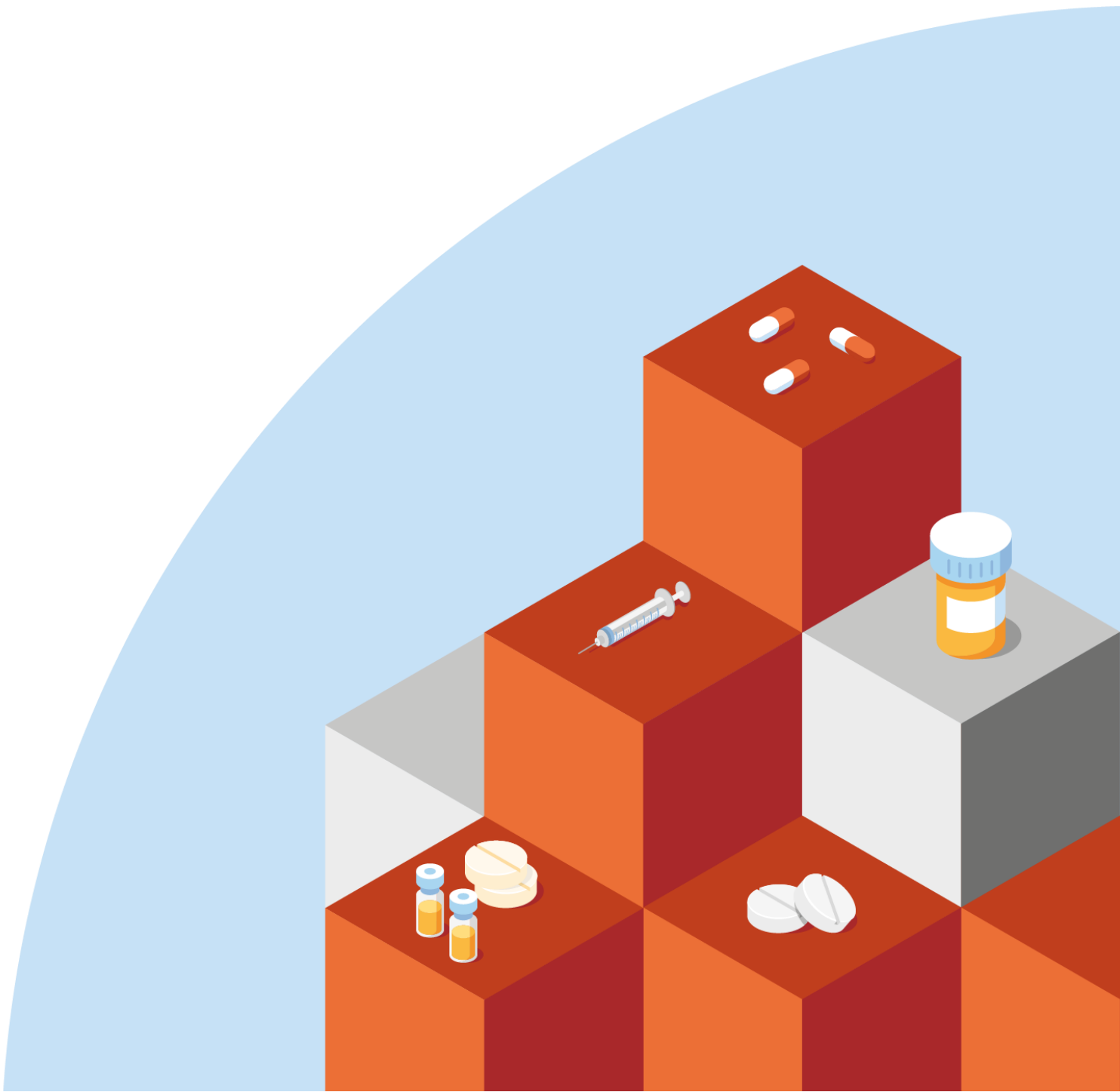
Stimulating Drug Repurposing

Towards a marketing authorisation for novel therapeutic indications of existing medicines



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Abbreviations

In this report, abbreviations are used as follows:

Abbreviation	Meaning
ACM	Authority for Consumers and Markets
ADR	Adverse drug reactions
AI	Artificial Intelligence
ATMP	Advanced-therapy medicinal products
CDCA	Chenodeoxycholic acid
CHMP	Committee for Medicinal Product for Human Use
COVID-19	Coronavirus disease 2019
CP	Centralised procedure
CTX	Cerebrotendinous xanthomatosis
CVD	Cardiovascular disease
DCP	Decentralised procedure
EC	European Commission
EMA	European Medicines Agency
EMVS	European medicines verification system
EPAR	European public assessment report
EU	European Union
FAST	Centre for Future Affordable Sustainable Therapies
FDA	The Food and Drug Administration
FMD	Falsified Medicines Directive
GGG	(programma) Goed Gebruik Geneesmiddelen
GMP	Good manufacturing practice
GVS	Geneesmiddelenvergoedingssysteem (Medicine reimbursement system)
HTA	Health technology assessment
IBD	Inflammatory bowel disease
LoDoCo2	Low-dose colchicine study (2)
MAH	Marketing authorisation holder
MEB	Medicines Evaluation Board (in Dutch: *College ter Beoordeling van Geneesmiddelen [CBG]*)
MRP	Mutual recognition procedure
NDM	Non-dystrophic myotonia
NIH	National Institute of Health

NIHR	National Institute for Health and Care Research
NP	National procedure
PAR	Public assessment report
PASS	Post authorisation safety study
PPPY	Per patient per year
PRAC	Pharmacovigilance risk assessment committee
PSUR	Periodic safety update reports
PUMA	Paediatric-use marketing authorisation
R&D	Research & development
RMP	Risk management plan
RWE	Real-world evidence
SmPC	Summary of product characteristic
SPC	Supplementary protection certificate
WGP	Wet geneesmiddelenprijzen (Medicines Prices Act)
ZIN	Zorginstituut Nederland (Dutch National Health Care Institute)

Executive summary

English summary

This report, which builds upon the insights from the earlier quick scan 'Stimulating Drug Rediscovery' (2012), provides an overview of the barriers to drug repurposing, along with a set of recommendations to potentially overcome them. Moreover, opportunities and challenges for drug repurposing in a pandemic and for paediatric applications are identified. The findings in this report are based on a review of relevant literature, interviews with key experts on medicine development and regulatory science, a survey among principal investigators of ZonMw GGG projects on drug repurposing, discussions of multiple drug repurposing cases and knowledge and experience of the authors.

The first chapters cover a number of areas which are important for a correct understanding of the problems, such as an outline of the regulation of medicines (Chapter 3), an exploration into the concept of drug repurposing (Chapter 4) and the legal and practical aspects of patents and regulatory protection of innovation (Chapter 5). The essence of the report can be found in Chapters 6, 7 and 8, in which the identified barriers and recommendations are discussed, as well as opportunities and challenges for drug repurposing in a pandemic and for paediatric applications.

Barriers

Chapter 6 contains an overview of the barriers to drug repurposing referred to by the literature, experts and our survey. The barriers are organised into five categories, roughly aligning with the stages of development for (repurposed) medicines, reflecting the specific barriers encountered at each stage: barriers associated with research & development, barriers associated with obtaining a marketing authorisation, barriers associated with market protection, barriers associated with pricing and reimbursement and other barriers.

Most barriers for product developers centre around (the lack of) an adequate business case. This prospect depends on a large number of factors, such as the costs and complexities related to research and development, as well as obtaining a marketing authorisation, the potential and certainty to obtain (effective) protection from competition, receiving adequate pricing and reimbursement and resources needed to comply with post-marketing obligations. Specific barriers in the context of academic institutions are also observed, such as limited regulatory expertise and the lack of an incentive or ambition to submit a marketing authorisation application. Many of these barriers were also identified in the seven drug repurposing cases discussed in Annex 1.

Recommendations

Chapter 7 contains an overview of recommendations on how to overcome the identified barriers and stimulate drug repurposing. The recommendations are organised into four categories.

Most recommendations revolve around reducing investments and increasing return on investment with adequate certainty for product developers. Key recommendations include granting sufficient exclusivity post-authorisation, limiting off-label use, cross-label use and pharmacy compounding, making better use of real-world evidence (RWE) in marketing authorisation dossiers, offering exemptions or reductions in regulatory process fees, and providing repurposed medicines with a privileged position in reimbursement systems. Beyond regulatory and legal incentives, drug repurposing can be further stimulated by facilitating collaborations among stakeholders and optimising existing national and international collaboration platforms to adopt a more global

outlook. For academic institutions, transitioning from an applicant-driven system to an evidence-driven system could offer further advantages.

Several of these recommendations require further research to assess their practicality and potential impacts. For example, further studies are needed to (1) evaluate the feasibility of integrating and relying on RWE in application dossiers for a marketing authorisation, and (2) evaluate the appropriate duration and form of protection (market and/or data exclusivity) that would ensure sufficient return on investment certainty for companies. Additionally, a careful assessment of the proposed amendments to the applicant-driven system in the new EU pharmaceutical legislation is needed. Moreover, regarding academic institutions, it is essential to conduct further research to understand the reasons why researchers may not always aim to obtain a marketing authorisation, and to develop strategies that could stimulate them to do so.

Pandemic preparedness and paediatric application

Chapter 8 discusses identified opportunities and challenges for drug repurposing in a pandemic and for paediatric applications. The COVID-19 pandemic showed the huge potential of drug repurposing for accelerating the drug development process for bringing effective treatments to patients. Many investments were made to encourage research for new treatments, with the vast majority focusing on drug repurposing of existing medicines (both patented and unpatented medicine). However, in order to maximise the potential of drug repurposing in a pandemic and to ensure sustainability and transparency of open research initiatives, more international collaborations are needed.

Drug repurposing also showed tremendous potential for developing new applications of existing treatments for children with unmet medical needs. However, paediatric drug development still faces many challenges. Public research initiatives play a key role in developing new methodologies for evidence generation in children. At the same time, marketing authorisation holders could be further encouraged to collect information on the appropriate use of existing medicines in children. While challenges persist in developing paediatric formulations for medicines, drug repurposing shows that it can provide a promising avenue for addressing unmet medical needs in children.

Nederlandse samenvatting

Dit rapport, dat voortbouwt op de inzichten van de eerdere quick-scan 'Stimulering van Drug Rediscovery' (2012), biedt een overzicht van de barrières bij drug repurposing, samen met een reeks aanbevelingen om deze mogelijk aan te pakken. Bovendien zijn kansen en uitdagingen voor drug repurposing in een pandemie en voor pediatrische toepassingen geïdentificeerd. De bevindingen in dit rapport zijn gebaseerd op een review van relevante literatuur, interviews met belangrijke deskundigen op het gebied van drug repurposing en regulatory science, een survey onder hoofdonderzoekers van ZonMw GGG-projecten over drug repurposing, een analyse van meerdere drug repurposing cases en kennis en ervaring van de auteurs.

De eerste hoofdstukken behandelen een aantal onderwerpen die belangrijk zijn voor een goed begrip van de problemen, zoals een overzicht van de regulering van geneesmiddelen (Hoofdstuk 3), een verkenning van het concept van drug repurposing (Hoofdstuk 4) en de juridische en praktische aspecten van patenten en regulatoire bescherming van innovatie (Hoofdstuk 5). De essentie van het rapport is te vinden in hoofdstukken 6, 7 en 8, waarin de geïdentificeerde barrières en aanbevelingen worden besproken, evenals kansen en uitdagingen voor drug repurposing in een pandemie en voor pediatrische toepassingen.

Barrières
Hoofdstuk 6 bevat een overzicht van de barrières bij drug repurposing op basis van literatuur, interviews en de survey. De barrières zijn ingedeeld in vijf categorieën, die in grote lijnen overeenkomen met de ontwikkelingsstadia van (repurposed) geneesmiddelen, waarbij de specifieke barrières van elk stadium worden weergegeven: barrières gerelateerd aan onderzoek & ontwikkeling, barrières gerelateerd aan het verkrijgen van een handelsvergunning, barrières gerelateerd aan marktbescherming, barrières gerelateerd aan prijsstelling en vergoeding, en andere barrières.

De meeste barrières voor productontwikkelaars draaien om (het gebrek aan) een adequate business case. Dit vooruitzicht hangt af van een groot aantal factoren, zoals de kosten en complexiteiten gerelateerd aan onderzoek en ontwikkeling, evenals het verkrijgen van een handelsvergunning, de potentie en zekerheid om (effectieve) bescherming tegen concurrentie te verkrijgen, het krijgen van adequate prijsstelling en vergoeding en de middelen die nodig zijn om te voldoen aan de verplichtingen na de marktintroductie. Specifieke barrières in de context van academische instellingen worden ook waargenomen, zoals beperkte expertise in regelgeving en het ontbreken van een stimulans of intentie om een aanvraag voor een handelsvergunning in te dienen. Een aantal van de geïdentificeerde barrières speelden ook een rol in de zeven geanalyseerde drug repurposing cases in Annex 1.

Aanbevelingen
Hoofdstuk 7 bevat aanbevelingen om de geïdentificeerde barrières aan te pakken en drug repurposing te stimuleren. De aanbevelingen zijn geordend in vier categorieën.

De meeste aanbevelingen richten zich op het verminderen van investeringen en het verhogen van het investeringsrendement met voldoende zekerheid voor productontwikkelaars. Aanbevelingen zijn onder andere het verlenen van voldoende exclusiviteit na het verkrijgen van een handelsvergunning, het beperken van off-label gebruik, cross-label gebruik en apotheekbereiding, het beter gebruik maken van real-world evidence (RWE) in registratiedossiers, het bieden van vrijstellingen of verminderingen in tarieven voor o.a. het aanvragen van een handelsvergunning, en het verlenen van een voorkeurspositie aan repurposed geneesmiddelen in vergoedingssystemen. Naast regelgevende en juridische stimulansen, kan drug repurposing verder worden gestimuleerd door samenwerkingen tussen belanghebbenden te faciliteren en door het voortzetten van de ondersteuning aan

(inter)nationale samenwerkingsplatformen. Voor academische instellingen kan de overstap van een aanvrager-gedreven systeem naar een op bewijs-gedreven systeem verdere voordelen bieden.

Verscheidene van deze aanbevelingen vereisen verder onderzoek om hun praktische bruikbaarheid en potentiële impact te beoordelen. Bijvoorbeeld, verdere studies zijn nodig om (1) de haalbaarheid te evalueren van het integreren en vertrouwen op RWE in het dossier voor de aanvraag van een handelsvergunning, en (2) de geschikte duur en vorm van bescherming (markt- en/of data exclusiviteit) te onderzoeken die zekerheid biedt voor een voldoende return on investment voor bedrijven. Daarnaast moet zorgvuldig gekeken worden naar de wijzigingen aan het aanvrager-gedreven systeem die de Europese Commissie heeft voorgesteld in het kader van de herziening van de Europese geneesmiddelenwetgeving. Bovendien, wat betreft academische instellingen, is het essentieel om verder onderzoek te verrichten om te begrijpen waarom onderzoekers niet altijd streven naar het verkrijgen van een handelsvergunning en om strategieën te ontwikkelen die hen daartoe kunnen stimuleren.

Pandemische paraatheid en pediatrische toepassingen
Hoofdstuk 8 bespreekt geïdentificeerde kansen en uitdagingen voor drug repurposing in een pandemie en voor pediatrische toepassingen. De COVID-19 pandemie toonde het enorme potentieel van drug repurposing voor het versnellen van het geneesmiddelenontwikkelingsproces om effectieve behandelingen naar patiënten te brengen. Tijdens de COVID-19 pandemie veel investeringen gedaan om onderzoek naar nieuwe behandelingen aan te moedigen, waarbij de overgrote meerderheid zich richtte op drug repurposing van bestaande geneesmiddelen (zowel gepatenteerde als niet-gepatenteerde geneesmiddelen). Echter, om het potentieel van drug repurposing in een pandemie te maximaliseren en om de duurzaamheid en transparantie van onderzoeksinitiatieven te waarborgen, zijn meer internationale samenwerkingen nodig.

Drug repurposing heeft ook een enorm potentieel voor het ontwikkelen van nieuwe toepassingen van bestaande behandelingen voor kinderen met een onvervulde behandelbehoefte (unmet medical need). Echter, pediatrische geneesmiddelenontwikkeling kent nog vele uitdagingen. Publiek gefinancierde onderzoeksinitiatieven spelen een sleutelrol in het ontwikkelen van nieuwe methodologieën voor het genereren van bewijs in kinderen. Tegelijkertijd kunnen houders van een handelsvergunning worden aangemoedigd om informatie te verzamelen over het passende gebruik van bestaande geneesmiddelen bij kinderen. Hoewel er uitdagingen blijven bestaan bij het ontwikkelen van pediatrische formuleringen van geneesmiddelen, vormt drug repurposing een veelbelovende methode voor het ontwikkelen van nieuwe behandelingen bij kinderen.

CHAPTER 1

Introduction

The development of a new medicine is a long, high-risk, and resource-intensive endeavour. After successful identification of a lead candidate in the early drug development phase, the medicine development process continues with non-clinical and clinical studies (Figure 1). If the quality has been demonstrated, and the safety and efficacy of the candidate medicine for the treatment of a specific condition have resulted in a positively evaluated benefit-risk balance by the competent authorities, a marketing authorisation can be granted.

Estimates for the costs of developing a single new medicine vary. When considering the costs of failed projects, the overall development cost for successful products can run into hundreds of millions, or even billions of euros, depending on the estimate.[1] To provide an incentive to innovators for investing in medicine development, new medicines are initially protected by patents and regulatory protection.

The initial use of an approved medicinal product, however, often represents only a subset of its potential spectrum of applications in clinical practice.[2] Innovation does not end with the initial market approval of a medicine and continues throughout the entire drug life cycle and in many cases even after the basic patent protection and regulatory protection have expired.

Figure 1. *From bench to patient - the drug development process in five steps*

Both academia and pharmaceutical companies may continue to develop new uses for existing medicinal products to address unmet medical needs for patients. This can be based on its pharmacological properties or may be discovered spontaneously in clinical practice as physicians and patients report unexpected favourable effects of a medicine on a disease for which it was not prescribed.[3] In some cases, a known side effect of a medicinal product can be the desired effect for another medical condition. For example, a commonly described side effect of amitriptyline, an anti-depressant medicine, is that it can cause a dry mouth due to its function on the salivary glands. Consequently, it has been found effective in the treatment of hypersalivation in which patients suffering from an excessive production of saliva.[4]

The development of a new use for an existing medicine is also referred to as ‘drug repurposing’. Drug repurposing has the potential to provide a faster and less costly alternative to traditional drug

[1] SiRM, L.E.K. Consulting & RAND Europe. The financial ecosystem of pharmaceutical R&D: An evidence base to inform further dialogue, 2022.
[2] Lisman JA. ‘De toelating van geneesmiddelen: Hoe effectief is ons systeem?’ (The authorisation of medicines: How effective is our system), in: Geneesmiddelen en Recht, Vereniging voor Gezondheidsrecht. 2006, p. 106.
[3] Léauté-Labrèze C, et al. Propranolol for severe hemangiomas of infancy. N. Engl. J. Med. 358, 2649–51. 2008.
[4] Apotheek.nl. ‘Overmatige speekselvloed’ (Excessive salivation) https://www.apotheek.nl/klachten-ziektes/overmatige-speekselvloed#welke-medicijnen-worden-gebruikt-bij-overmatige-speekselvloed, last accessed 10 January 2024; Verbaanderd C, Rooman I, Meheus L, Huys I. On-Label or Off-Label? Overcoming Regulatory and Financial Barriers to Bring Repurposed Medicines to Cancer Patients. Front Pharmacol. 2020.

development involving a new medicine with a new active substance. One of the efficiency gains is that drug repurposing can build on the existing knowledge about the medicine.[5] Certain pharmacological and pharmacokinetic properties may already be known, which may obviate the need for pre-clinical studies. Moreover, key features of the safety profile may already be known, which can reduce or target the number of clinical studies aimed at gathering evidence about the safety profile. Likewise, in some instances, evidence about the efficacy for the new use is already available. Overall, this can expedite drug development and accelerate patient access to novel treatment approaches that address an unmet medical need.

The term 'drug repurposing' has been used to describe a wide range of new therapeutic applications of existing medicines, which is further outlined in Chapter 4. However, in the context of this report, we define drug repurposing as the development of a new therapeutic indication for an existing medicine in which:[6]

- a new therapeutic indication relates to a condition which is distinct from the initial indication;
- an existing medicine refers to an active substance for which in any form for any therapeutic indication previously a marketing authorisation has been granted (even though that medicine may have been withdrawn from the market);
- the development is aimed at obtaining a marketing authorisation, which can be a new marketing authorisation or the extension of an existing marketing authorisation; and
- the existing medicine is out of its basic patent and regulatory protection.

