugs and has described how drugs are approved to treat specific populations of patients with clearly defined medical indications. Drug repurposing seeks to extend these indications to include new conditions which are not included in the approval – a process known as label extension. Off-label use is an alternative option, here patients are treated with drugs even if the conditions they are being treated for are not included in the approval. In most cases this is a sub-optimal method of granting access to drugs for patients who would benefit from them.

Given the complex pharmaceutical market landscape, a company has a limited period in which to gain ROI by being protected from competitor products. There are incentives in place to extend this market exclusivity period by seeking repurposing opportunities, though this must be balanced by the costs incurred in doing so. For many companies, the trajectory of development for a drug is decided even before the first approval and therefore the development of repurposing opportunities outside of those plans is often not supported. Companies may also judge the likelihood of competitor products becoming available when the drug is near the end of the exclusivity period, and also the possibility that other drugs in the same class might be used in the new indication and therefore reduce the chance of a positive ROI from their repurposing investment.

For organisations seeking to fund repurposing projects involving drugs that are still within the marketing exclusivity period, or in which there are no competitor products available, there are many issues at stake. Firstly, assuming the development

is successful, they may still find that the drug does not gain approval for the new indication if the MAH is unwilling to file for a label extension. If the MAH does seek the new approval, the repurposing organisation may find that it has to provide the data to the MAH to be used in the filing of the application. In this case the MAH may benefit financially while the repurposing organisation that invested in the clinical development does not gain a financial return. One option to avoid this predicament is to sign an agreement with the MAH prior to commencing the repurposing study. Health system funders, for example, could reach agreement on drug pricing post-approval, as the UK NIHR has done. An alternative is to seek a financial return directly. Given the possibility that a MAH could use bibliographic data in a label extension application, a repurposing funder may also want to consider what it publishes in terms of the results of its trials in case it inadvertently provides sufficient data so that a MAH bypasses it completely.

The balance between providing benefit to patients with high unmet needs and providing benefit to commercial organisations as a by-product is not an easy one. However, some of the preliminary data presented previously suggests that there are many not-for-profit and academic institutions active in this type of drug repurposing in oncology. Further data analysis could help to identify who those organisations are, how they are cooperating (or not) with pharmaceutical companies and the types of clinical studies they are funding. Such additional would certainly cast more light on an under-studied area and help inform other organisations looking to invest in this area. An outline of possible further analysis is included in the appendix.



Revenue Sharing

Data produced during a clinical trial of a repurposed drug funded by academia, public funders or philanthropic sources may constitute a valuable commercial asset. In the case of drugs that are still within the marketing exclusivity period, such data can be used by the originator company to seek a label extension or a new marketing authorisation, thereby increasing revenue. In such situations it is common for some funders to seek revenue sharing agreements with the originator companies prior to supporting a project.

The aim of these agreements is to find a formula by which the funder can receive payment based on the increased revenue generated by the new indications for the originator company. This payment may take a number of forms:

- A fixed amount based on projected sales of the drug in the new indication
- A royalty-based payment
- Non-payment agreements – for example for public health funders an agreement for fee reductions on the price of the drug

Such revenue sharing agreements are complex, highly confidential and are negotiated on a case-by-case basis. Examples of organisations which have agreed revenue sharing agreements for on-patent drug repurposing include:

- CRUK – Cancer Research UK, a major funder of cancer research
- LifeArc – a large UK repurposing funder
- Cures Within Reach – a small US repurposing funder
- NHS Drug Repurposing Program – UK public health system
- NIHR – National Institute for Health and Care Research – UK public research funder

In the case of the NIHR they have supported on-patent repurposing after agreeing with the originator company that a successful trial will lead to price reductions for the NHS. For the NHS Drug Repurposing program there is a legal requirement to find a revenue sharing formula otherwise their support for a trial may be seen to constitute a contravention of state aid law. Both CRUK and LifeArc have extensive commercial experience on which to draw. LifeArc clearly differentiate between philanthropic studies which they support (i.e. trials with off-patent/generic drugs), and non-philanthropic studies (i.e. new compounds and on-patent/non-generic drugs).

To conclude, there are some examples of funders coming to revenue sharing agreements with originator companies, such examples are usually negotiated by teams with substantial commercial experience in pharma and are normally highly confidential.

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About Us

Rising Tide Foundation for Clinical Cancer Research (RTFCCR)



RTFCCR is a charitable, non-profit organizations established in 2010 in Switzerland. The philanthropic approach is to support the best Phase I to Phase III interventional clinical trials to bring maximum patient benefit in the shortest time possible. RTFCCR would like to establish a new norm in clinical cancer research, where patients are treated as partners, from the creation of research questions to the dissemination of results. The importance and merit of patient involvement in research are widely acknowledged. When patients are involved, everyone benefits, because it ensures clinical and medical research work is performed more effectively and advances the delivery of what patients really need. This can only be achieved based on the collaborative identification and understanding of patients' unmet needs. Receiving patient input throughout the design, implementation, and evaluation of clinical trials helps improve the discovery, development, and evaluation of new treatments.

RTFCCR mission is to promote freedom to improve quality of life everywhere with the vision to be the partner that empowers individuals to live on their own terms.

To do so, three focus areas were developed:

1. **Improved Patients Outcomes** to advance therapeutic approaches that produce the best possible outcome with the least toxicity possible. This focus area also includes effective interventions that support symptom management during and after treatment.
2. **Science of Early Detection and Intervention** supports novel strategies for high impact clinical research in prevention, early detection, and interception of precursors or early cancer.
3. **Advancing Cancer Research in Underserved Areas:** there is a global need for quality research in underserved areas. RTFCCR is piloting a patient-centred clinical cancer research grant-making program.

Anticancer Fund (ACF)



The Anticancer Fund is a non-profit foundation based in Belgium, that operates worldwide. We are a philanthropic organisation dedicated to improving outcomes for people with cancer. We support research and clinical trials that aim to bring improved cancer treatment options to patients. Our work is not motivated by commercial concerns, and we focus on cancers and treatment options that are often neglected by for-profit organisations. The ultimate goal is to ensure that people facing cancer live better and longer lives, and that all avenues to achieving this are explored

As part of our mission, we offer cancer patients free access to My Cancer Navigator, a personalised information service. You can inquire about your disease and treatment, and our experts will provide

you with reliable answers and information so that you can share in the decision-making in your cancer journey. My Cancer Navigator is also available to healthcare professionals who are looking for evidence-based information on cancer treatments.

Beyond our work in cancer research and care, we strive for change. We actively engage with governments and decision-makers, particularly on the European stage, championing policies that prioritize genuine benefits for patients in cancer-related policy, regulation, and legislation.

We don't have business investors or outside groups setting our agenda. Our organisation is funded entirely by donations and private contributions.