Drug repurposing has shown significant potential in providing new treatment options to patients, with recent examples of propranolol and fenfluramine (see Annex 1). However, while the potential value of drug repurposing has been widely recognised by all stakeholders, it still experiences many barriers.[7] This report assesses these barriers from a systemic drug development perspective, i.e. creating a sustainable research and development (R&D) climate for investments in drug repurposing initiatives with the ultimate goal to obtain a marketing authorisation. To this end, this report discusses opportunities and recommendations for stimulating future drug repurposing initiatives.

Drug repurposing may also provide opportunities to expedite the development of treatments in a global pandemic. Therefore, this report also explores the role of drug repurposing in a pandemic situation and how it can contribute to the pandemic preparedness of regulatory systems. Furthermore, this report shortly touches upon drug repurposing for paediatric populations.

This report was commissioned by ZonMw as part of the Regulatory Pandemic Preparedness programme, and builds on an earlier report with the title 'Stimulating Drug Rediscovery' (2012).[8] This report focusses primarily on the Netherlands and the Dutch healthcare system although the results can be seen in the broader European context.

This report consists of nine chapters. The next chapter sets out the approach of the analysis. Chapter 3 sets out the regulatory procedures and dynamics of medicine development. Drug repurposing is further elaborated on in Chapter 4. Patents and regulatory protection are a key aspect for drug

[5] Pushpakom S, Iorio F, Eyers P, et al. Drug repurposing: progress, challenges and recommendations. Nat Rev Drug Discov 18, 41–58, 2019.
[6] Langedijk J, Mantel-Teeuwisse AK, Slijkerman DS, Schutjens MH. Drug repositioning and repurposing: terminology and definitions in literature. Drug Discov Today. 2015.
[7] Verbaanderd C, Rooman I, Meheus L, Huys I. On-Label or Off-Label? Overcoming Regulatory and Financial Barriers to Bring Repurposed Medicines to Cancer Patients. Front Pharmacol. 2020
[8] Langedijk J, Lisman J, Stolk P, Mantel-Teeuwisse A, Schutjens MH. 'Stimulating Drug Rediscovery: Towards a marketing authorisation for new application of existing medicines', 2012.

repurposing and therefore briefly introduced in Chapter 5. The emphasis of this report lies on Chapters 6, 7 and 8 in which the identified barriers and recommendations are discussed, as well as opportunities and challenges for drug repurposing in a pandemic and for paediatric applications. The report ends with a discussion and conclusion regarding the findings of this report.

CHAPTER 2

Approach

This report provides a quick-scan of the current situation of drug repurposing based on interviews with key experts on medicine development and regulatory science, a survey among principal investigators of ZonMw Goed Gebruik Geneesmiddelen (GGG) programme on drug repurposing, a review of relevant literature, discussions of multiple drug repurposing cases and knowledge and experience of the authors.

For the literature review, we searched PubMed for all articles published between January 2012 and April 2023 using the keywords 'drug' AND ('repurposing' or 'repositioning' or 'rediscovery') AND ('barriers' or 'hurdles' or 'challenges' or 'facilitators' or 'recommendations' or 'opportunities') in the title or abstract. The search was limited to the English language and journal articles, thereby excluding books, letters and essays. The primary objective of this review was to identify relevant developments (new barriers, facilitators, initiatives) that have occurred after the publication of the previous report in 2012. Moreover, the review aimed to identify key recommendations for drug repurposing as reported in the current literature.

A total of ten expert interviews were conducted with selected experts. The experts represented a mix of different stakeholders with experience in the fields of medicine regulation, health technology assessment (HTA)/payers and reimbursement, government, pharmaceutical companies and clinical practice. Each interview involved a semi-structured approach to identify barriers and recommendations for stimulating research and development including financing of drug repurposing initiatives, manufacturing, marketing authorisation and reimbursement.

In addition, a survey was conducted among principal investigators of ZonMw GGG projects that received financial support from the drug rediscovery subsidy program. A total of 45 projects were identified and invited to participate in the survey. A total of 21 (47%) responses were gathered and analysed, and the results contributed to the identification of the barriers and recommendations.

Moreover, we used seven case studies for in-depth analysis in this report. These cases were selected based on the expert opinions of both the authors and the consulted experts and intend to represent the variety of typical drug repurposing cases. The selection was thus made to provide a comprehensive view on the barriers, facilitators and overall landscape of drug repurposing. The analysis of each case was guided by key facts that were considered essential for inclusion.

Lastly, we specifically focused on drug repurposing in the context of pandemic preparedness and paediatric applications. This was integrated into our expert interviews. The report also includes one case in the context of the coronavirus disease 2019 (COVID-19) pandemic and two cases involving paediatric medicines.

Barriers and recommendations that were identified in this quick-scan were shared with a selection of key experts for review before preparation of the final report.

CHAPTER 3

Regulation of medicines: safety efficacy and quality

Medicines regulation plays a key role in ensuring that only safe and effective medicines of high quality are authorised before being placed on the market. Within Europe, the establishment of the first piece of pharmaceutical legislation, Directive 65/65/EC, followed upon a severe public health incidence in which unsafe medicine were placed on the market. The thalidomide tragedy of the late 1950s might be the best-known incident in Europe, which marks the start of the regulation of medicines to promote pharmaceutical safety and quality and to protect the public health from unsafe and ineffective medicines.[9] Directive 65/65/EC had been amended several times since to incorporate scientific progress and experience with the legislation.

3.1 The EU regulatory system for medicines

The legislation on medicines stipulates that only medicines with a positive benefit-risk ratio and that are of good quality may be granted a marketing authorisation and are allowed to be placed on the market. A positive benefit-risk ratio means that the benefits, i.e. the positive therapeutic effect of the medicine, outweigh any risks (i.e. undesirable effects) relating to the use of the medicine. Once a medicine developer has submitted a marketing authorisation application, the benefits, risks and quality of a medicine are scientifically evaluated by a competent authority such as the European Medicines Agency (EMA) or national bodies such as the Dutch *Medicines Evaluation Board* (MEB).

The marketing authorisation documentation plays an important role in describing the characteristics of medicines and in providing information about medicines to patients and healthcare practitioners. The key characteristics of the medicine are outlined in the summary of product characteristics (SmPC), such as the therapeutic indication(s) for which the medicine has been approved as well as the corresponding posology and method(s) of administration. The package leaflet contains information on the medicine for patients. In addition, the European public assessment report (EPAR), or public assessment report (PAR) describes the scientific evaluation of a medicine by the competent authority. The publication of the information ensures that every medicine with a marketing authorisation is accompanied with the necessary information for informed clinical decision making.

3.2 Different regulatory pathways for demonstrating the efficacy, safety and quality of a medicine

The organisation submitting a marketing authorisation application needs to provide data to the competent authority to demonstrate the efficacy, safety and quality of the medicine for the use in a specific therapeutic indication. The data may be the result of non-clinical and clinical studies performed by the applicant to support the marketing authorisation. A marketing authorisation based on a full submission, including pharmaceutical documentation, pre-clinical testing and clinical studies, is called a full application under Article 8(3) of Directive 2001/83/EC.

For the submission of a marketing authorisation application with a known active substance, the applicant may also use existing knowledge such as data on clinical trials published in a scientific journal. The applicant may even completely rely on data from the scientific literature when applying for a marketing authorisation if the active substance of a medicine has been used for more than 10

[9] European Commission (EC). 'Legal framework governing medicinal products for human use in the EU' https://health.ec.europa.eu/medical-products/legal-framework-governing-medicinal-products-human-use-eu_en#1, last accessed 7 January 2024.

years in clinical practice (e.g. when a medicine has been used off-label, see also section 4.2) and the safety and efficacy for that indication has been well-established. This is referred to as the well-established use application under Article 10a of Directive 2001/83/EC.

Generic medicines can refer to safety and efficacy data from the marketing authorisation dossier of the reference medicine that has already been approved. The traditional generic pathway, under Article 10(1) of Directive 2001/83/EC, allows the applicant of a marketing authorisation for a generic medicine to demonstrate that the medicinal product is identical or bioequivalent to the medicinal product that has already been authorised, used at the same dose(s) and for the same therapeutic indication. However, if a medicine is not the same as an authorised medicine, for example because it differs in dosage form and/or therapeutic indication, it may refer to the marketing authorisation dossier of the authorised medicine and add data to bridge the differences. Such an application, which partly relies on an already authorised medicine and partly on additional data, is known as a hybrid application under Article 10(3).

The format for the marketing authorisation application – that describes all the details and data that is needed to assess the quality, safety and efficacy of a medicine – are laid down in Annex I of Directive 2001/83/EC. In addition, the requirements to obtain a marketing authorisation and the European Commission's interpretation of the legislation is specified in more detail in the Commission's Notice to Applicants.[10] Also, the EMA provides substantial guidance to applicants of a marketing authorisation as well as to marketing authorisation holders (MAHs).[11] This includes scientific guidelines on how to perform the clinical evaluation of medicines used in specific conditions.[12] The EMA – as well as most national competent authorities – also provides scientific advice and protocol assistance to developers of medicines on how to perform the appropriate tests and studies to generate robust evidence on a medicine's benefits and risks.[13]

3.3 Marketing authorisation procedures in the EU

In the EU, marketing authorisations can be granted either at the European level, under the centralised procedure (CP), or via individual European Member States through national authorisation procedures. Marketing authorisations that are granted under the centralised procedure lead to a single evaluation and centralised marketing authorisation via the European Commission, which is valid in each Member State of the EU as well as Iceland, Norway and Liechtenstein. The centralised procedure is compulsory for many novel and innovative medicines. Examples are medicines containing a new active substance to treat human immunodeficiency virus (HIV) or acquired immune deficiency syndrome (AIDS), cancer, diabetes, neurodegenerative diseases, autoimmune and other immune dysfunctions, and viral diseases. Moreover, medicines derived from biotechnology processes, such as genetic engineering, and advanced-therapy medicinal products (ATMPs), such as gene-therapy, somatic cell-therapy or tissue-engineered medicines can only gain marketing authorisation in the EU via the centralised procedure. This also applies for medicine with an orphan designation, which are medicines for the treatment of life-threatening or chronically debilitating

[10] European Commission. 'EudraLex - Volume 2 - Pharmaceutical legislation on notice to applicants and regulatory guidelines for medicinal products for human use' https://health.ec.europa.eu/medicinal-products/eudralex/eudralex-volume-2_en, last accessed 7 January 2024.
[11] European Medicines Agency. 'Scientific guidelines' https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/scientific-guidelines, last accessed 7 January 2024.
[12] European Medicines Agency. 'Clinical efficacy and safety guidelines' https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-guidelines/clinical-efficacy-safety-guidelines, last accessed 7 January 2024.
[13] European Medicines Agency. 'Scientific advice and protocol assistance' https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance, last accessed 7 January 2024.

conditions that is rare and do not affect more than five in 10,000 individuals in the EU, and for which no satisfactory treatment alternatives exist. [14]

At the EMA medicinal products for human use are evaluated by the Committee for Medicinal Products for Human Use (CHMP), which issues a scientific opinion on whether the medicine may be authorised or not. Subsequently it is the European Commission that grants a single marketing authorisation based on CHMP's recommendation.

For medicines that are not within the scope of the compulsory centralised procedure, it is also possible to apply for a marketing authorisation in a single Member State under a national procedure (NP), or simultaneous in multiple Member States under a decentralised procedure (DCP) if no prior marketing authorisation exists. Once a marketing authorisation has been granted in one or more Member States, the marketing authorisation can be recognised by other Member States. This procedure is called the mutual recognition procedures (MRP). Regardless of the procedure (CP, NP, DCP or MRP) the requirements to obtain a marketing authorisation are identical.

3.4 Post-authorisation obligations

The regulation of medicines does not end with the market approval. It continues after the initial marketing authorisation throughout the entire lifecycle of the medicinal product, for example with pharmacovigilance activities to continuously collect reports of side effects, also known as adverse drug reactions (ADRs) and assess whether new data necessitates a change in the assessment of the benefit-risk balance, amendment of the product information or the need for other safety measures. After market approval, medicines need to comply with requirements of the so-called Falsified Medicines Directive (FMD) that contains requirements that should prevent falsified medicines from entering the legal supply chain and reaching patients.[15] And of course, after the initial marketing authorisation, the MAH may apply for an extension of the therapeutic indication to add new therapeutic indications to the marketing authorisation.

[14] European Medicines Agency. 'Orphan designation: Overview https://www.ema.europa.eu/en/human-regulatory-overview/orphan-designation-overview, last accessed 7 January 2024.
[15] European Medicines Agency. 'Falsified medicines: overview' https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/falsified-medicines-overview, last accessed 7 January 2024.

CHAPTER 4

What is drug repurposing?

4.1 Drug repurposing terminology

Since the publication of the report on drug repurposing in 2012 there has been much debate about drug repurposing with an abundance of publications in scientific literature. Various terms and definitions are being used to describe the same or similar drug development activities and strategies. This includes 'drug repositioning', 'drug repurposing', 'drug reprofiling', 'drug redirecting' and 'drug rediscovery'. However, there still is no consistent use of terminology and standard definition. This underlines the importance of defining drug repurposing (or any other terminology used) in the context of a particular initiative, discussion or publication, including in the context of this report.[16]

For this report we have chosen for the term 'drug repurposing' instead of 'drug rediscovery' (which has been used in the previous report from 2012), because 'drug repurposing' seems to have become the most commonly used term. Moreover 'drug repurposing' is now used by the European Commission in its proposals for the reform of the EU pharmaceutical legislation.[17]

As described in Chapter 1, drug repurposing refers to the development of new therapeutic indications for an existing medicine. However, in recent discussions drug repurposing is sometimes used in a different context, such as a new route of administration, pharmaceutical form, or patient population (e.g. children), within the same indication.

We therefore would like to emphasise that we strictly apply the original definition of drug repurposing that is mostly seen in literature, with the focus on obtaining a marketing authorisation for a new therapeutic indication.[18] An aspect to consider is to what extent the new therapeutic indication should differ from the therapeutic indication for which the medicine has already been authorised. For example, the new therapeutic indication may be completely distinct from already approved therapeutic indications of the medicine, such as ketoconazole which was already approved as antifungal treatment and later was approved for the treatment of Cushing syndrome.[19] Or the new and existing therapeutic indications could be more related such as an anti-cancer medicine that is used to treat a different type of cancer. Another aspect to consider when defining drug repurposing is the extent to which the medicine still benefits from basic patent and/or regulatory protection. As will become clear from Chapter 6, the extent to which competitors can be excluded from the market is of great importance to the development of new uses for existing medicines.

[16] Langedijk J, Mantel-Teeuwisse AK, Slijkerman DS, Schutjens MH. Drug repositioning and repurposing: terminology and definitions in literature. Drug Discov Today. 2015.
17 Proposal by the European Commission for the directive: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52023PC0192, last accessed 7 January 2024.
[18] Verbaanderd C, Rooman I, Meheus L, Huys I. On-Label or Off-Label? Overcoming Regulatory and Financial Barriers to Bring Repurposed Medicines to Cancer Patients. Front Pharmacol. 2020; Breckenridge, A., Jacob, R. Overcoming the legal and regulatory barriers to drug repurposing. Nat Rev Drug Discov 18, 1–2. 2019.
[19] Langedijk J. 'Continuous innovation in the drug life cycle', Utrecht University. 2016.

In this report, and as outlined in Chapter 1, we strictly define drug repurposing as the development of a new therapeutic indication for an existing medicine in which:

- a new therapeutic indication relates to a condition which is distinct from the initial indication;
- an existing medicine refers to an active substance for which in any form, for any therapeutic indication, previously a marketing authorisation has been granted (even though that medicine may have been withdrawn from the market);
- the development is aimed at obtaining a marketing authorisation, which can be a new marketing authorisation or the extension of an existing marketing authorisation; and
- the existing medicine is out of its basic patent and regulatory protection.

4.2 Rationale for obtaining a marketing authorisation

In this report, we focus with drug repurposing on obtaining a marketing authorisation for a medicine with the new therapeutic indication. This can be a new marketing authorisation or the extension of an existing marketing authorisation. The requirement of a marketing authorisation constitutes the primary rule in the system and legislation of medicines in the EU.[20] In practice, physicians sometimes prescribe medicines for other indications than those for which they have received a marketing authorisation. The use of a medical product outside of the scope of the marketing authorisation (e.g. approved indication, patient population, posology etc.) is called off-label use.[21]

Off-label use is sometimes applied in cases where evidence from clinical studies, clinical experience or theoretical grounds suggest a clinical benefit for the patient outside the scope of the marketing authorisation.[22] However, the scientific and clinical evidence of uses not included in a marketing authorisation differs from case to case. Sometimes, the evidence for an off-label application is robust and comparable to the required standards and scientific quality needed to obtain a marketing authorisation. In other cases, the evidence is poor and relies on a therapeutic hypothesis.[23] Moreover, individual physicians and pharmacists are not as qualified to make the independent assessment of the benefit-risk balance as the competent authorities as the EMA and the MEB. Off-label use may be included in clinical guidelines, however the quality of the assessment to include the off-label indication in the guideline may strongly differ between associations of medical professionals who draft the guidelines.[24] Also, for the off-label uses there is no publicly accessible information for health care professionals and patients such as in the SmPC and the package leaflet, while some of the official information about the medicine might not be applicable in regard to the off-label use of a medicine.[25] Furthermore, in some EU Member States, medicines are not reimbursed by the national health insurance scheme if the medicine is used off-label.[26] Also, physicians may be reluctant to

[20] Langedijk J. 'Continuous innovation in the drug life cycle'. Utrecht University; 2016. p. 129-153.
[21] European Medicines Agency. 'Off-label use' https://www.ema.europa.eu/en/glossary/label-use, last accessed 7 January 2024; National Institute for Public Health and Environment. 'Off-label use of medicines: Exploring the complexity and problems' https://www.rivm.nl/publicaties/off-labelgebruik-van-geneesmiddelen-verkenning-van-complexiteit-en-problematiek , last accessed 7 January 2024.
[22] National Institute for Public Health and Environment [Rijksinstituut voor Volksgezondheid en Milieu (RIVM)]. 'Off-label use of medicinal products: Exploring the complexity and problems', 2017.
[23] Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. Arch Intern Med. 2006; Bayoumy, A. B., De Boer NKH, Ansari AR, Crouwel F & Mulder CJJ. Unrealized potential of drug repositioning in europe during COVID-19 and beyond: A physcian's perspective. Journal of Pharmaceutical Policy and Practice, 13(1), 1–9. 2020.
[24] Abernethy AP, et al. "Systematic review: reliability of compendia methods for off-label oncology indications." Annals of Internal Medicine. 2009.
[25] Verbaanderd C, Rooman I, Meheus L, Huys I. On-Label or Off-Label? Overcoming Regulatory and Financial Barriers to Bring Repurposed Medicines to Cancer Patients. Front Pharmacol. 2020.
[26] Marjolein W, Hoebert J, Vervloet M, Moltó Puigmarti C, Damen N, Marchange S, Langeijk J, Lisman J, van Dijk L. 'Study on off-label use of medicinal products in the European Union. 2017; Mulder J, Verjans R, Verbaanderd C, Pean E, Weemers J, Leufkens HGM, Pignatti F, de Boer A, Voest EE, Stoyanova-Beninska VV, Pasmooij AMG. Extension of Indication for Authorised Oncology Products in the European Union: A Joint Effort of Multiple Stakeholders. Front Med (Lausanne). 2021.

prescribe a medicine for an off-label use as they become responsible (and liable) for the assessment of the benefit-risk balance in regard to the off-label use. This may hinder a patient's access to the treatment with the medicine.[27] Finally, sustainable availability of and hence patient access to a medicine can be jeopardised when the medicine is only used off-label, such as happened with etidronate. The bisphosphonate etidronate was originally developed to prevent and treat osteoporosis. Later in academic trials it was shown that etidronate is also effective in the treatment of pseudoxanthoma elasticum - a rare autosomal recessive disorder. However, meanwhile other bisphosphonates with a better benefit-risk profile replaced etidronate in the prevention and treatment of osteoporosis. Etidronate was withdrawn from the market. This hampered the further use and development of etidronate in the treatment of pseudoxanthoma elasticum.[28]

In clinical practice it is also common to use pharmacy preparations. Pharmacy preparations may address a medical need of a specific patient, for example if no authorised medicine is available with the needed strength or dosage form. Pharmacy preparations may also be used if a medicine with a specific active substance is no longer available as an authorised medicinal product. Pharmacy preparations face the same disadvantages as off-label use, while also the quality of the medicine may not be of the identical standards as medicines authorised nowadays.

Considering that the marketing authorisation constitutes the premise of the EU medicines law and the disadvantages of off-label use and pharmacy preparations for drug repurposing programmes, it seems most appropriate to aim for (an extension of) a marketing authorisation. To accept off-label use of authorised medicines or a pharmacy preparation as standard therapy seems at odds with the intent of the drug regulatory system, although that should not detract from the fact that in some cases off-label use or the use of a pharmacy preparation is the best treatment available to a patient. Accordingly, pharmacy preparations (or other unlicensed medicinal products) and off-label use of authorised medicines should not be considered to be an adequate primary vehicle to provide patients access to drug repurposing.[29]

In practice, it might not be possible for all drug repurposing initiatives to end with the application of a new marketing authorisation or an extension of an existing marketing authorisation. Such an application may simply be beyond the scope of a project. However, drug repurposing initiatives such as funded by national governments or the EU should aim at collecting data that complies with the requirements of competent authorities to be used in the application of (the extension of) a marketing authorisation.[30]

In addition to the reflection on off-label use above a specific type of off-label use must be mentioned. The term cross-label use is currently used to describe that a medicine is used to treat a condition for which another MAH of a medicine with the same active substance, dosage form and strength has obtained a marketing authorisation. In literature the term is specifically used in circumstances where the generic medicine omits the use in its label because the use is subject to patent protection.[31] However, the term may also be used if the medicine that has the new therapeutic use in its label still benefits from regulatory protection, such as data exclusivity or market exclusivity.

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[27] Federaal Kenniscentrum voor de Gezondheidszorg [Federal Knowledge Center for Healthcare]. 'Towards a better managed off-label use of drugs'', 2015.
[28] van den Berg S, de Visser S, Leufkens HGM, Hollak CEM. Drug Repurposing for Rare Diseases: A Role for Academia. Front Pharmacol. 2021
[29] Langedijk J. 'Continuous innovation in the drug life cycle', Utrecht University. 2016 (p. 129-153).
[30] Liddicoat J, Liddell K, Darrow J, et al. Repositioning Generic Drugs: Empirical Findings and Policy Implications. 2022
[31] Idem.

CHAPTER 5

The function of patents and regulatory protection

The roles of patent law, the supplementary protection certificate (SPC), and regulatory protection are of great importance in establishing a business case for drug repurposing. These three forms of protection are briefly described in this chapter. Irrespective of the form, innovation protection is paradoxical in nature: protection encourages innovation but can also constitute a barrier to other innovations. Both the existence and lack of adequate protection mechanisms could therefore be regarded as a barrier to drug repurposing.

5.1 Intellectual property rights (including regulatory protection)

5.1.1 Patents and supplementary protection certificate

Patent law (and, by extension, the SPC) gives a patent holder a temporary exclusive right to prevent others from using the invention commercially (e.g. to make, use, supply, import or stock a product).[32] The holder has the exclusive right to exploit the patented invention commercially during the term of the patent, which is in principle a 20-years period from the date of filing the patent application at the European or national patent office. In return, the invention is made public by publishing the patent. This allows others to access the knowledge that led to the invention and build upon the knowledge for further innovations. Patent law ultimately aims to make knowledge available in order to stimulate innovation.

It may take more than 10 years to develop a medicine based on a new active substance and obtain market approval for it. During this period of time, the patent holder will not benefit from the patent because the new medicine is not allowed yet onto the market.[33] Due to the long interval between applying for a patent and the actual market introduction (due to the requirements and procedures for testing and market approval), the effective period of a patent for medicines is considerably shorter than 20 years. The EU legislator, being aware of the shorter effective protection, introduced a specific protection mechanism for medicines: the SPC.[34] The SPC extends the effective period of a patent by a maximum of 5 years.[35]

However, the exclusive right resulting from a patent or SPC does not necessarily constitute a monopoly. Although the patent prevents exact copies of the medicine from coming onto the market during the term of the patent and SPC, competition in the form of medicines which contain other active substances, but have the same application, is still possible. Additionally, the patent may sometimes be circumvented. For example, if the patent covers a technology to manufacture an

[32] This invention needs to satisfy several requirements; see Section 3 of the (Dutch) Patents Act 1995: “Inventions that are new, that involve an inventive step and that are susceptible to industrial application shall be patentable.”
[33] See Chapter 3.
[34] European Commission. ‘Supplementary protection certificates for pharmaceutical and plant protection products’ https://single-market-economy.ec.europa.eu/industry/strategy/intellectual-property/patent-protection-eu/supplementary-protection-certificates-pharmaceutical-and-plant-protection-products_en, last accessed 7 January 2024.
[35] Regulation (EC) No. 469/2009. This regulation is a recodification of Council Regulation (EEC) No. 1768/92. The regulations on supplementary protection certificates are being reformed, but no significant changes to the duration of the SPC for medicinal products are expected: https://single-market-economy.ec.europa.eu/publications/proposals-regulations-supplementary-protection-certificates_en. The SPC is extended by 6 months to a maximum of 5.5 years if for a medicine authorised across the EU the results of studies from a paediatric investigation plan (PIP) are included in the product information; even when the studies' results are negative. A PIP is a development plan aimed at ensuring that the necessary data are obtained through studies in children, to support the authorisation of a medicine for children. For more information on the PIP see https://www.ema.europa.eu/en/human-regulatory-overview/research-and-development/paediatric-medicines-research-and-development/paediatric-investigation-plans.

active substance, a competitor may manufacture the active substance by making use of another technology.[36]

5.1.2 Regulatory protection

In addition to patent and SPC-based protection, there is regulatory protection such as data exclusivity and market protection (collectively known as dossier protection or in Dutch: *dossierbescherming).*[37]

5.1.2.a Data exclusivity and market protection

During the period of data exclusivity, others may not refer to the non-clinical and clinical data in the dossier to substantiate their own (generic or hybrid) application for a marketing authorisation. It basically protects the knowledge in the dossier for being used by other applicants of a marketing authorisation. In the EU, the data exclusivity period lasts 8 years and is complemented by a period of 2 years of market protection. During the market protection period, generic and hybrid products can be approved but cannot be placed on the market yet. So, a generic or hybrid version of a medicinal product may only be placed on the market 10 years after the initial authorisation of the original medicinal product.[38]

The period of data exclusivity and market protection can be extended to a maximum of 11 years if one (or more) new therapeutic indication(s) which is (or are) considered to have a significant clinical benefit in comparison with existing therapies, are added to the label during the first 8 years after market approval.[39] However, if an application is made for a new indication after those 8 years, only a non-cumulative period of 1 year of data exclusivity shall be granted that covers the data submitted in the application for the extension of the indication, provided that significant non-clinical or clinical studies were carried out - by the MAH or sponsored by the MAH - in relation to the new indication.[40] Just like a patent and a SPC, data exclusivity and market protection do not necessarily constitute a monopoly, since a competitor might obtain a marketing authorisation by submitting its own data and not referring to the dossier of a medicinal product that has already been approved.

It should be noted that a MAH may benefit only once from a data exclusivity and market protection period per active substance. All (additional) forms of the medicinal product (e.g. strengths, pharmaceutical forms, administration routes and presentations) with the active substance are considered to belong to the so-called same 'global marketing authorisation'. The data exclusivity and market protection period of all authorised forms of the medicinal product are considered to have started at the date of granting the marketing authorisation of the first medicinal product with the concerned active substance by that MAH.[41] Other MAHs may still benefit from their own period of data exclusivity and market protection if they obtain a marketing authorisation based on a full dossier for a medicinal product with that same active substance.

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[36] See Article 54c(e) of the (Dutch) Patents Act 1995.
[37] For an overview of the regulatory protection for medicines in the EU see: https://www.ema.europa.eu/en/documents/presentation/presentation-data-exclusivity-market-protection-orphan-and-paediatric-rewards-s-ribeiro_en.pdf, last accessed 13 January 2024.
[38] Article 10(1) and (2) of Directive 2001/83/EC.
[39] Article 10(1) fourth paragraph of Directive 2001/83/EC.
[40] Article 10(5) of Directive 2001/83/EC; European Commission, 'Guidance on a new therapeutic indication for a well-established substance (November 2007)': https://health.ec.europa.eu/system/files/2016-11/10%252520_5_%252520guideline_11-2007_en_0.pdf, last accessed 13 January 2024.
[41] Article 6(1) second paragraph of Directive 2001/83/EC.

5.1.2.b Market exclusivity for orphan medicinal products

Furthermore, for orphan medicinal products (i.e. medicinal products for rare diseases) a possibility to obtain special market exclusivity period of 10 years exists. This market exclusivity prevents similar medicinal products for the same therapeutic indication to obtain market approval.[42] As with the forms of protection, market exclusivity for orphan medicinal products does not necessarily constitute a monopoly, since the restriction to obtain market approval only applies to similar medicinal products.[43] A similar medicinal product means as a medicinal product containing a similar active substance as contained in a currently authorised orphan medicinal product, and which is intended for the same therapeutic indication. This definition is further clarified in more detail by the European Commission in an implementing regulation and a guideline.[44] Medicinal products with a different active substance may still obtain a marketing authorisation for the same therapeutic indication. Moreover, other companies may obtain market approval for medicinal products with the same active substance for another therapeutic indication.

5.1.2.c Data exclusivity and market protection for paediatric-use marketing authorisations

Finally, a paediatric-use marketing authorisation (PUMA) provides a data exclusivity period of 8 years and a market protection period of 2 years. This exclusivity also applies if the MAH previously has benefitted from a data exclusivity and a market protection period for a medicinal product with the same active substance. A PUMA can be obtained for a medicinal product which is already licensed, but that is no longer under patent protection, and which is developed specifically for a paediatric therapeutic indication with a new formulation. The PUMA does not prevent other companies to conduct similar clinical trials with the active substance and apply for market approval for the same therapeutic indication as the medicinal product that was granted the PUMA. Therefore, the PUMA also does not necessarily constitute a monopoly.

5.2 Reform of the regulatory protection – proposals by the European Commission

Ultimately, the various forms of protection are a political compromise between two public interests. On the one hand, governments intend to stimulate innovation and the availability of new medicines by extending the temporary exclusivity to those who invest in a new medicine. On the other, they safeguard the disclosure of knowledge and the availability of affordable medicines following a reasonable term of protection. In that context, it is interesting that in the ongoing reform of the EU pharmaceutical legislation the European Commission has proposed substantial amendments to the system of regulatory protection and explicitly refers to drug repurposing.[45] In their proposal the European Commission even states “the inclusion of new therapeutic indications to an authorised

[42] Regulation (EC) No 141/2000 of the European Parliament and of the Council on orphan medicinal products, OJ 2000 L18/1; Commission Regulation (EC) No 847/2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts ‘similar medicinal product’ and ‘clinical superiority’, OJ 2000 L103/5. For more information about the market exclusivity for orphan medicinal products see https://www.ema.europa.eu/en/orphan-designation-post-authorisation/market-exclusivity-orphan-medicines.

[43] European Medicines Agency. ‘Applying for marketing authorisation: orphan medicines’ https://www.ema.europa.eu/en/orphan-designation-marketing-authorisation/applying-marketing-authorisation-orphan-medicines, last accessed 7 January 2024.

[44] Commission Regulation (EC) No 847/2000 laying down the provisions for implementation of the criteria for designation of a medicinal product as an orphan medicinal product and definitions of the concepts ‘similar medicinal product’ and ‘clinical superiority’, OJ 2000 L103/5; Guideline on aspects of the application of Article 8(1) and (3) of Regulation (EC) No 141/2000: Assessing similarity of medicinal products versus authorised orphan medicinal products benefiting from market exclusivity and applying derogations from that market exclusivity, OJ 2008 C242/12.

[45] In the 'Reform of the EU pharmaceutical legislation’ the European Commission has made a proposal for a new directive as to replace Directive 2001/83/EC as well as for a new regulation to replace Regulation (EC) No 726/2004, see: https://health.ec.europa.eu/medicinal-products/pharmaceutical-strategy-europe/reform-eu-pharmaceutical-legislation_en.

medicinal product contributes to the access of patients to additional therapies and therefore should be incentivised."[46]

The European Commission has proposed to establish a regulatory data protection period of 4 years, specifically for repurposed medicinal products.[47] Although it is referred to as 'data protection' in the proposal for the reform of EU pharmaceutical legislation, it has the same meaning as data exclusivity under the current legislation. The 4 years of data protection shall be granted for a medicinal product with respect to a new therapeutic indication not previously authorised in the EU, provided that adequate non-clinical or clinical studies were carried out in relation to the therapeutic indication demonstrating that it is of significant clinical benefit.[48] Moreover, the data protection can only be granted to medicinal products that have not previously benefited from a data protection period (e.g. generics, hybrids, biosimilars), or to medicinal products that were granted a marketing authorisation more than 25 years ago.[49] The data protection period of 4 years may only be granted once to any given medicinal product.[50] This means that a MAH may not benefit twice from a 4 years regulatory data protection period by repurposing a particular medicinal product for two new therapeutic indications. The 4 years of data protection is followed by 2 years of market protection during which another applicant for a subsequent marketing authorisation may not refer to the submitted data.[51]

The proposed data protection period for repurposed medicinal products is longer compared to the current legislation. However, the data protection does not prevent the off-label use (or cross-label use) of generic medicinal products that were already placed on the market. Also, the protection period might not always be sufficient to recoup all investments. Moreover, be used off-label/cross-label use the medicine developer may choose to apply for a marketing authorisation based on a full-dossier (under Article 8(3) of Directive 2001/83/EC) in order to benefit from a longer period of regulatory protection. Therefore, it remains to be seen whether the proposed regulatory protection provides better opportunities to create a viable business case for repurposed medicines and will depend on specific circumstance.

Furthermore, the European Commission has proposed to reduce the standard period of data exclusivity (which the proposal refers to as regulatory data protection) from 8 to 6 years, which is still complemented by a period of 2 years of market protection.[52] This data exclusivity period can be prolonged if certain conditions are met. If, for example, the medicinal product is released and sufficiently supplied within 2 years after market approval in all Member States in which the marketing authorisation is valid, the holder receives an additional period of 2 years of data exclusivity.[53] Six months are added to the data exclusivity period if the medicinal product addresses an unmet medical need.[54] Orphan medicinal products are as standard considered as addressing an

[46] Recital 51 of the proposal by the European Commission for the directive: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52023PC0192, last accessed 7 January 2024.
[47] Article 84 of the proposal by the European Commission for the directive: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52023PC0192, last accessed 7 January 2024.
[48] Article 84(1)(a) of the proposal by the European Commission for the directive.
[49] Article 84(1)(b) of the proposal by the European Commission for the directive.
[50] Article 84(2) of the proposal by the European Commission for the directive.
[51] Article 84 of the proposal by the European Commission for the directive does not explicitly mention the 2 years of market protection. However, this must follow from article 80(1) and (2) because article 80(1) defines the rights during regulatory data protection period (while article 84 does not) and article 80(2) grants the market protection period to all medicinal products that benefit from a regulatory data protection period as in article 80(1). It would be helpful if it would be made clearer in the text of the legislation that the market protection period of 2 years also applies to repurposed medicinal products that benefit from regulatory data protection under article 84.
[52] Article 80(1) and (2) and Article 81(1) of the proposal by the European Commission for the directive: https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:52023PC0192.
[53] Article 81(2)(a) and Article 82(1) of the proposal by the European Commission for the directive.
[54] Article 81(2)(b) and Article 83(1) of the proposal by the European Commission for the directive.

unmet medical need.[55] Six months are also added to the data exclusivity period if the medicinal product contains a new active substance and in the clinical trials a relevant and evidence-based comparator has been used in accordance with scientific advice provided by the EMA.[56] Lastly, the regulatory data protection period is prolonged by 1 year if during the regulatory data protection period the MAH obtains an authorisation for an additional therapeutic indication provided that the MAH has demonstrated, with supporting data, a significant clinical benefit in comparison with existing therapies.[57] The latter prolongation may only be granted once.

The incentive of a PUMA as outlined in section 5.1.2.c above, are in essence not amended under the proposal by the European Commission. The regulatory protection for a PUMA follows the same principals as for the PUMA under the current legislation. The medicinal product under a PUMA shall benefit from its own data and marketing protection period.[58]

The European Commission has also proposed a reform of market exclusivity for orphan medicinal products. In the proposal by the European Commission the standard market exclusivity period for orphan medicinal products is 9 years.[59] Orphan medicinal products addressing a high unmet medical receive market exclusivity for a period of 10 years.[60] However, the market exclusivity period for orphan medicinal products authorised based on a well-established use application under Article 10a is strongly reduced to 5 years instead of 10 years under the current legislation.[61]

The duration of the market exclusivity period may be extended if specific conditions are met. Except for the orphan medicinal products authorised based on a well-established use application, the market exclusivity period for orphan medicinal products can be prolonged by 1 year if the medicinal product is released and sufficiently supplied within 2 years in all EU Member States.[62] An additional year of market exclusivity is granted if at least 2 years before the end of the market exclusivity period, a marketing authorisation is obtained for a new therapeutic indication for a different orphan condition.[63] This prolongation may be granted twice if the new therapeutic indications are for different orphan conditions. The possibility of extending the marketing exclusivity period through an extension of the indication does not apply to orphan medicinal products authorised based on a well-established use application.

Moreover, the European Commission proposes that a MAH of an orphan medicinal product may only benefit from one market exclusivity period per active substance. If the MAH holds more than one orphan marketing authorisations for the same active substance, those authorisations shall not benefit from separate market exclusivity periods. The duration of the market exclusivity shall start from the date when the first orphan marketing authorisation was granted in the EU.[64]

Finally, it is highly relevant – although it does not concern regulatory protection – that the European Commission has proposed the introduction of a framework for not-for-profit organisations to submit to the EMA or a national competent authority non-clinical and clinical evidence for a new therapeutic indication that is expected to fulfil an unmet medical need. If the scientific evaluation of the benefit-

[55] Article 83(2) of the proposal by the European Commission for the directive.
[56] Article 81(2)(c) of the proposal by the European Commission for the directive.
[57] Article 81(2)(d) of the proposal by the European Commission for the directive.
[58] Articles 92 and 93 of the proposal by the European Commission for the regulation.
[59] Article 71(2)(a) of the proposal by the European Commission for the regulation.
[60] Article 71(2)(b) of the proposal by the European Commission for the regulation.
[61] Article 71(2)(c) of the proposal by the European Commission for the regulation.
[62] Article 72(1) of the proposal by the European Commission for the regulation.
[63] Article 72(2) of the proposal by the European Commission for the regulation.
[64] Article 71(3) of the proposal by the European Commission for the regulation.

risk of the use of a medicinal product is favourable, MAHs of the medicinal products concerned shall submit an application to update the product information with the new therapeutic indication.[65] The MAH will not benefit from an extension of the data protection period for the extension of the indication through this procedure.[66]

The proposal of the European commission to reform the EU pharmaceutical legislation, including the system of regulatory protection, is currently under review by the European Parliament and the Council of the EU (also known as 'the Council'). Negotiations on the text of the pharmaceutical legislation will take at least one or two more years and the proposals by the European Commission may be amended substantially in the process.

[65] Article 48(1) and (2) of the proposal by the European Commission for the regulation.
[66] Article 48(3) of the proposal by the European Commission for the regulation – in which it is expected that the reference to Article 81(2) point (c) should be a reference to point (d).

CHAPTER 6

Barriers in drug repurposing

This chapter aims to provide an in-depth analysis of the barriers faced in drug repurposing, informed by the literature, expert interviews, case studies, a survey and the authors' experiences. The barriers are categorised into five categories: barriers associated with research & development; barriers associated with obtaining a marketing authorisation, barriers associated with market protection, barriers associated with pricing and reimbursement, and other barriers. It is important to note that the barriers discussed in this chapter should be viewed holistically to fully understand the complexities of drug repurposing. An overview of the categorised barriers is presented in Table 1.

Table 1. *Categorised overview of the barriers faced in drug repurposing*

Category	Barriers
Research & development	- Costs and complexity of research - Risk of failure
Marketing authorisation	- Marketing authorisation application (and maintenance) - Compliance with modern good manufacturing practice (GMP) standards - Access to data at originator - Post-authorisation measures
Market protection	- No or limited protection - Lack of effective protection (off-label use/cross-label use, pharmacy preparations)
Pricing and reimbursement	- Limited reimbursement mechanisms - Dutch Medicines Pricing Act
Other barriers	- Post-marketing costs - Limited knowledge, incentive and ambition in academic institutions to work towards a marketing authorisation - Applicant driven system - Lack of incentive for MAH to extend marketing authorisation - Cost of capital

6.1 Barriers associated with research & development

6.1.1 Costs and complexity of research

Despite existing data supporting the efficacy of a medicine for a new indication, additional studies are often necessary to obtain a marketing authorisation. This necessity may arise when the available data fail to meet the strict regulatory standards for marketing authorisation. These trials, necessitated by strict EMA and ICH guidelines, are both costly and complex. Adhering to regulatory standards demands specific knowledge, skills and a well-organised approach, alongside considerable financial investments.[67]

Moreover, the use of real-world evidence (RWE) to complement evidence from other sources such as randomized controlled trials has great potential to reduce drug development costs, in particular in the context of drug repurposing. However, RWE is still facing many challenges, which need to be addressed to make it an accepted method of evidence collection in regulatory decision-making and ultimately obtaining a marketing authorisation.

6.1.2 Risk of failure

A significant advantage of drug repurposing is the prior understanding of the medicine's safety profile and pharmacokinetics. Nonetheless, repurposed medicines still carry a risk of failure. This could be due to the lack of efficacy of the medicine for its new indication.

Moreover, modifications in the administration route may lead to previously unobserved side effects. A medicine, when administered orally for its original indication, may exhibit a different safety profile when administered intravenously for another indication.

Additionally, alterations in therapeutic dose often necessitate further research. For instance, if the therapeutic window for the new indication demands a higher dose than the initial indication, one must determine whether any observed lack of efficacy arises from a too low dosage or from the real absence of a therapeutic effect in the new indication.[68]

Furthermore, the target population of the medicine may change for the new indication. For instance, a medicine originally authorised for use in adults could transition to paediatric use (for the new indication), or to a population with specific co-morbidities. Such alterations in target populations necessitate further research to validate both safety and efficacy.

The challenges described above are some of the main reasons why drug repurposing carries an inherent risk of failure. A substantial fraction of drug repurposing initiatives does not transition successfully to clinical practice. While precise data on the number of drug repurposing initiatives that are discontinued are lacking, it is understood that discontinuation does occur early in the process.[69] The costs associated with the risk of failure are often disregarded in the public debate about drug repurposing.

6.2 Barriers associated with obtaining a marketing authorisation

6.2.1 Marketing authorisation application (and maintenance)

An application for a marketing authorisation or an extension thereof must be accompanied by a large amount of information in a structured format (the Common Technical Document). Obtaining and compiling all the information required for the application is a complex matter, requiring significant

[67] Verbaanderd C, Rooman I, Meheus L, Huys I. On-Label or Off-Label? Overcoming Regulatory and Financial Barriers to Bring Repurposed Medicines to Cancer Patients. Front Pharmacol. 2020.
[68] Begley CG, et al. Drug repurposing: Misconceptions, challenges, and opportunities for academic researchers.Sci. Tranl. Med. 2021
[69] Krishnamurthy N, Grimshaw AA, Axson SA, Choe SH, & Miller JE. Drug repurposing: a systematic review on root causes, barriers and facilitators. BMC Health Services Research, 22(1). 2022.

investment. Furthermore, fees must be paid to the competent authorities for the application of a marketing authorisation and for extensions thereof, and maintaining this authorisation also incurs an annual fee to the same authorities. Moreover, obtaining a marketing authorisation often requires hiring experts/consultants, who may charge substantial rates.

6.2.2 Compliance with modern GMP-standards

Manufacturers must comply with EU good manufacturing practice (GMP) to obtain a manufacturing or import authorisation. Manufacturers can ensure that they meet all their legal obligations by following the EU GMP standards. Modern GMP-standards for active pharmaceutical substances differ notably from those set in the past. To meet these standards, modifications in for instance active substance acquisitions and manufacturing procedures may be required. This may drive up the costs of production.

6.2.3 Access to data at originator

Limited access to the originator's data may hinder drug repurposing efforts. In contrast to generic applications under Article 10(1), which typically only require bioequivalence studies, repurposing a medicine may necessitate additional studies. Without access to for instance safety data within the clinical study report of the originator, (additional) studies may become necessary, leading to an increase in costs. Even when data access is granted, the originator may command high fees for the use of the data.

6.2.4 Post-authorisation measures

Post-authorisation requirements may pose a barrier to drug repurposing. For instance, when repurposing a medicine, competent authorities require an updated or new risk management plan (RMP) to address the different safety profile related to its new indication. The development, maintenance, and execution of these plans can entail significant costs. Post-authorisation safety studies (PASSs) are often required as part of the RMP and are intended to gather more data about a medicine's safety in its new indication. MAHs may be obliged to carry out PASSs if requested by the Pharmacovigilance Risk Assessment Committee (PRAC). Additionally periodic safety update reports (PSURs) are legally required to be submitted by the MAH. This also entails significant costs. In cases where the repurposed medicine is designated for a comparatively small patient population, the increased turnover resulting from the additional patient population(s) may not always offset the costs of the post-authorisation measures.

6.3 Barriers associated with market protection

6.3.1 No or limited protection

A significant barrier to drug repurposing is that a MAH does not receive sufficient additional data exclusivity and market protection for extending the marketing authorisation with a new indication if the medicinal product has been granted a marketing authorisation for over 8 years, see section 5.1.2. In such cases, only a non-cumulative one-year data exclusivity is granted, provided that significant non-clinical or clinical studies had been conducted for the new indication. While the product developer has undertaken the financial risk of repurposing, they are not granted sufficient forms of protection for the newly repurposed medicine. The lack of sufficient protection limits their prospect for an adequate return on investment.

Medical use patents could offer protection for new uses of existing medicines. However, obtaining such a patent might be impossible if the new use is not novel or inventive. Furthermore, prospective patentees might need to wait until they have sufficient evidence before filing, posing a risk of public disclosure. Moreover, enforcing medical use patents is difficult due to the disconnect among those involved in the supply chain of a medicine. Many countries already promote or require the use of less

expensive generic medicines when available. Moreover, literature indicates that medical use patents are often weak and easily bypassed by competitors.[70]

6.3.2 Lack of effective protection

6.3.2.a Off-label use/Cross-label use

Off-label use competes with repurposed medicines, therefore constituting a barrier to drug repurposing. In many jurisdictions, physicians can freely prescribe approved medicines for non-approved indications.[71] Thus, by off-label use, the medicine is used in the treatment of new indications with a medicinal product without being included in the marketing authorisation. Companies might benefit from this, as it broadens the patient population without the need to obtain an extension of their marketing authorisation.[72] This may disincentivise companies to apply for an extension of the indication of its marketing authorisation.

Cross-label use (the use of a generic medicine to treat a condition for which another product developer has obtained a marketing authorisation) substantially reduces the opportunity of product developers to recoup investments in drug repurposing.[73] Practitioners often prescribe medicines using their International Non-Proprietary Names (INNs). This practice can inadvertently and unbeknownst to the prescribers lead to cross-label use, despite any patent or regulatory protection for the on-label alternative.

6.3.2.b Pharmacy preparations

Pharmacy preparations may compete with repurposed medicines approved for the use in a new therapeutic indication. Therefore, pharmacy preparations may constitute a barrier to drug repurposing, as existing protective mechanisms for authorised medicines can be bypassed by pharmacy preparations. Although authorised medicinal products are prioritised, the law provides an exemption for pharmacy compounding, provided they comply with specific conditions. Pharmacy preparations may undermine the market for repurposed medicines that obtained a marketing authorisation for a new therapeutic indication, especially if the compounded version is available at significantly lower prices. In the Netherlands, this barrier for drug repurposing was reinforced by the introduction of an additional exemption in February 2019 under the Dutch Patent Act 1995, allowing pharmacists to prepare patented medicines for direct use in individual cases on medical prescription.[74] This amendment aimed to align the Dutch patent legislation with similar laws in other European countries.

6.4 Barriers associated with pricing and reimbursement

6.4.1 Limited reimbursement mechanisms

The limited out-patient reimbursement across various European Member States, including the Netherlands, constitutes a barrier to drug repurposing. It is important for the manufacturer of a

[70] Pushpakom, S, Iorio F. et al. Drug repurposing: progress, challenges and recommendations. Nature Reviews. Drug Discovery, 18(1), 41–58. 2019; Verbaanderd C, Rooman I. et al. On-Label or Off-Label? Overcoming Regulatory and Financial Barriers to Bring Repurposed Medicines to Cancer Patients. Front Pharmacol. 2020.

[71] Verbaanderd C, Rooman I, Meheus L, Huys I. On-Label or Off-Label? Overcoming Regulatory and Financial Barriers to Bring Repurposed Medicines to Cancer Patients. Front Pharmacol. 2020.

[72] Mulder J, Verjans R, Verbaanderd C, Pean E, Weemers J, Leufkens HGM, Pignatti F, de Boer A, Voest EE, Stoyanova-Beninska VV, Pasmooij AMG. Extension of Indication for Authorised Oncology Products in the European Union: A Joint Effort of Multiple Stakeholders. Front Med (Lausanne). 2021; Bayoumy, A. B., De Boer, N. K. H., Ansari, A. R., Crouwel, F., & Mulder, C. J. J. Unrealized potential of drug repositioning in europe during COVID-19 and beyond: A physcian's perspective. Journal of Pharmaceutical Policy and Practice, 13(1), 1–9. 2020.

[73] See section 4.2.

[74] Medicines Law & Policy. 'Faced with unreasonable medicines prices, the Netherlands introduces pharmacy exemption in patent law' https://medicineslawandpolicy.org/2019/02/faced-with-unreasonable-medicines-prices-the-netherlands-introduces-pharmacy-exemption-in-patent-law/, last accessed 7 January 2024; Wegwijzer informatie en diensten van alle overheden. 'Besluit van 5 december 2018, houdende vaststelling van het tijdstip van inwerkingtreding van artikel 53, derde lid, tweede volzin, van de Rijksoctrooiwet 1995' https://zoek.officielebekendmakingen.nl/stb-2018-469.html#extrainformatie.

medicine to know whether and, if so, the repurposed medicine is reimbursed under the national health reimbursement system at a price and under conditions that provide a profitable return for the MAH.

In the Netherlands, the medicine reimbursement system (in Dutch: *geneesmiddelenvergoedingssysteem* [GVS]) determines the reimbursement status of medicines for out-patient care such as dispensed by local pharmacies. Within the GVS, medicines that are considered therapeutically substitutable are placed into a cluster with a maximum reimbursement price: the reimbursement limit). Medicines are considered therapeutically substitutable if they have 1) a similar indication; 2) a similar route of administration; and 3) are generally indicated for the same age category. Medicines with similar active substances and slightly different therapeutic indications can still be considered as therapeutically substitutable.[75]

A repurposed medicine may be clustered with – and therefore have the same reimbursement limit as – other medicines with the same active substance, same dosage form and strength as the repurposed medicine – while these other medicines did not require the investments for the repurposing. The prospect that a medicine will be included in a cluster with a (relatively low) reimbursement limit constitutes a barrier to drug repurposing. This particular barrier has recently come to focus through a position paper released by the centre for Future Affordable Sustainable Therapies (FAST), see also section 7.3.[76]

Reimbursement criteria and policies for medicines differ between EU Member States. However, demonstrating cost-effectiveness typically plays a crucial role in reimbursement decisions and inclusion in national reimbursement systems. Establishing cost-effectiveness can be challenging when the repurposed medicine is priced substantially higher than the medicine that is already on the market (which is often a generic medicine).[77] Therefore, payers are generally reluctant to endorse a higher price for repurposed medicines. Instead, they may opt for lower cost (unapproved) alternatives like pharmacy preparations and off-label or cross-label use of (generic) medicines).

Furthermore, reimbursement systems across the EU are heavily inclined towards incentivising pharmacists to dispense less expensive generic medicines.[78] Such a policy with a preference to use generic medicines, as in countries like Germany and the Netherlands, creates an environment where the expected return on investment for repurposed medicines is low.

Medicines in used in a hospital treatment are usually eligible for reimbursement.[79] However, the medicines of which the costs are expected to exceed specific limit are excluded from reimbursement while the Dutch National Health Care Institute (in Dutch: *Zorginstituut Nederland [ZIN]*) performs an assessment of the effectiveness and cost-effectiveness and price negotiations of the Minister of Health, Welfare, and Sport with the MAH. The medicine is only eligible for reimbursement from health insurance if the Minister considers that justified based on the assessment of the ZIN and the

[75] For a more detailed overview of the Dutch reimbursement system for medicines see K. van Lessen Kloeke 'Pricing & Reimbursement Laws and Regulations 2023 - Netherlands: https://www.globallegalinsights.com/practice-areas/pricing-and-reimbursement-laws-and-regulations/netherlands, last accessed 13 January 2024.
[76] FAST rapport (November 2023). Drug repurposing als snelle route naar betaalbare nieuwe behandelingen- Uitzonderingspositie (FAST report (November 2023). Drug repurposing as a fast route to affordable new treatments - Privileged position).
voor generiek merk moet bedrijven stimuleren.
[77] Verbaanderd C, Rooman I, Meheus L, Huys I. On-Label or Off-Label? Overcoming Regulatory and Financial Barriers to Bring Repurposed Medicines to Cancer Patients. Front Pharmacol. 2020.
[78] Bayoumy AB, De Boer NKH. et. al. Unrealized potential of drug repositioning in europe during COVID-19 and beyond: A physcian's perspective. Journal of Pharmaceutical Policy and Practice, 13(1), 1–9. 2020.
[79] Zorginstituut Nederland [National Health Care Institute]. 'Medisch-specialistische zorg (Zvw) [Medical specialist care] https://www.zorginstituutnederland.nl/Verzekerde+zorg/medisch-specialistische-zorg-zvw, last accessed 7 January 2024.

outcome of the price negotiations. This procedure makes the business case for the product developer less predictable.

6.4.2 Dutch Medicines Pricing Act

The MAH is not completely free to set the price of a medicine in the Netherlands. Under the Dutch Medicines Prices Act (in Dutch: *Wet geneesmiddelenprijzen [WGP]*), the Minister of Health, Welfare and Sport can set a maximum price for a medicine that has been granted a marketing authorisation. The maximum prices are determined by the average of the prices of comparable medicines included in the price lists of four reference countries designated by law: France, Belgium, Norway and the United Kingdom. The maximum price may be set at such a low level that it becomes commercially unattractive for a company to market the medicine in the Netherlands. Moreover, due to a system called reference pricing, a low public price in the Netherlands may also result in lower prices in other countries.[80]

6.5 Other barriers

6.5.1 Post-marketing costs

6.5.1.a Marketing and informing prescribers

Effective marketing campaigns and educational initiatives aimed at informing prescribers may be crucial to ensure physicians are aware of new treatment options, including newly repurposed medicines. The investments in marketing campaigns and educational materials can pose a significant cost element for drug repurposing.

6.5.1.b Falsified Medicines Directive

The FMD introduces additional costs for repurposed medicines, as every medicine placed on the market needs to adhere to strict packaging requirements, including a unique identifier and anti-tampering seal. Implementing and ensuring all packaging complies with these requirements can involve significant costs. Ensuring compliance with the FMD also involves regulatory activities, including documentation, submission of necessary information to the European Medicines Verification System (EMVS), and regular compliance checks.

6.5.1.c Updating labels and packaging

After an extension of the therapeutic indication of a medicine that is already on the market, the packaging, labels and/or package leaflet must be updated by the MAH to include the new indication. This involves additional costs for production and distribution.

6.5.1.d Legal costs

Following the approval of a repurposed medicine, enforcing (medical use) patents and maintaining compliance with diverse legal and regulatory standards across (multiple) jurisdictions can be difficult and costly.

6.5.2 Limited knowledge, incentive and ambition of academic institutions to work towards a marketing authorisation

Although a significant portion of initial research in drug repurposing originates from academic institutions, academia often encounters challenges when trying to obtain a marketing authorisation.[81] Academic institutions may lack an understanding of the complexities and requirements associated with obtaining a marketing authorisation. For instance, academic

[80] Rémuzat C, Urbinati D, et al. Overview of external reference pricing systems in Europe. J Mark Access Health Policy. 2015.
[81] van den Berg S, de Visser S, Leufkens HGM, Hollak CEM. Drug Repurposing for Rare Diseases: A Role for Academia. Front Pharmacol. 2021; Verbaanderd C, Rooman I. et al. On-Label or Off-Label? Overcoming Regulatory and Financial Barriers to Bring Repurposed Medicines to Cancer Patients. Front Pharmacol. 2020.

researchers might be unaware of or unfamiliar with the specific evidence standards necessary for obtaining a marketing authorisation.[82] Furthermore, the majority of academic institutions often lack the ambition (e.g. because of limited incentives) to obtain a marketing authorisation. Instead, they prioritise scientific discovery and knowledge dissemination. In addition, they are not systematically rewarded for obtaining a marketing authorisation.[83] As a consequence, their findings are most likely to result in a scientific publication and/or an addition of a new off-label use to a clinical guideline.

The aforementioned problems are consistent with the findings of our survey (Annex 3). Based on our results, most researchers only intended to collect clinical evidence about the effectiveness of an existing medicine for a new indication. Only 3/21 (14%) respondents indicated that their drug repurposing research project had the initial ambition to submit a marketing authorisation application. Consequently, most researchers only had their results published a in scientific journal, which in some cases lead to inclusion of the medicine in a guideline. None of the GGG-funded projects succeeded in obtaining a marketing authorisation.

6.5.3 Applicant driven system

The MAH has the discretion to either extend or not extend its marketing authorisation with a new therapeutic indication. Hence, if third parties gather data with the intention of extending a marketing authorisation, this process will require the cooperation of the MAH. Other parties cannot initiate an extension of the existing marketing authorisation. For instance, if another pharmaceutical company or a patient organisation would like to submit an application for a marketing authorisation, it has to prepare its own marketing authorisation dossier. Likewise, competent authorities, such as the MEB and EMA, are also limited to a passive role, even if the extension would be in the interest of public health.

6.5.4 Lack of incentive for MAH to extend marketing authorisation

The MAH may abstain from extending its marketing authorisation, even when presented with favourable clinical data. The choice to extend or not extend a marketing authorisation is influenced by several factors. Firstly, the process requires the MAH to invest time and resources in preparing and submitting an application, with no guaranteed positive outcome. Additionally, the MAH might prioritise other products in their development pipeline or may not see the value in extending the therapeutic indication, especially if the new indication is outside their therapeutic focus. Furthermore, in certain EU countries, introducing a new therapeutic indication starts re-negotiation procedures of the medicinal product's price, potentially leading to a reduction in the overall price of the medicinal product.[84]

6.5.5 Cost of capital

The capital required to bring a repurposed medicine to the market is substantial. Companies that invest in drug repurposing need to know how much profit will be needed to offset the cost of the investment, but also the level of profit necessary to sustain their business operations and fund future investments.[85] The prolonged and uncertain process of obtaining marketing authorisation and reimbursement, as well as the consistently changing legal and market landscapes, all contribute to the high cost of capital.

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[82] Starokozhko V, Heß A. et al. Strategic recommendations from the STARS project to foster academic drug development. Nat Rev Drug Discov. 2023; Breckenridge, A., Jacob, R. Overcoming the legal and regulatory barriers to drug repurposing. Nat Rev Drug Discov 18, 1–2. 2019.

[83] Verbaanderd C, Rooman I, Meheus L, Huys I. On-Label or Off-Label? Overcoming Regulatory and Financial Barriers to Bring Repurposed Medicines to Cancer Patients. Front Pharmacol. 2020.

[84] Mulder J, Verjans R. et al. Extension of Indication for Authorised Oncology Products in the European Union: A Joint Effort of Multiple Stakeholders. Front Med (Lausanne). 2021.

[85] Harrington S. Cost of Capital for Pharmaceutical, Biotechnology, and Medical Device Firms. The Oxford Handbook of the Economics of the Biopharmaceutical Industry. 2009.

CHAPTER 7

Recommendations

This chapter presents a set of recommendations for overcoming the barriers to drug repurposing identified in the Chapter 6. These recommendations are the culmination of a comprehensive analysis that incorporates extensive literature review, expert interviews, case studies, a survey among 45 drug repurposing projects and our own experiences in the field. An overview of the recommendations is presented in Table 2.

The recommendations should be considered holistically, as their potential to stimulate drug repurposing can vary depending on the specific combination of recommendations applied. While some combinations may result in a positive business case for certain products, other combinations may not. The primary objective of these recommendations is to create a level of certainty and predictability regarding investment and return on investment. This entails minimising investments while maximising returns, with the goal of making the investment-return balance sufficiently attractive for product developers.

Table 2. *Overview of recommendations to stimulate drug repurposing*

Goal	Recommendations
Facilitating research and authorisation within the current regulatory framework	- Encourage collaboration between industry and academia - Conduct further research to understand why researchers may not always aim to obtain marketing authorisation and to develop strategies that may encourage them to do so - Consider making government funding of academic research conditional upon the intent to seek market approval - Assess and clarify the feasibility of incorporating and relying on RWE to substantiate the positive benefit-risk balance - Encourage originator companies to be transparent and share data - Establish fee exemptions or reductions for regulatory procedures
Enhancing protection of repurposed medicines	- Conduct further research to determine both the necessary duration and the type of protection (market and/or data exclusivity) required to facilitate an adequate return on investment for product developers - Restrict cross-label use; strengthen the enforcement of patents and regulatory protection, and include the indication on prescriptions - Restrict off-label use by providing guidance to physicians and pharmacist and providing MAHs with an incentive for extending the indication - Consider legal changes to ensure that pharmacy preparations are only used if no authorised adequate alternative medicine (with the

Goal	Recommendations
	same active substance, dosage form, and strength) is available on the market
Facilitating adequate reimbursement	- Grant repurposed medicines a privileged position for reimbursement - Exemption from reimbursement and pricing limits - Promote awareness of the significance and potential of drug repurposing, as well as the drug development and investment decisions required, among policymakers and health insurers
Other recommendations	- Sustaining support for (inter)national collaboration platforms - Changing the applicant driven system

7.1 Facilitating research and authorisation within the current regulatory framework

Academic institutions often lack the knowledge, practical experience and (organisational) capacity necessary to successfully obtain a marketing authorisation on their own. Therefore, academic institutions could for example benefit from support by industry stakeholders when trying to obtain a marketing authorisation. Such collaboration should (continue to) be encouraged by the EU and national governments.

Academic institutions should be stimulated to work towards a marketing authorisation, whether independently or in collaboration with the industry. However, academic researchers often seem to aim for implementation of their findings in medical guidelines rather than seeking marketing authorisation. Further research is required to comprehend why researchers may not always aim to obtain marketing authorisation and to develop strategies that may encourage them to do so.

Government funding of academic research could be made conditional upon the intent to seek market approval. This would incentivise researchers to take into account the requirements for obtaining a marketing authorisation. This could ensure that clinical trials conducted by academic institutions align with regulatory standards, thereby increasing the likelihood that the outcomes of academic trials are eligible for the application of (an extension of) a marketing authorisation.

Drug repurposing candidates often have extensive RWE available due to their widespread off-label use. The feasibility of incorporating and relying on RWE to substantiate a positive benefit-risk balance needs further research and clarification for both public and private product developers. Increased use of RWE in relation to the authorisation procedure could reduce research costs and streamline the authorisation process for repurposed medicines with substantial RWE. It is important to create more support for RWE and to lay down criteria which provide the appropriate basis for its use in marketing authorisation.

Furthermore, encouraging transparency and data sharing from originator companies, through legal mandates or financial incentivisation, could lower the barriers related to access to essential data for obtaining a marketing authorisation.

Finally, to facilitate the process of obtaining a marketing authorisation for drug repurposing, it may be beneficial to consider fee exemptions or reductions for regulatory procedures for all applicants.

7.2 Enhancing protection of repurposed medicines

The absence of adequate protection measures against competitors presents a significant barrier to drug repurposing. It adds to the uncertainty for the (future) MAH whether it may obtain an adequate return on investment. This barrier centres around intellectual property rights, but also off-label use and pharmacy preparations. Without adequate protection, a product developer may not recoup its investment, thereby undermining the incentive to engage in drug repurposing. Additional protective measures are therefore needed, as discussed in the next paragraphs.

7.2.1 Examination of additional protection

As discussed in section 6.3.1, when an extension of indication of an already authorised medicine is approved for a new therapeutic indication, the repurposed medicine does not receive much (additional) protection. This limits the potential for an adequate return on investment. Further research should therefore be conducted to determine both the necessary duration and the type of protection required to facilitate an adequate return on investment for product developers, like granting a specified number of years of market and/or data exclusivity following the approval of a new indication.[86] Third parties should ultimately be prevented from taking advantage of the investments made by the initial applicant of the marketing authorisation of the repurposed medicine for a pre-defined period.

7.2.2 Restriction of cross-label use, off-label use and pharmacy compounding

Effective protection of repurposed medicine against generics necessitates a reduction in cross-label use, see sections 4.2 and 6.3.2.a. A recommendation to protect repurposed medicines from cross-label use is to strengthen the enforcement of patents and regulatory protection. When prescribing a medicine, the inclusion of indications enables pharmacists to dispense the medicine that still benefits from patent or regulatory protection (in relation to the repurposed use). For example, implementing software solutions that align prescriptions and dispensing practices with protected uses may help to enforce the intellectual property rights of repurposed medicines.[87]

As noted in section 6.3.2.a off-label use may disincentivise companies to apply for an extension of the indication of its marketing authorisation. If physicians and pharmacists can readily provide medicines for treating a condition not included in the label, there is no incentive for a MAH to apply for an extension of the indication. An overall restriction on off-label use might not be an appropriate solution as it would deny patients access to a medical treatment. However, considering the benefits of the marketing authorisation as outlined in section 4.2 physicians and pharmacists should be more educated in the benefits and risks of off-label use. Their professional associations may issue guidelines on off-label use. In addition, MAH should be provided with an incentive to apply for an extension of the indication of their medicine as proposed in section 7.2.1.

As discussed in section 6.3.2.b, pharmacy compounding may also constitute a barrier to drug repurposing because the current protective mechanisms for authorised medicines can be bypassed by pharmacy preparations. To address this barrier, pharmacists and policy makers may put more emphasis on the need to thoroughly assess the availability of authorised medicines before compounding a medicine that may have been approved for a particular indication. To ensure that pharmacy preparations are only used if no authorised adequate alternative medicine (with the same active substance, dosage form, and strength) is available on the market, legal changes should be considered.

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[86] See the reflection in section 5.2 on the proposal by the European Commission to amend the regulatory protection with regard to drug repurposing.

[87] Breckenridge A, Jacob R. Overcoming the legal and regulatory barriers to drug repurposing. Nat Rev Drug Discov 18, 1–2. 2019.

7.3 Facilitating adequate reimbursement

In the context of drug repurposing, inadequate reimbursement of repurposed medicines presents a barrier that significantly undermines the business case. This issue is, in the Netherlands, intrinsically linked to the current medicine reimbursement system GVS and the practice having a preference for the use of generic medicines as pointed out in section 6.4. Measures should be considered to facilitate adequate reimbursement and pricing for repurposed medicines as proposed below.

7.3.1 Privileged position for reimbursement

To increase the possibility to make an adequate return on investment, repurposed medicines should be granted a privileged position for reimbursement. In practice, this requires that when a medicine is prescribed for its repurposed indication, patients should specifically receive the brand associated with the repurposed indication. This approach should prevent substitution by other generic brands or pharmacy preparations. This also requires that if a physician prescribes a medicine with the active substance of any repurposed medicine, the prescriber needs to include the indication on the prescription. Otherwise, the pharmacy will not be able to dispense the correct repurposed product. The privileged position of a repurposed medicine needs to be enforceable by law in order to provide sufficient certainty and predictability to developers and their investors to create a special status for repurposed medicines. In regard to reimbursement, the paper released by FAST as referred to in section 6.4.1 offers additional recommendations and underscores the importance of legal regulation to ensure certainty and predictability for product developers to have their medicine reimbursed.[88] We align with the idea that an incentive to drug repurposing through the reimbursement of medicine should be legally instituted and sustained.[89]

7.3.2 Exemption from reimbursement limits

If a repurposed medicine is clustered with other medicines in the Dutch medicine reimbursement system GVS, the repurposed medicine is set at the same reimbursement limit as other medicines in the cluster, including other medicines with the same active substance. For those other medicines the MAH did not have to make additional investments for obtaining the market authorisation for the new therapeutic indication. To sell the medicine for a price equal to the reimbursement limit may not provide a profitable return on investment for the MAH. Similarly, the statutory maximum price established by the Dutch Medicines Prices Act may also pose a barrier to an adequate return on investment. Therefore, it should be considered to provide the MAH of a repurposed medicine an exemption from these legal reimbursement or pricing limits.

7.3.3 Promoting awareness among policymakers and health insurers

To successfully facilitate adequate reimbursement of repurposed medicines, greater awareness and understanding are necessary among policymakers and health insurers regarding the significance and potential of drug repurposing, as well as understanding of the drug development process and investment decisions required. This may start with a more in-depth assessment of the considerations and decisions made by pharmaceutical companies and their investors in the course of drug repurposing ventures. By addressing current knowledge gaps and creating more consensus and awareness among all stakeholders about justifiable return of investments in repurposed medicines, the potential of drug repurposing can be further increased.

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[88] FAST rapport (November 2023). Drug repurposing als snelle route naar betaalbare nieuwe behandelingen- Uitzonderingspositie (FAST report (November 2023). Drug repurposing as a fast route to affordable new treatments - Privileged position).
voor generiek merk moet bedrijven stimuleren.

[89] The legal department of the Ministry of Health Welfare and Sport notes a number of limitations to the possibility for reducing (financial obstacles for drug repurposing. See the report 'Verkenning naar de mogelijkheden tot het verminderen van de (financiële) obstakels bij drug repurposing' of 8 August 2023: https://www.rijksoverheid.nl/documenten/rapporten/2023/08/04/rapport-drug-repurposing last accessed 12 January 2024.

7.4 Other recommendations

7.4.1 Sustaining support for (inter)national collaboration platforms

Several (inter)national platforms are in place or are being set up to facilitate the communication and collaboration among various stakeholders, including EU-funded initiatives like REMEDi4ALL and REPO4EU, alongside national initiatives such as Future Sustainable Affordable Therapies (FAST).[90] These initiatives encourage collaboration in research, funding and regulatory aspects of drug repurposing, and support the establishment of comprehensive data hubs that support information sharing, training and matchmaking. Annex 2 discusses these initiatives, among others, in more detail.

Recognising that pharmaceutical companies operate on a global scale, it is important to engage in international discussions and agreements regarding protection, pricing, reimbursement, and other key factors. The international platforms (REMEDi4ALL, REPO4EU) are currently in the process of being established and are anticipated to become operational by 2027. Within REMEDi4ALL for instance, there are specific work packages focused on addressing major barriers, such as facilitating authorisation and reimbursement for product developers, and collaboration is ongoing with a policy board comprising various national and international organisations. Moreover, due to the diverse reimbursement procedures across EU Member States, more international harmonisation could be beneficial for stimulating drug repurposing. The issue of differing reimbursement policies within Europe is already a topic of discussion within REMEDi4al.

The international initiatives like REMEDi4all and REPO4EU as well as the national initiative under the umbrella of FAST are key in enhancing collaboration among various stakeholders of drug repurposing. Such initiatives should be sustained support, and the focus should remain not only national but also internationally.

7.4.2 Changing the applicant driven system

Section 6.5.3 refers to the applicant driven system as a barrier to drug repurposing. The European Commission has proposed the introduction of a framework that would enable not-for-profit organizations to present both non-clinical and clinical evidence to the EMA or the national competent authority, advocating for new therapeutic uses of existing medicines to address unmet medical needs, as is outlined in section 5.2. Should the assessment of the proposed use be positive in terms of benefits and risks, the MAHs of the medicines in question are then required to submit an application to incorporate the new therapeutic indication into their SmPC.[91] This changes the current applicant driven system to an *evidence driven system*.

The proposed framework may have the potential to stimulate drug repurposing. Academic institutions may benefit as they can implement their research findings with the prospect of MAHs applying for an extension of the indication. This reduces the need of academic institutions to obtain a marketing authorisation themselves, if the MAH does not cooperate. However, further research and discussion are necessary to fully grasp the potential consequences of these amendments. For instance, if MAHs are obligated to apply for an extension of the indication, the reform could lead to new challenges, such as financial complications for MAHs. The costs associated with submitting such an application may not be offset by the benefits of a potentially broader patient population, for example if their medicine was already used off-label for the 'new' therapeutic indication, or if the MAH foresees liability issues regarding the new therapeutic indication. In such cases, MAHs might opt to withdraw their product from market, inadvertently limiting access to such medicines. Additionally, the reform introduces the risk that academic institutions may submit evidence for the

[90] Website REPO4EU: https://repo4.eu/, last accessed 7 January 2024.
Website REMEDi4ALL: https://remedi4all.org/, last accessed 7 January 2024.
Website FAST: https://www.fast.nl/, last accessed 7 January 2024.
[91] Article 48(1) and (2) of the proposal by the European Commission for the regulation.

new use of a medicinal product to the competent authority, while the MAH is simultaneously developing a dossier for the same medicinal product. This may lead to unnecessary investments, which may make MAHs more reluctant to start such developments at all.

CHAPTER 8

Drug repurposing in the context of a pandemic and paediatric applications

8.1 Opportunities and challenges for drug repurposing in a pandemic

During the COVID-19 pandemic starting in 2020, many drug repurposing initiatives were launched to study the effectiveness of existing medicines for the treatment of COVID-19 patients.[92] The drug repurposing case of dexamethasone (see Annex 1) demonstrates how close collaborations between academic institutions can quickly result in a marketing authorisation for a repurposed indication.

However, several challenges were identified during the pandemic. Firstly, the lack of an efficient monitoring centre for the many drug repurposing initiatives limited coordination of parallel initiatives that could have benefited from more alignment. International collaborations such as CURE ID, a joint initiative between the in the United States Food and Drug Administration (FDA) and the National Institutes of Health (NIH), can be exemplary for building multi-stakeholder partnerships for coordinating and advancing drug repurposing collectively in a global public health crisis such as a pandemic.[93] These international drug repurposing collaborations can also help to avoid potential duplication of research efforts, simplify the process of verifying research quality, and ultimately lead to more efficient use of funds and participants. It is recommended that comparable initiatives are set up at the European level.

Secondly, in the context of a pandemic, the short-term market demand is a challenge. On the one hand, the urgency and demand for treatments during a pandemic create a favourable market for repurposed medicines. On the other hand, this demand may significantly diminish in the post-pandemic phase, which can affect the business case for investing in drug repurposing. Additionally, repurposed medicines will not only compete amongst each other, but also with medicines developed through de novo pathways.

8.2 Opportunities and challenges for drug repurposing for paediatric applications

Children have different metabolic rates, organ maturity, and developmental stages, which significantly alter the pharmacokinetics and pharmacodynamics of medicines. Moreover, certain diseases are specific to paediatric populations. Paediatric medicine development aims to facilitate the development of new applications and access to medicines for children. However, many medicines, for example those that are initially developed for adults, may not have been adequately studied in paediatric populations. This lack of paediatric trials means that there is limited data on safety and efficacy, and optimal dosages in this population. This has contributed to a situation where more than half of all paediatric formulations are used off-label due to the lack of a formal marketing authorisation.[94]

Despite the challenges for obtaining marketing authorisation in paediatric populations, for example due to the lack of robust clinical studies in children, drug repurposing has been successful in bringing

[92] Open Source Pharma Foundation. 'Covid-19 response' https://www.ospfound.org/open-research-platform.html, last accessed 7 January 2024.
[93] Office of the Assistant Secretary for Planning and Evaluation. 'CURE ID: Aggregating and Analyzing COVID-19 Treatments from EHRs & Registries Globally' https://aspe.hhs.gov/cure-id-aggregating-analyzing-covid-19-treatments-ehrs-registries-globally#:~:text=CURE%20ID%20is%20a%20joint,directly%20from%20healthcare%20providers%20worldwide, last accessed 7 January 2024.
[94] Centre of Future Affordable Sustainable Therapies. 'Uitgelicht traject: Van off-label naar effectieve en veilige geneesmiddeltherapie voor kinderen' [Highlighted trajectory: From off-label to effective and safe medicine therapy for children] https://www.fast.nl/news/van-offlabel-naar-effectieve-geneesmiddeltherapie-voor-kinderen/, last accessed 7 January 2024.

new therapeutic options to children, such as the recently approved paediatric indication for fenfluramine in the treatment of Dravet- and Lennox-Gastaut Syndrome (see Annex 1). This shows the significant potential of drug repurposing for developing new indications for existing medicines not only for adults, but also for paediatric populations.

Pharmaceutical companies, in particular innovator companies that aim to bring novel medicines to the market, should be stimulated to include assessments of the safety and effectiveness in children, and where necessary develop appropriate formulations for use in paediatric populations. Paediatric investigation plans (PIPs) are in place in the EU that require companies to provide the necessary data obtained from clinical studies in children (unless a waiver is granted). However, if the proposed indication of a newly approved medicine is not intended for paediatric populations, and a waiver is granted, no studies in children have to be done.[95] Moreover, old medicines of which the patent and SPC protection expired before 2007 did not fall under the PIP requirement.[96] This also applies to medicines that obtain a marketing authorisation based on a generic, hybrid or well-established use application.[97] Hence, this may create challenges for drug repurposing initiatives for developing new applications for children where clinical data and age-appropriate formulation are not available.

While regulatory science initiatives can play an important role in facilitating evidence generation for paediatric applications as well as identifying age-appropriate formulations for children where this has not available, MAHs should be encouraged to provide more information on appropriate use in children. Stimulating paediatric development programmes as well as facilitating public research initiatives can ultimately help to expedite drug repurposing initiatives for developing new paediatric applications for existing medicines. Moreover, public research initiatives can help to investigate how to better generate knowledge from available clinical studies and clinical data such as RWE to inform clinical decision-making in paediatric populations. This should involve the exploration of new methods to generate evidence, simulation methods or additional clinical studies to gather evidence. Projects like the paediatric research initiatives from FAST are essential drivers for developing novel methods for timely assessments of the efficacy and safety of new applications of medicines in children.[98]

[95] Ivanovska V, Rademaker CM, van Dijk L, Mantel-Teeuwisse AK. Pediatric drug formulations: a review of challenges and progress. Pediatrics. 2014.
[96] Article 7 and Article 8 of Regulation (EC) No 1901/2006.
[97] Article 9 of Regulation (EC) No 1901/2006.
[98] Centre of Future Affordable Sustainable Therapies. 'Uitgelicht traject: Van off-label naar effectieve en veilige geneesmiddeltherapie voor kinderen' (Highlighted trajectory: From off-label to effective and safe medicine therapy for children) https://www.fast.nl/news/van-offlabel-naar-effectieve-geneesmiddeltherapie-voor-kinderen/, last accessed 7 January 2024.

CHAPTER 9

Reflection and concluding remarks

Significant developments have occurred in the drug repurposing landscape since the 2012 report was published. For instance, there has been considerable progress in aspects such as funding, increased awareness, and technological innovations. The 2012 report concluded that there was little practical research being carried out on drug repurposing, ascribed to insufficient financing and the relatively poor scientific status of such research. This has since changed. Over the past decade, there has been a substantial increase in practical research within the field of drug repurposing. Factors contributing to this increase include overall more funding for drug repurposing research, more national initiatives like the ZonMw GGG-programme, including a dedicated programme for drug repurposing, and Future Affordable Sustainable Therapies (FAST), as well as more international initiatives such as EU funded projects REMEDi4All and REPO4EU. Moreover, increased awareness of the potential of drug repurposing, partly due to the COVID-19 pandemic, has stimulated research efforts. Furthermore, technological advancements, particularly in artificial intelligence (AI)-driven in silico research, have facilitated the identification of potential compounds for drug repurposing.[99] These trends are substantiated by the findings of the expert consultations and survey, and are observable in the growing number of publications on scholarly search platforms.[100]

Another barrier discussed in the prior report was limited government involvement and a missing toolbox for regulatory/government authorities to incentivise drug repurposing. With recent initiatives like FAST and the GGG programme, there is a clear indication of the government's increased involvement and improved approach to stimulate drug repurposing. While a comprehensive toolbox for incentives may not yet exist, the government's efforts have notably improved the drug repurposing landscape.

Furthermore, a small market was considered as a potential barrier in the 2012 report. This barrier was related to the potential challenges of realising a return on investment in the context of orphan diseases. Despite receiving support in research and development and being granted ten years of orphan market exclusivity, it was argued that the likelihood of achieving an adequate return on investment remained uncertain. However, in the current landscape various authorised repurposed medicines target orphan diseases; as is also evident from drug repurposing cases discussed in Annex 1. The orphan market exclusivity of 10-years appears to be an incentive for pharmaceutical companies to invest in drug repurposing.

In order to address the barriers to drug repurposing identified in this report, we recommend that policymakers, such as the Ministry of Health, Welfare and Sport, prioritise several key areas, preferably addressed in conjunction with each other:

- encourage (more) collaboration between academic institutions and the industry;
- support and stimulate academic institutions to work towards a marketing authorisation;
- address issues related to market protection and reimbursement to increase the likelihood and predictability of an adequate return on investment;
- sustaining support for (inter)national collaboration platforms.

[99] Mullins JGL. Drug repurposing in silico screening platforms. Biochem Soc Trans. 2022.
[100] De Vita S, Chini MG, Bifulco G, Lauro G. Target identification by structure-based computational approaches: Recent advances and perspectives, Bioorganic & Medicinal Chemistry Letters, Volume 83. 2023.

We also recommend considering specific measures for drug repurposing in the contexts of pandemic preparedness and paediatric applications:

- promote monitoring and coordination efforts in future pandemics, through international collaboration and coordination platforms specifically focused on pandemic preparedness;
- stimulate pharmaceutical companies to routinely incorporate paediatric assessments of efficacy and appropriate formulations into their standard drug development programmes.

To specifically address the primary challenge - the business case for product developers - we recommend a follow-up research on industry-driven drug repurposing research initiatives. This study would provide deeper insights into the industry's unique challenges and perspectives concerning drug repurposing.

ANNEX 1

Drug repurposing cases

In the annex presented here, we discuss seven drug repurposing cases. These cases have helped in identifying and understanding the various barriers, facilitators, and the overarching context surrounding drug repurposing efforts. Each case offers unique insights and contributes significantly to the comprehensive analysis provided in this report. The table presented below offers a broad overview of the cases. It includes information such as the name of each medicine, its original and new indications, along with the corresponding approval dates. Additionally, for each drug repurposing case the table highlights the main study that supported the new use and approval, and it incorporates comments on the outcome of each case.

Overview of seven cases of successful drug repurposing trajectories

Name of medicine	Original indication(s)	New indication(s)	Approval date original indication	Approval date new indication	Main study	Comments on outcome
Mexiletine (Namuscla)	Cardiac arrhythmias	Non-dystrophic myotonia (NDM)	1975 (MEB)	2018 (EMA)	Phase-III clinical trial (MYOMEX)	Approved for the treatment of NDM in the EU and obtained 10 years of orphan market exclusivity. Not included in the Dutch GVS due to the presumption by ZIN that the price is excessive. Pharmacy preparations and imported mexiletine are the current treatment options.
Colchicine	Gout	Prevention cardiovascular disease (CVD)	1998 (MEB)	2023 (FDA), not approved by EMA[101]	Phase-III clinical trial (LoDoCo2)	Approved to reduce the risk of myocardial infarction, stroke, coronary revascularization, and cardiovascular death in The United States. Not approved in the EU.
Dexamethasone	Inflammatory conditions, allergies,	Coronavirus disease 2019 (COVID-19)	1966 (MEB)	2020 (EMA)	Phase-III clinical trial (RECOVERY)	Approved for the treatment of COVID-19, in the EU and The United States. Two pharmaceutical

[101] Marketing authorisation application has not (yet) been submitted to the EMA.

	autoimmune diseases, and certain cancers					companies included the new indication to their SmPC's.
Chenodeoxycholic acid (CDCA-Leadiant)	Gallstones	Cerebrotendinous xanthomatosis (CTX)	1976 (MEB)	2017 (EMA)	Retrospective single arm cohort study	Approved for the treatment of CTX and obtained 10 years of orphan market exclusivity. However, not included in the Dutch GVS due to the presumption by ZIN that the price is excessive. Pharmacy preparations are the current treatment option.
Fenfluramine (Fintepla)	Appetite suppressant for adult obesity	Dravet syndrome, Lennox-Gastaut syndrome	1963 (MEB)	2020 (EMA) for Dravet syndrome; 2023 (EMA) for Lennox-Gastaut syndrome	Phase-III clinical trial	Approved as add-on for the treatment of Dravet syndrome and Lennox-Gastaut syndrome, and obtained 10 years of orphan market exclusivity. Received positive advice from ZIN, for inclusion in the Dutch GVS.
Propranolol (Hemangiol)	Cardiovascular diseases, prophylaxis of migraine, and management of essential tremor.	Proliferating infantile haemangioma	1983 (MEB)	2014 (EMA)	Phase II/III randomized placebo-controlled clinical trial	Received a PUMA for the treatment of proliferating infantile haemangioma. Currently first-choice therapy for infantile haemangioma and it is included in the Dutch GVS.
6-Thioguanine (Thiosix)	Leukaemia in children	Inflammatory bowel disease (IBD)	1975 (MEB)	2022 (MEB)	Available data from clinical trials on the safety and efficacy. MAH only conducted a bioequivalence study.	Approved for the treatment IBD, after a timeline of 15 years. It was the first medicine in the Netherlands to be granted a conditional marketing approval, via the MEB. It is also included in the Dutch GVS.

Abbreviations: COVID-19 = Coronavirus disease 2019, CTX = Cerebrotendinous Xanthomatosis, CVD = Cardiovascular Disease, EMA = European Medicines Agency, GVS = Geneesmiddelenvergoedingssysteem (Medicine reimbursement system), IBD = Inflammatory Bowel Disease, LoDoCo2 = Low-Dose Colchicine study (2) , MAH = MAH, MEB = Medicines Evaluation Board (in Dutch: *College ter Beoordeling van Geneesmiddelen [CBG]*), NDM = Non-dystrophic myotonia, PUMA = Paediatric-Use Marketing Authorisation, SmPC = Summary of Product Characteristics, ZIN = Zorginstituut Nederland (Dutch National Health Care Institute).

Mexiletine (Namuscla)

Case description

Mexiletine, an off-patent medicine, was first approved in Europe during the 1970's for the treatment of cardiac arrhythmias. In the Netherlands, it was first approved in 1975. For commercial reasons, however, it was withdrawn from the market in 2004.[102] Subsequently, pharmacy preparations and imported mexiletine (approved elsewhere) have been used to treat patients with cardiac arrhythmias. Mexiletine was also used off-label to treat non-dystrophic myotonia (NDM), a rare type of muscular dystrophy.[103]

NDM is a genetic condition that causes muscle stiffness and weakness, with an estimated prevalence of ~1 per 100,000 people.[104] The efficacy of mexiletine in treating NDM was first established in a Phase 2 clinical trial, with findings published in 1992.[105] Since 1992, numerous case studies, phase 2 trials, and retrospective studies have been published that support the use of mexiletine in the treatment of NDM.

The MYOMEX study was the first Phase 3 clinical trial that assessed the safety and efficacy of mexiletine in the treatment of NDM. The MYOMEX study was a randomized, double-blind, placebo-controlled trial, which concluded that mexiletine was significantly more effective than placebo in reducing muscle stiffness and improving quality of life in patients with NDM. The MYOMEX study was conducted from 2011 to 2014 and was funded and supported by the Assistance Publique-Hôpitaux de Paris and AFM-Téléthon.[106] In 2016, the Assistance Publique-Hôpitaux de Paris entered into a partnership with the pharmaceutical company Lupin.[107]

In 2017, Lupin submitted an application for marketing authorisation to the European Medicines Agency for Namuscla (the new brand name for mexiletine) for the treatment of NDM. This was a full application under Article 8(3) of Directive 2001/83/EC. Namuscla has been developed as an orphan medicinal product to treat symptoms of myotonia in adult patients with NDM and has been approved in 2018. It has been granted 10 years of orphan market exclusivity. The market approval is based on the results of the MYOMEX study.[108]

In 2020, Lupin submitted an application for inclusion of Namuscla in the GVS. ZIN advised against including Namuscla in the GVS, because of the low cost-effectiveness (compared to alternatives) and significant price increase compared to the previously authorised and the imported mexiletine. Prior to the withdrawal from the market in the 2000s, mexiletine was widely available at costs ranging from €198 to €249 per patient per year (PPPY). Subsequently, the importation of mexiletine led to a price increase, ranging from €1,777 to €4,643 PPPY (list prices). Following the market approval of Namuscla, the price of mexiletine increased further, reaching between €30,707 and €60,730 PPPY.[109] ZIN disapproved the behaviour of unsubstantiated price increases, and stated that the higher price of Namuscla was not proportionate to the efforts required to obtain the market authorisation for Namuscla. ZIN also concluded that Namuscla was not more cost-effective than the alternatives (pharmacy preparations and imported mexiletine).

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[102] Zorginstituut Nederland (Dutch National Health Care Institute). 'GVS-advies mexiletine (Namuscla)'. 2021

[103] Van den Berg S, de Visser S, Leufkens HGM, Hollak CEM. Drug Repurposing for Rare Diseases: A Role for Academia. Front Pharmacol. 2021.

[104] Auranen, Mari, et al. "Improving The Management of Non-dystrophic Myotonia to Benefit Care Delivery and Improve Patient Outcomes." Neurology. 2022.

[105] Kwieciński H, Ryniewicz B, Ostrzycki A. Treatment of myotonia with antiarrhythmic drugs. Acta Neurol Scand. 1992.

[106] National Library of Medicine. 'Mexiletine and Non Dystrophic Myotonias (MYOMEX)' https://classic.clinicaltrials.gov/ct2/show/NCT02336477, last accessed 8 January 2024.

[107] Scrip. 'Lupin Gears For Europe Specialty Push With Orphan NaMuscla' https://scrip.citeline.com/SC124035/Lupin-Gears-For-Europe-Specialty-Push-With-Orphan-Namuscla®. Last accessed 8 January 2024.

[108] European Medicines Agency. 'Namuscla: EPAR - Product information'. 2023.

[109] Van den Berg S, van der Wel V, de Visser SJ, Stunnenberg BC, Timmers L, van der Ree MH, Postema PG, Hollak CEM. Cost-Based Price Calculation of Mexiletine for Nondystrophic Myotonia. Value Health. 2021.

The Minister of Health, Welfare and Sport decided not to include Namuscla in the GVS, following the advice of ZIN. In a letter to the Chair of the House of Representatives of the States General, the incumbent Minister of Health, Welfare and Sport also expressed her opposition to the practice of 'polishing' old medicine in order to charge a high price. Pharmacy preparations and imported mexiletine have remained the current treatment option for patients.[110]

Reflection

This case shows barriers in the pricing and reimbursement of repurposed medicines. The price increase resulted in a political debate on repurposed medicine despite the benefits of having a medicine with a marketing authorisation for the new therapeutic indication. The case shows the need for society to have clear and predictable regulations on pricing and reimbursement limits for medicines.

[110] Van Ark, T. 'Brief van de Minister voor Medische Zorg' (Letter from the Minister for Medical Care). https://zoek.officielebekendmakingen.nl/kst-29477-713.pdf. 2021.

Colchicine

Case description

Colchicine is an off-patent anti-inflammatory medicine that has been used for centuries to treat gout. In the Netherlands, the first colchicine generics were approved in 1998. In recent years, it has also been researched for its potential to treat other diseases, such as cardiovascular disease (CVD).

In November 2020, the low-dose colchicine 2 (LoDoCo2) study was published in the New England Journal of Medicine.[111] The LoDoCo2 trial was a randomized controlled trial to investigate the efficacy and safety of low-dose colchicine in the secondary prevention of cardiovascular events in patients with CVD. It was funded by Dutch and Australian government funds and investments from two pharmaceutical companies (Teva and Tiofarma). LoDoCo2 concluded that colchicine could reduce the risk of another heart attack or stroke in heart patients by 30%.

The results of the LoDoCo2 trial provided strong evidence for the safety and efficacy of low-dose colchicine as a preventive measure against cardiovascular events in a wide range of patients with CVD. However, the indication for colchicine to treat CVD was not approved in any country at the time of the publication of the clinical trial.

After publication of the research results, Teva and Tiofarma asked the Dutch Ministry of Health and health insurers for assistance. Their request was to seek permission to set a higher price (compared to the already marketed generic colchicine medicines) and to receive a period of market protection against potential competitors entering the colchicine market for the use of colchicine in the prevention of cardiovascular events in patients with CVD. However, their request was rejected by the Dutch Ministry of Health, Welfare and Sports.

Three years later, FDA approved colchicine to reduce the risk of myocardial infarction, stroke, coronary revascularization, and cardiovascular death in adult patients in the United States. It was approved through a 505(b)(2) application, which is comparable to the hybrid application under Article 10(3) in the EU. FDA's decision was based on the publication of the LoDoCo2 trial.[112] Neither Teva nor Tiofarma (or any of the other stakeholders involved in the LoDoCo2 trial) were involved in the application process for the marketing authorisation in the United States. While the applicant (AGEPHA Pharma) did not obtain market exclusivity from the FDA, they did however acquire several medical use patents for the new indications.[113]

Reflection

Teva and Tiofarma showed reluctance to initiate the authorisation procedure, which was mainly attributed to a low expected return on investment. This underscores the barriers associated with inadequate market protection and reimbursement. In contrast, AGEPHA Pharma had a higher expected return on investment, capitalising on the research previously conducted by Teva, Tiofarma and other stakeholder involved in the LoDoCo2 trial. AGEPHA Pharma is also the first company in the United States to receive authorisation for the 0.5mg dosage of colchicine. In the United States, all colchicine generics are at 0.6mg dosage, which means that there are no generic alternatives to

[111] Nidorf, Stefan M., et al. 'Colchicine in patients with chronic coronary disease', New England journal of medicine 383.19. 2020.
[112] Ebrahimi F, Hirt J, Schönenberger C, Ewald H, Briel M, Janiaud P, Hemkens LG. Colchicine for the secondary prevention of cardiovascular events. Cochrane Database Syst Rev. 2023; U.S. Food and Drug Administration. 'NDA APPROVAL' https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2023/215727Orig1s000ltr.pdf. 2023.
[113] U.S. Food and Drug Administration. ' Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations - COLCHICINE (LODOCO) TABLET 0.5MG https://www.accessdata.fda.gov/scripts/cder/ob/patent_info.cfm?Product_No=001&Appl_No=215727&Appl_type=N, last accessed 9 January 2024.

compete with the newly authorised colchicine version. This may have also increased the expected return on investment.

This case emphasises the need for supportive measures that enhance return on investment prospects for pharmaceutical companies, such as increased market protection and more favourable reimbursement agreements.

Dexamethasone

Case description

Dexamethasone is an off-patent corticosteroid medicine that has been available for several decades, having been first approved in the Netherlands in 1966.[114] It can be used orally and by injection for treating a range of inflammatory conditions and for reducing the body's immune response in the treatment of allergies and autoimmune diseases. It is also used with anti-cancer medicines to treat certain cancers and prevent vomiting.

At the onset of the COVID-19 pandemic, the University of Oxford launched the RECOVERY trial to investigate the potential therapeutic applications of dexamethasone and other medicines in the treatment of the disease. Dexamethasone was considered a potential treatment for COVID-19 because of its ability to reduce inflammation, which plays an important role in the disease process in some patients who have been admitted to hospital with COVID-19. The RECOVERY trial is still ongoing through other study arms, and is supported by grants from several organisations, including the National Institute for Health and Care Research (NIHR), UK Research and Innovation and the Bill and Melinda Gates Foundation.[115]

In June 2020, preliminary results of the RECOVERY Trial were published in a preprint.[116] The dexamethasone study arm concluded that low-dose dexamethasone treatment reduced the death rate by one third in hospitalised people needing ventilators due to severe COVID-19 infection, and by one fifth in people treated with oxygen therapy. There was no benefit among patients who did not require oxygen. The preliminary report was published in The New England Journal of Medicine.[117]

In July 2020, the EMA started to review the results from the RECOVERY trial. The review by the CHMP was initiated under Article 5(3) of Regulation 726/2004 following preliminary discussion with the COVID-19 EMA pandemic task force. Article 5(3) of the Regulation allows the executive director of the EMA or the European Commission representative, to request the CHMP to draw up an opinion on any scientific matter concerning the evaluation of medicinal products for human use.

In September 2020, EMA's CHMP completed its review of the results. They concluded that dexamethasone can be considered as a treatment option for patients who require oxygen therapy (from supplemental oxygen to mechanical ventilation).[118] Subsequently, dexamethasone was approved in adults and adolescents (from twelve years of age) who require supplemental oxygen therapy. It was authorised as oral therapy or given as an injection or infusion into the vein. Companies that market dexamethasone could submit a request to add the new therapeutic indication to their product's license by submitting an application to the competent authority or to the EMA. The proposed changes to the dexamethasone product information for patients and healthcare professionals were also made publicly available by the EMA.[119]

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[114] College ter Beoordeling van Geneesmiddelen (Medicines Evaluation Board). 'Sofradex' https://www.geneesmiddeleninformatiebank.nl/ords/f?p=111:3::SEARCH:::P0_DOMAIN,P0_LANG,P3_RVG1:H,NL,04961, last accessed 8 January 2024.

[115] Recoverytrial.net. 'Funders' https://www.recoverytrial.net/, last accessed 13 January 2024.

[116] European Medicines Agency. 'EMA starts review of dexamethasone for treating adults with COVID-19 requiring respiratory support' https://www.ema.europa.eu/en/news/ema-starts-review-dexamethasone-treating-adults-covid-19-requiring-respiratory-support, last accessed 8 January 2024.

[117] RECOVERY Collaborative Group; Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19. N Engl J Med. 2020.

[118] European Medicines Agency. 'EMA endorses use of dexamethasone in COVID-19 patients on oxygen or mechanical ventilation' https://www.ema.europa.eu/en/news/ema-endorses-use-dexamethasone-covid-19-patients-oxygen-or-mechanical-ventilation, last accessed 8 January 2024.

[119] European Medicines Agency. 'Outcome of Art 5(3) procedure - Product Information' https://www.ema.europa.eu/system/files/documents/other/dexamethasone_covid19_-_art_53_-_product_information_en.pdf. 2020

In the Netherlands, two pharmaceutical companies held marketing authorisations for generic dexamethasone in tablet and/or injection form: Teva and Centrafarm. Both companies subsequently added the new COVID-19 indication to their respective SmPCs.[120] While Teva applied the indication extension to their oral dexamethasone tablets, Centrafarm applied it to their injection solution. Centrafarm also had a marketing authorisation for dexamethasone tablets, but did not include the COVID-19 indication in the SmPC of the tablet formulation.

Reflection

Despite the associated costs of adding new indications to existing marketing authorisations, pharmaceutical companies were apparently sufficiently motivated to do so. Dexamethasone fulfilled a high unmet medical need, thereby presenting a market opportunity with potential for an adequate return on investment.

The expedited regulatory process for obtaining marketing authorisation, along with the advantage that extensive public funds were available to support clinical trials, facilitated the authorisation of dexamethasone for COVID-19. The authorisation process was expedited because the CHMP had already reviewed and approved the results of the RECOVERY trial, and made the proposed changes to the dexamethasone product information available to pharmaceutical companies to voluntarily include the COVID-19 indication to their marketing authorisation for dexamethasone.

[120]Geneesmiddeleninformatiebank.
https://www.geneesmiddeleninformatiebank.nl/ords/f?p=111:3::SEARCH:::P0_DOMAIN,P0_LANG,P3_RVG1:H,NL,56080 (see SmPC).
https://www.geneesmiddeleninformatiebank.nl/ords/f?p=111:3::SEARCH:::P0_DOMAIN,P0_LANG,P3_RVG1:H,NL,55091 (see SmPC).

Fenfluramine (Fintepla)

Case description

Fenfluramine, an off-patent medicine, was originally approved in the 1960s in Europe as an appetite suppressant for adult obesity treatment.[121] It was removed from the European market in 1997 due to its association with cardiac valve abnormalities and pulmonary arterial hypertension.[122] Multiple studies, however, have demonstrated that fenfluramine is effective in treating seizures related to Dravet syndrome, a rare and severe type of epilepsy.[123]

Dravet syndrome is an autosomal dominant genetic disorder characterized by a catastrophic form of epilepsy. It typically presents with prolonged seizures, often triggered by high temperatures or fever, and usually starts before the age of one year, with most cases beginning around six months of age.[124] The prevalence of this condition is about 1 in 15,700 children. In the Netherlands, there are approximately 200-250 children who suffer from Dravet syndrome.[125]

Fenfluramine's potential in treating Dravet syndrome stemmed from open-label long-term studies conducted in Belgium, which demonstrated promising results in seizure control.[126] The results were followed by studies in experimental models of seizures and epilepsy, and by double-blind adjunctive-therapy placebo-controlled trials that demonstrated the efficacy of fenfluramine in reducing convulsive seizure frequency in patients with Dravet syndrome.[127]

Based on these studies, on 5 February 2019 the pharmaceutical company Zogenix GmbH submitted a marketing authorisation application to EMA for fenfluramine under the brand name Fintepla for the treatment of seizures associated with Dravet syndrome. Fintepla was approved on 18 December 2020 based on a full dossier via Article 8(3) with orphan designation, and was therefore granted 10 years of orphan market exclusivity. However, Fintepla was only authorised in the treatment of Dravet syndrome as an add-on therapy to other antiepileptic medicines. The EMA also mandated the MAH to conduct an observational registry to collect data on the long-term safety of fenfluramine in regular clinical practice. This includes identifying and quantifying cardiovascular side effects and monitoring growth retardation as a secondary objective. On March 7, 2022, Zogenix and its product Fintepla were acquired by UCB, a Belgian pharmaceutical company. In January 2023, Fintepla was also authorised as an add-on in treating Lennox-Gastaut syndrome, another rare form of epilepsy.

When UCB applied for the inclusion of Fintepla in the Dutch GVS, the company stated that adding Fintepla to the standard treatment offers comparable therapeutic value to the addition of cannabidiol (Epidyolex) combined with clobazam in standard therapy.[128] The cost of treatment with Epidyolex is

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[121] Fintepla: EPAR – European Public assessment report

[122] Dini G, Di Cara G, Ferrara P, Striano P, Verrotti A. Reintroducing Fenfluramine as a Treatment for Seizures: Current Knowledge, Recommendations and Gaps in Understanding. *Neuropsychiatr Dis Treat*. 2023.

[123] Simon K, Sheckley H, Anderson CL, Liu Z, Carney PR. A review of fenfluramine for the treatment of Dravet syndrome patients. Curr Res Pharmacol Drug Discov. 2021.

[124] National Institute of Neurological Disorders and Stroke. 'Dravet Syndrome' https://www.ninds.nih.gov/health-information/disorders/dravet-syndrome, last accessed 9 January 2024.

[125] Dravet syndrome foundation. 'Wat is het Dravet syndroom?' (What is Dravet syndrome?') https://dravetfoundation.org/what-is-dravet-syndrome/, last accessed 9 January 2024; Dravetsyndroom.eu. 'Home' https://www.dravetsyndroom.eu/, last accessed 9 January 2024.

[126] Fintepla: EPAR – European Public assessment report

[127] Idem.

[128] Zorginstituut Nederland (Dutch National Healthcare Institute). 'GVS-advies fenfluramine (Fintepla®) voor de behandeling van epileptische aanvallen bij het dravetsyndroom of lennox-gastautsyndroom' (GVS advice fenfluramine (Fintepla®) for the treatment of epileptic seizures in Dravet syndrome or Lennox-Gastaut syndrome) https://www.zorginstituutnederland.nl/publicaties/adviezen/2023/08/31/gvs-advies-fenfluramine-fintepla-voor-de-behandeling-van-epileptische-aanvallen-bij-het-dravetsyndroom-of-lennox-gastautsyndroom#:~:text=De%20registratiehouder%20heeft%20vergoeding%20aangevraagd,met%20de%20huidige%20beschikbare%20behandelingen, last accessed 9 January 2023.

€74.69/day, potentially higher than the treatment costs for Fintepla.[129] In light of this, ZIN conducted an assessment of mutual substitutability (in Dutch: *Toets Onderlinge Vervangbaarheid*). In October 2023, based on the criteria for mutual substitutability, ZIN concluded that Fintepla is substitutable with Epidyolex and meets the current standards of scientific knowledge and practice. At that time, Epidyolex was listed in Annex 1B of the GVS, with specific reimbursement conditions. Subsequently, ZIN advised the Minister of Health, Welfare, and Sport to include Fintepla in a new cluster with Epidyolex within Annex 1A of the GVS. ZIN also advised the minister to start price negotiations with UCB to ensure that, if included in the GVS, the net cost of Fintepla remains lower than or equal to the price of the comparative treatment (Epidyolex).[130]

Reflection

The designation of Fintepla as an orphan medicinal product and the granting of 10 years of orphan market exclusivity as the only fenfluramine containing medicinal product in the treatment of Dravet syndrome as well as Lennox-Gastaut syndrome, provided a sufficient business case for investing in its repurposing.

[129] Farmacotherapeutisch Kompas (Pharmacotherapeutic compass). 'Cannabidiol' https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/c/cannabidiol#kosten, last accessed 9 January 2024.

[130] Zorginstituut Nederland (Dutch National Health Care Institute). 'GVS-advies fenfluramine (Fintepla®)' (GVS advice fenfluramine (Fintepla®) https://www.zorginstituutnederland.nl/binaries/zinl/documenten/adviezen/2023/08/31/gvs-advies-fenfluramine-fintepla-voor-de-behandeling-van-epileptische-aanvallen-bij-het-dravetsyndroom-of-lennox-gastautsyndroom/GVS-advies+fenfluramine+%28Fintepla%C2%AE%29+voor+de+behandeling+van+epileptische+aanvallen+bij+het+dravetsyndroom+of+lennox-gastautsyndroom+%28gecorrigeerde+versie%29.pdf. 2023

Chenodeoxycholic acid (CDCA-Leadiant)

Case description

Chenodeoxycholic acid (CDCA) is an off-patent medicine originally developed and approved for the treatment of gallstones. It was available under the brand name Chenofalk in the Netherlands from 1976 to 2008, priced at €0.28 per capsule. Chenofalk has been used as an off-label treatment for cerebrotendinous xanthomatosis (CTX) since 1999, which costed at that time €308 per patient per treatment year.[131]

CTX is a rare genetic disorder leading to the accumulation of cholesterol in the body, affecting multiple organs and causing symptoms like diarrhoea, cataracts, and neurological abnormalities.[132] Globally, there have only been around 300 documented cases of CTX.[133] In the Netherlands, the number of patients is estimated to be around 65.[134] Early findings of CDCA's efficacy against CTX were reported in 1982 and has been supported by clinical experiences and retrospective cohort studies.[135] So far, no Phase III clinical trials have been conducted to investigate the use of CDCA in the treatment of CTX.

The pharmaceutical company Sigma-Tau developed CDCA as Xenbilox. This company acquired the rights for Chenofalk in 2008, and later for Chenix (another CDCA brand name). As Chenofalk and Xenbilox were the only CDCA medicines available, Sigma-Tau progressively increased the price of CDCA capsules to approximately €29 each. In 2015, CDCA was withdrawn from the Dutch market.

Following this, Sigma-Tau rebranded itself as Leadiant in 2017. Subsequently, CDCA Leadiant was approved as an orphan medicine and the company increased the public list price of CDCA to approximately €150,000 per patient per year in the Netherlands. The legal basis for this application was a hybrid application under Article 10(3).

The price increase of CDCA resulted in widespread criticism and scrutiny regarding reimbursement and cost-effectiveness. Amsterdam UMC started developing CDCA capsules from raw materials imported from China, at approximately €20,000 per patient annually, which was significantly less than Leadiant's pricing albeit notably higher than the original Chenofalk. Leadiant criticised the compounding of CDCA arguing that the lower price was only achievable by circumventing the investment required for EU-wide marketing authorisation and EMA-approved production facilities. Leadiant also highlighted that the raw material was tested based on Chinese pharmacopoeia standards from 1995, and that the exporter did not comply with Good Distribution Practices (GDP).

Leadiant attempted to negotiate reimbursement terms, but faced no response from major insurers and ZIN. ZIN concluded that based on the criteria applied, CDCA Leadiant was not suitable for listing on Annex 1A, and while it could potentially be included in Annex 1B, this would lead to substantially

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[131] Bayoumy, A.B., de Boer, N.K.H., Ansari, A.R. et al. Unrealized potential of drug repositioning in Europe during COVID-19 and beyond: a physician's perspective. J of Pharm Policy and Pract 13, 45. 2020.

[132] Salen G, Steiner RD. Epidemiology, diagnosis, and treatment of cerebrotendinous xanthomatosis (CTX). J Inherit Metab Dis. 2017.

[133] Orphanet. 'Cerebrotendineuze xanthomatose' (Cerebrotendinous xanthomatosis) https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=NL&Expert=909, last accessed 9 January 2024.

[134] Zorginstituut Nederland (Dutch National Health Care Institute). 'GVS-beoordeling chenodeoxycholic acid Leadiant®' (GVS assessment chenodeoxycholic acid Leadiant®) https://www.zorginstituutnederland.nl/binaries/zinl/documenten/adviezen/2018/11/22/gvs-advies-chenodeoxycholzuur-chenodeoxycholic-acid-leadiant-bij-de-behandeling-van-cerebrotendineuze-xanthomatose-ctx/GVS-advies+chenodeoxycholzuur+%28Chenodeoxycholic+acid+Leadiant%C2%AE%29+bij+de+behandeling+van+cerebrotendineuze+xanthomatose+%28CTX%29.pdf. 2018.

[135] Maton PN, Iser JH, Reuben A, Saxton HM, Murphy GM, Dowling RH. Outcome of chenodeoxycholic acid (CDCA) treatment in 125 patients with radiolucent gallstones. Factors influencing efficacy, withdrawal, symptoms and side effects and post-dissolution recurrence. Medicine (Baltimore). 1982;
Verrips A, Dotti MT, Mignarri A, Stelten BML, Verma S, Federico A. The safety and effectiveness of chenodeoxycholic acid treatment in patients with cerebrotendinous xanthomatosis: two retrospective cohort studies. Neurol Sci. 2020;
Amador MDM, Masingue M, Debs R, Lamari F, Perlbarg V, Roze E, Degos B, Mochel F. Treatment with chenodeoxycholic acid in cerebrotendinous xanthomatosis: clinical, neurophysiological, and quantitative brain structural outcomes. J Inherit Metab Dis. 2018.

higher healthcare costs. ZIN emphasised the cost disparity between CDCA-Leadiant and the earlier Xenbilox as well as pharmacy preparations, arguing that the substantially higher price could not be justified by costs related to the development and marketing authorisation and that no new clinical studies were conducted. Leadiant justified its pricing-decision among others, by claiming the necessity to rebuild the dossier for the EMA from scratch, and the need to comply with high standards and more stringent regulatory requirements related to production and marketing authorisation.[136]

As of now, CDCA Leadiant has not been included in the Dutch GVS, with pharmacy preparations through Amsterdam UMC being the current treatment option. In 2021, Leadiant was fined 17€ million by the Dutch Authority for Consumers and Markets (ACM) for ''excessively pricing a critical medicine and exploiting its market dominance, underpinning the delicate balance between pharmaceutical innovation, corporate practices, and the imperative of accessible healthcare'' - although the legal procedures regarding the fine are still ongoing.[137]

Reflection

Similar to the mexiletine case, this case highlights the barriers in the pricing and reimbursement of repurposed medicines. It also underscores the barrier regarding competition from pharmacy preparations, which may not meet the quality standards of authorised medicines. In light of these barriers, it is important to facilitate collaboration between payers and the industry, to develop fair pricing models that result in predictable pricing and reimbursement decisions which benefit both parties.

[136] Leadiant Biosciences. 'Follow-up naar aanleiding van onze bespreking op 5 september 2019' (follow-up following our discussion on September 5, 2019) https://www.vbb.com/media/Insights_Newsletters/190913_BriefLeadiantBiosciencesaanministerBruins.pdf. 2019.
[137] Authority for Consumers and Markets. ' Decision on objection against fine on Leadiant for excessive price of prescription drug CDCA' https://www.acm.nl/en/publications/decision-objection-against-fine-leadiant-excessive-price-prescription-drug-cdca, last accessed 10 January 2024.

Propranolol (Hemangiol)

Case description

Propranolol is an off-patent medicine that has been used since the 1960's in the treatment of cardiovascular diseases, the prophylaxis of migraine and management of essential tremor.[138] Propranolol was first authorised In the Netherlands in 1983.[139]

In 2014, the EMA authorised Hemangiol (an oral solution of propranolol) for the treatment of proliferating infantile haemangioma. This is a benign vascular tumour in infancy, characterised by endothelial cell proliferation, which occurs in 3 to 10% of the population.

Hemangiol's development started after a serendipitous discovery by the French physician Léauté-Labrèze. The effect of propranolol on hemangiomas was first discovered during the treatment of a heart condition in an infant who also had a haemangioma.[140] In the pivotal published case report, it was stated that the treatment of a heart condition with propranolol also led to the rapid diminishment of a haemangioma. After this, Labrèze treated 12 infants with propranolol for their haemangioma, resulting in beneficial effects.[141] A follow-up study was conducted that confirmed the beneficial results of the propranolol treatment. Soon propranolol became an off-label and/or pharmacy preparation based therapy for the treatment of infantile haemangioma.[142]

In 2009, the French pharmaceutical company Pierre Fabre Dermatologie obtained scientific advice from the EMA with regard to the non-clinical and clinical requirements for the development of Hemangiol. For the clinical part they conducted three studies: two phase I pharmacokinetic studies (one in 12 adults and one in 23 children) and one phase II/III randomised placebo controlled clinical trial with 456 children. The studies confirmed the efficacy and safety of the propranolol treatment and were complemented by literature data and data from compassionate use programmes in France and Switzerland, which included severe cases of infantile haemangioma that were not eligible for inclusion in the clinical trial.[143] Nowadays propranolol has become the first-choice therapy for infantile haemangioma.

In 2014, Pierre Fabre Dermatologie filed for a full application under Article 8(3). The company was granted a PUMA in the treatment of proliferating infantile haemangioma requiring systemic therapy, as per Article 31 of Regulation (EC) 1901/2006. This provided Pierre Fabre Dermatologie a number of benefits including access to the European centralised marketing authorisation, a partial exemption from regulatory fees, data exclusivity for 8 years and a 2-year market protection, even though the product belongs to an existing global marketing authorisation.

Hemangiol is included in the Dutch National Health Care System, with full reimbursement provided.

[138] Srinivasan AV. Propranolol: A 50-Year Historical Perspective. Ann Indian Acad Neurol. 2019.
[139] College ter Beoordeling van Geneesmiddelen (Medicines Evaluation Board). 'Propranolol HCl Teva 10 mg' https://www.geneesmiddeleninformatiebank.nl/ords/f?p=111:3::SEARCH:::P0_DOMAIN,P0_LANG,P3_RVG1:H,NL,10216, last accessed 9 January 2024.
[140] Léauté-Labrèze C. et al. Propranolol for severe hemangiomas of infancy. N. Engl. J. Med. 358, 2649–51 (2008).
[141] Langedijk J. 'Continuous innovation in the drug life cycle', Utrecht University. 2016.
[142] Idem.
[143] Idem.

Reflection

The PUMA for Hemangiol, which included incentives as reduced regulatory fees, 8 years of data exclusivity, and 2 years of market protection, helped to create a sufficient business case for the French company to repurpose the medicine. Its subsequent inclusion in the GVS, attributed to its low budget impact, which further highlights the success of this repurposing case.

Thioguanine (Thiosix)

Case description

Thioguanine, an off-patent medicine, was first developed in 1950 for treating leukaemia in children. Initially, thioguanine was widely used but gradually saw a reduction in its clinical use due to the introduction of more effective alternatives. Despite its declining use in haematological conditions, thioguanine's significant immunosuppressive effects led to its adoption in managing chronic idiopathic inflammatory diseases, such as rheumatoid arthritis and inflammatory bowel disease (IBD). It has been used off-label in the Netherlands since 2001 for the treatment of patients with IBD who do not respond to standard thiopurine treatment.

Thioguanine, along with its analogues azathioprine and mercaptopurine, undergoes metabolic conversion to the active 6-thioguanine nucleotides. Unique to thioguanine is its simpler metabolic pathway, producing fewer toxic metabolites compared to azathioprine and mercaptopurine. The distinct profile and product characteristics positioned thioguanine as a viable alternative for IBD patients who are intolerant or resistant to azathioprine or mercaptopurine. Clinical trials revealed that up to 80% of these patients could tolerate thioguanine and experience substantial clinical benefits.[144]

In 2007, discussions about approving thioguanine for IBD were initiated and continued in the following years with governmental institutions like the Ministry of Health, Welfare and Sports and the MEB.[145] Scientific advice by the MEB was given in December 2010 with regard to the dossier requirements for a marketing authorisation application. In 2015, thioguanine was conditionally approved for IBD treatment in the Netherlands, subject to maintaining a patient registry and the collection of additional efficacy data.[146] It was the first medicine in the Netherlands to be granted a conditional marketing approval via the MEB.

In 2022, following an extensive review of quality, safety, and efficacy data, the MEB granted a regular marketing authorisation to Teva for thioguanine in 10mg and 20mg tablet forms under the brand name Thiosix. This approval was for IBD patients who did not respond adequately to standard treatments for conditions like Crohn's disease and ulcerative colitis. The application concerned a hybrid application under Article 10(3), claiming essential similarity with the innovator product Lanvis 40mg tablets, which has been approved in the Netherlands in 1975.

Thiosix is included the Dutch National Health Care System, and therefore granted full reimbursement.

Reflection

The timeline of obtaining the regular marketing authorisation for Thiosix spanned over 15 years, beginning with its initial proposal to the Ministry of Health, Welfare and Sports and MEB. The conditional marketing authorisation served as a significant facilitator for the eventual standard approval. Without the conditional approval, Teva may have discontinued the process of obtaining a regular marketing authorisation. This highlights the importance of cooperation with regulatory agencies and an adaptive regulatory process.

[144] Simsek M, Meijer B, van Bodegraven AA, de Boer NKH, Mulder CJJ. Finding hidden treasures in old drugs: the challenges and importance of licensing generics. Drug Discov Today. 2018
[145] Idem.
[146] Idem.

ANNEX 2

Drug repurposing initiatives

	Goed Gebruik Geneesmiddelen programma (Good Use Medicines programme)	Medicijn voor de Maatschappij (Medicine for Society)	Centre for Future Affordable Sustainable Therapies (FAST)	EMA drug repurposing pilot	REMEDi4ALL	REPO4EU
Year of initiation:	**2012**	**2019**	**2020**	**2021**	**2022**	**2022**
Description:	Within the Good Use of Medicines programme, public and private parties (for example, the pharmaceutical industry and health insurers) are given the opportunity to collaborate financially and substantively at program, theme, and/or project level. The objective of the Good Use Medicines of programme is to use existing medicines more effectively, safely, and efficiently. The programme focuses on improving pharmacotherapeutic care at the level of the medicine itself and its use in daily care. To achieve the program's goal, research is facilitated, infrastructure is established, and initiatives, including drug repurposing (or drug	Medicine for Society is a platform for affordable medicines for rare diseases and the continued availability of these medicine. It facilitates knowledge sharing about the availability of medicines for rare diseases among doctors, pharmacists, patients, companies, and other organisations. It is also the FAST-hub for rare diseases and drug repurposing. The objective of Medicine for Society is to keep medicines for rare diseases available and affordable by	FAST provides a central place where innovators from academia, start-ups, and companies can easily be assisted and receive (regulatory) multidisciplinary support. FAST has a guiding function and assists in the development of solutions, the establishment and guidance of use cases, experiments, and research for validation. The core activity of FAST is to strengthen developments that offer opportunities for the improvement of therapy development, where the Netherlands can excel	EMA and the Heads of Medicines Agencies launched the pilot project to support the repurposing of medicines for not-for-profit organisations and academia in drug repurposing. As part of the pilot, EMA and the national competent authorities will provide regulatory support, primarily scientific advice, to help those stakeholders generate a data package robust enough to support a future application by a pharmaceutical company. The aim of this initiative is to support not-for-profit organisations and academia to gather or generate sufficient	REMEDi4ALL is a large-scale collaboration, under the leadership of EATRIS. 24 organisations in the fields of clinical and translational research, clinical operations, patient engagement and education, regulatory framework, funding, governance, health technology assessment and pricing and reimbursement will closely collaborate to make drug repurposing mainstream. The EU through the Horizon Europe programme will invest 23 million euros in REMEDi4ALL over the next 5 years. REMEDi4ALL aims to drive forward the repurposing of medicines in Europe by advancing knowledge in this field and addressing substantial obstacles, like fragmented and	REPO4EU is a large-scale collaboration involving 28 partners from 10 countries, including the Netherlands, Germany, Austria, Spain, Sweden, Belgium, Portugal, Switzerland, and the United States. These partners come from various sectors, including higher education establishments, private for-profit entities, and small and medium-sized enterprises. 23 million euros will be invested by the EU to support REPO4EU. REPO4EU's ultimate goal is to host and grow an EU industry-level online platform for validated

	rediscovery) initiatives, are encouraged. These efforts ensure that knowledge about the use of available medicines becomes available (more quickly) in practice and is actually utilised.[147]	sharing knowledge, conducting research, and implementing projects. They also conduct research into the laws and regulations surrounding medicines for rare diseases.[148]	and take a leading position. FAST focuses on current developments and on preparing for the therapies of tomorrow. For example, FAST has published a positioning paper that clarifies and describes possible robust policy solutions that enable a sustainable business model for drug repurposing initiatives.[149]	evidence on the use of an established medicine in a new indication with the view to have this new use formally authorised by a competent authority.[150]	siloed research; non-standardised datasets; heterogenous quality of computational tools; poor patient engagement or lack of incentives and policies to support and enhance drug repurposing. It is expected that, due to REMEDi4ALL, more (and better) repurposed therapeutics will be widely available thanks to more agile, cutting-edge development processes, ultimately contributing to increased sustainability of health systems.[151]	precision drug repurposing with a global reach. This platform will operate as a data hub for key information, training resources, matchmaking and collaboration in drug repurposing.[152]

[147] Website ZonMw Goed Gebruik Geneesmiddelen programme (ZonMw Good Use Medicines programme): https://www.zonmw.nl/nl/programma/goed-gebruik-geneesmiddelen, last accessed 7 January 2024.
[148] Website Medicijn voor de Maatschappij (Medicine for Society): https://medicijnvoordemaatschappij.nl/, last accessed 7 January 2024.
[149] Website FAST: https://www.fast.nl/, last accessed 7 January 2024.
[150] European Medicines Agency. 'Repurposing of authorised medicines: pilot to support not-for-profit organisations and academia' https://www.ema.europa.eu/en/news/repurposing-authorised-medicines-pilot-support-not-profit-organisations-and-academia, last accessed 7 January 2024.
[151] Website REMEDi4ALL: https://remedi4all.org/, last accessed 7 January 2024.
[152] Website REPO4EU: https://repo4.eu/, last accessed 7 January 2024.

ANNEX 3

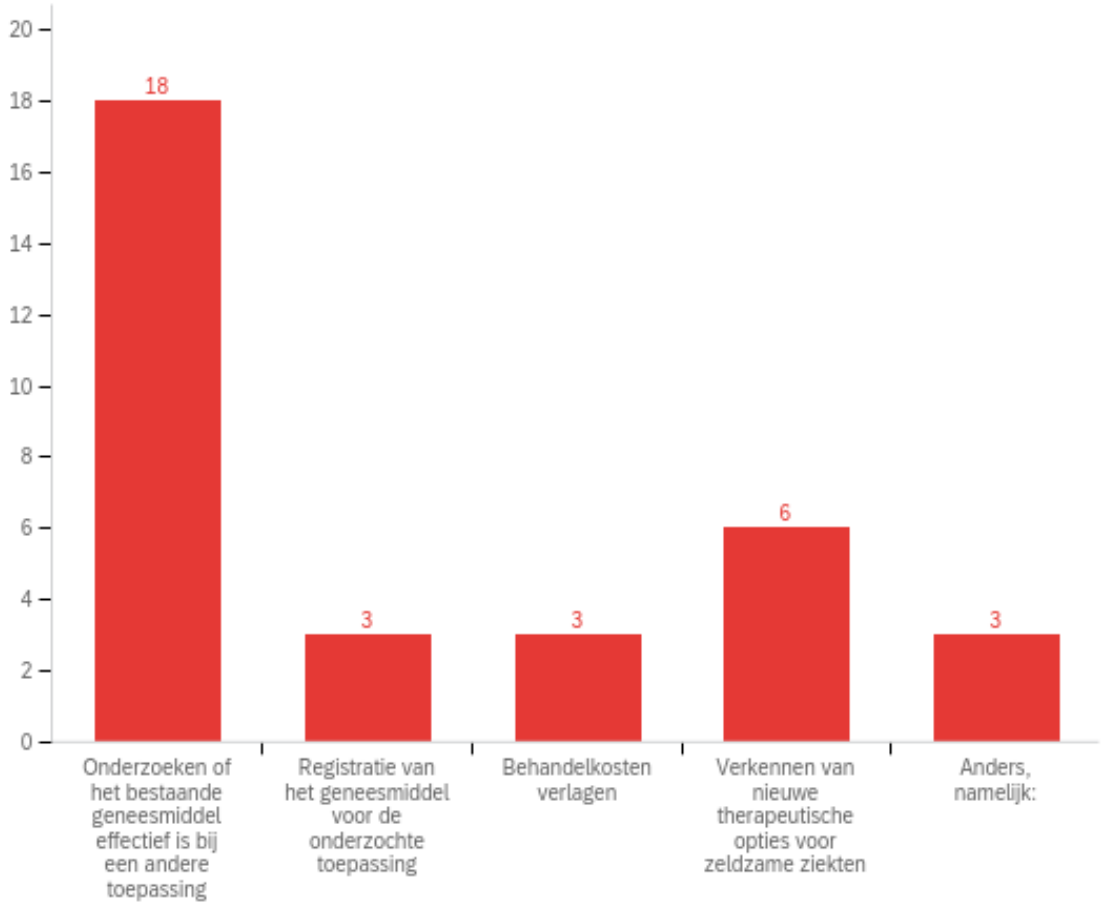
Survey results

The survey was conducted in Dutch to cater to the linguistic preferences of the target audience. A total of 45 projects were identified and invited to participate in the survey. A total of 21 (47%) responses were gathered.

For the purposes of this survey, the term 'Drug Rediscovery' was used instead of 'Drug Repurposing'. This decision was made considering that the researchers might have greater familiarity with the term 'Drug Rediscovery', as their projects were part of the Drug Rediscovery Round of ZonMw's GGG-Programme.

Survey questions not relevant to the content of the report have been excluded.

Wat was de intentie van het onderzoek? *Meerdere antwoorden zijn mogelijk.*



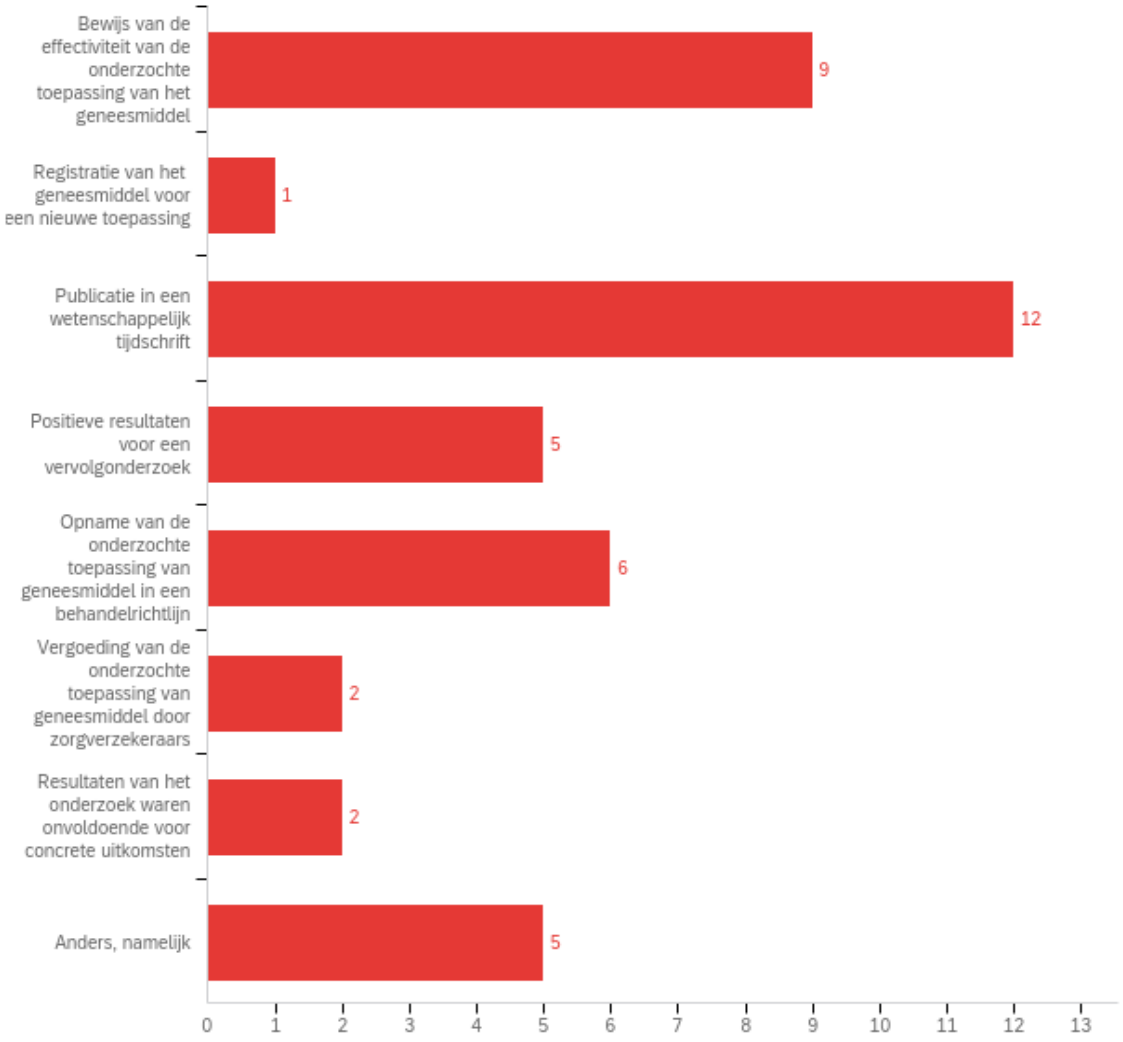
#	Answer	%	Count
1	Onderzoeken of het bestaande geneesmiddel effectief is bij een andere toepassing	86%	18
2	Registratie van het geneesmiddel voor de onderzochte toepassing	14%	3
3	Behandelkosten verlagen	14%	3
4	Verkennen van nieuwe therapeutische opties voor zeldzame ziekten	29%	6
5	Anders, namelijk:	14%	3
	Total	-	**33**

The total percentage does not add up to 100% due to the option for respondents to select multiple answers.

Responses voor "Anders, namelijk" voor bovenstaande vraag:

- Onderzoeken of het geneesmiddel preventief werkt op het ontstaan van een fistel
- Dose finding om optimale dosis nieuwe indicatie te vinden
- Onderzoeken of een bestaand geneesmiddel effectief is bij de aandoening waar het voor bedoeld is

Welke concrete uitkomsten zijn behaald door uw onderzoek? *Meerdere antwoorden zijn mogelijk.*



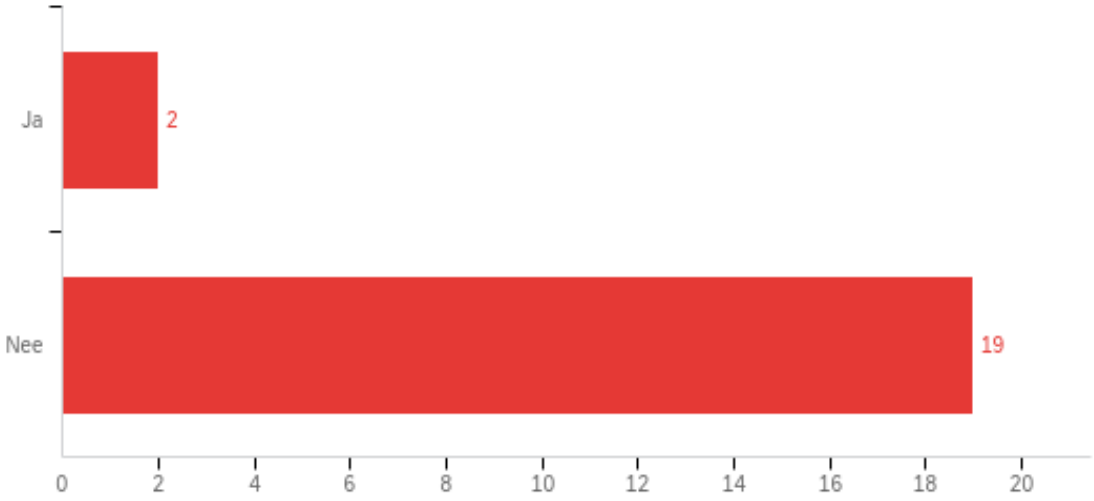
#	Answer	%	Count
1	Bewijs van de effectiviteit van de onderzochte toepassing van het geneesmiddel	43%	9
2	Registratie van het geneesmiddel voor een nieuwe toepassing	5%	1
3	Publicatie in een wetenschappelijk tijdschrift	57%	12
4	Positieve resultaten voor een vervolgonderzoek	24%	5
5	Opname van de onderzochte toepassing van geneesmiddel in een behandelrichtlijn	29%	6
6	Vergoeding van de onderzochte toepassing van geneesmiddel door zorgverzekeraars	10%	2
7	Resultaten van het onderzoek waren onvoldoende voor concrete uitkomsten	10%	2
8	Anders, namelijk	24%	5
	Total	-	**42**

The total percentage does not add up to 100% due to the option for respondents to select multiple answers.

Responses voor ''Anders, namelijk'' voor bovenstaande vraag:

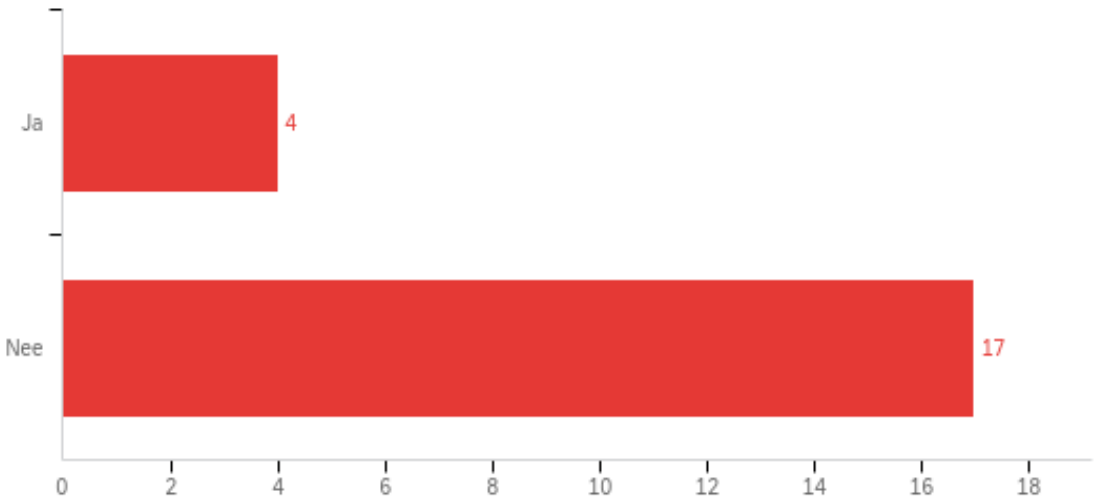
- Bewijs van INeffectiviteit van de onderzochte toepassing van het middel
- We zijn nog bezig met registratie van het geneesmiddel op Europees niveau maar ook bij de FDA in samenwerking met centra in de USA
- Nog bezig met wetenschappelijke publicatie over de hoofdeindpunten.
- Registratie wordt aangevraagd
- Er worden nog resultaten van een ander project afgewacht

Heeft u tijdens het project samengewerkt met de farmaceutische industrie?



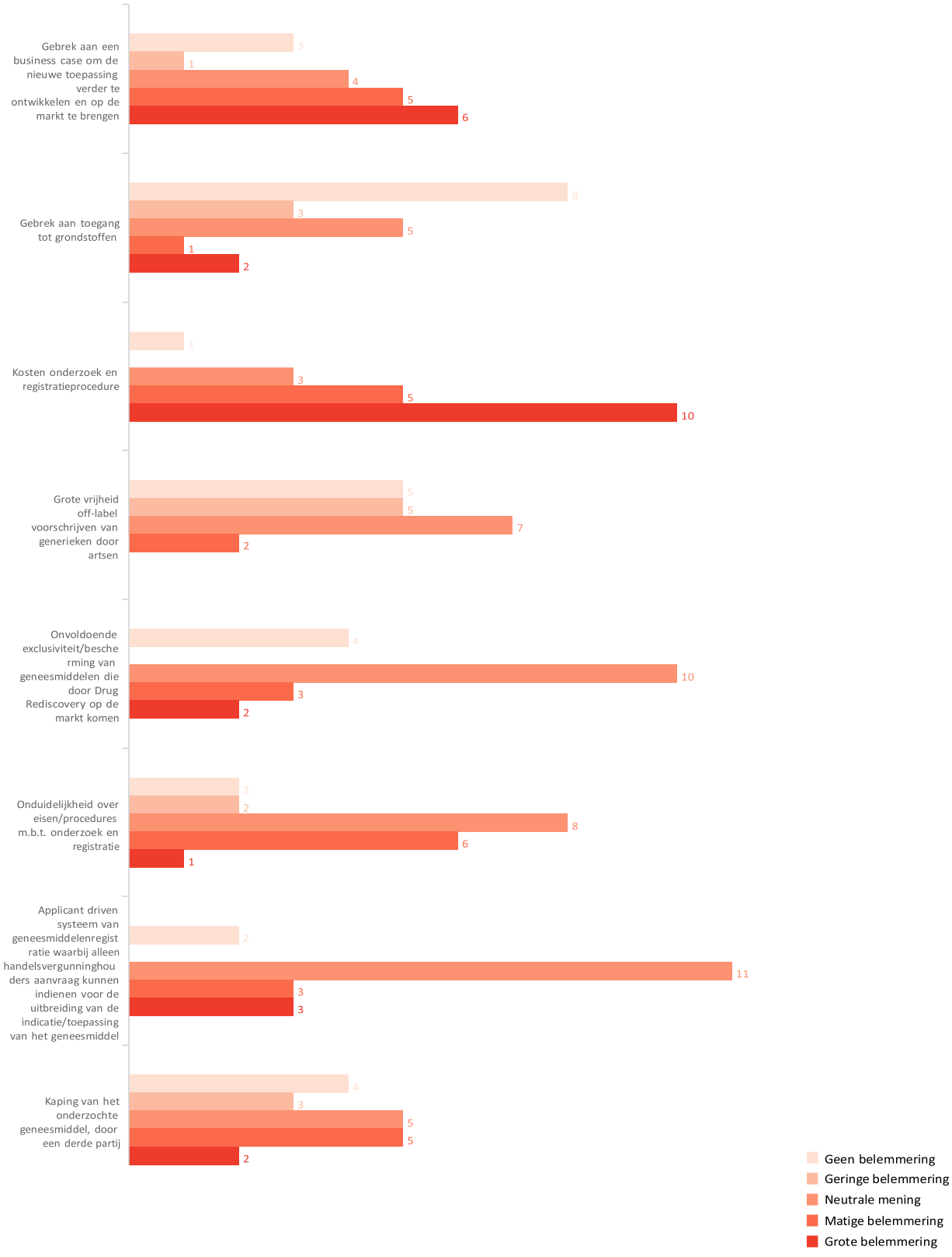
#	Answer	%	Count
2	Nee	90%	19
1	Ja	10%	2
	Total	**100%**	**21**

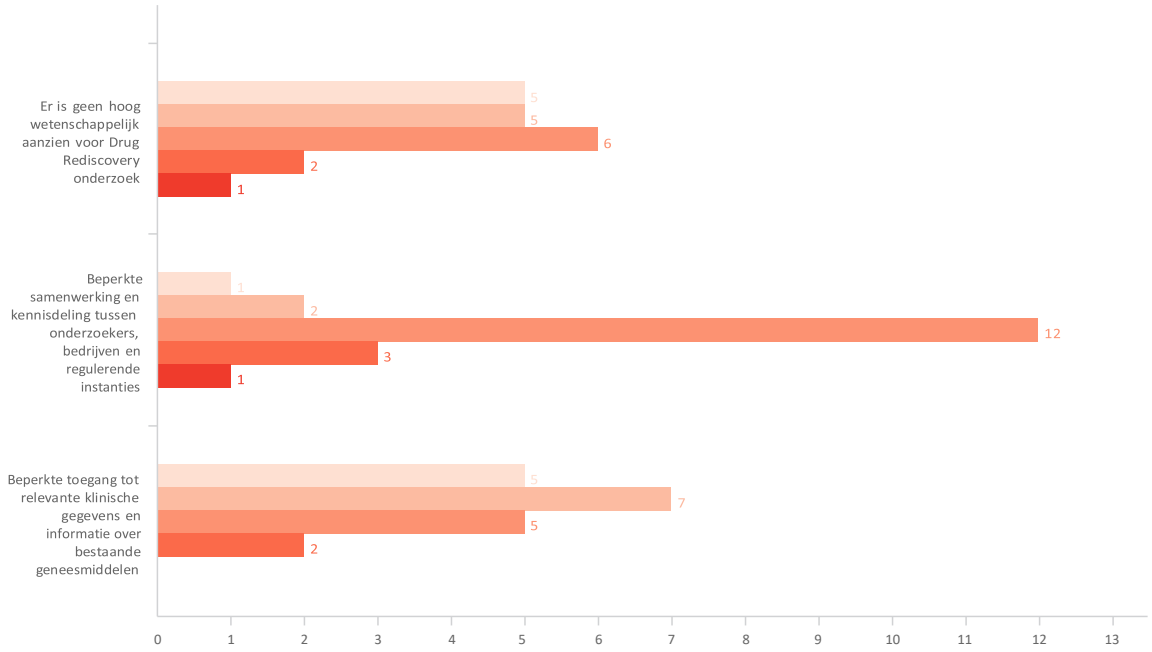
Heeft u tijdens het project om scientific advice gevraagd aan het College ter Beoordeling van Geneesmiddelen (CBG) of de European Medicines Agency (EMA)?



#	Answer	%	Count
1	Ja	19%	4
2	Nee	81%	17
	Total	**100%**	**21**

Op een schaal van 1 tot 5, in hoeverre denkt u dat de volgende factoren een belemmering vormen voor Drug Rediscovery?





#	Question	Geen belemmering		Geringe belemmering		Neutrale mening		Matige belemmering		Grote belemmering		Total
1	Gebrek aan een business case om de nieuwe toepassing verder te ontwikkelen en op de markt te brengen	16%	3	5%	1	21%	4	26%	5	32%	6	19
2	Gebrek aan toegang tot grondstoffen	42%	8	16%	3	26%	5	5%	1	11%	2	19
3	Kosten onderzoek en registratieprocedure	5%	1	0%	0	16%	3	26%	5	53%	10	19
4	Grote vrijheid off-label voorschrijven van generieken door artsen	26%	5	26%	5	37%	7	11%	2	0%	0	19
5	Onvoldoende exclusiviteit/bescherming van geneesmiddelen die door Drug Rediscovery op de markt komen	21%	4	0%	0	53%	10	16%	3	11%	2	19
6	Onduidelijkheid over eisen/procedures m.b.t. onderzoek en registratie	11%	2	11%	2	42%	8	32%	6	5%	1	19
7	Applicant driven systeem van geneesmiddelenregistratie waarbij alleen handelsvergunninghouders aanvraag kunnen indienen voor de uitbreiding van de indicatie/toepassing van het geneesmiddel	11%	2	0%	0	58%	11	16%	3	16%	3	19
8	Kaping van het onderzochte geneesmiddel, door een derde partij	21%	4	16%	3	26%	5	26%	5	11%	2	19
9	Er is geen hoog wetenschappelijk aanzien voor Drug Rediscovery onderzoek	26%	5	26%	5	32%	6	11%	2	5%	1	19
10	Beperkte samenwerking en kennisdeling tussen onderzoekers, bedrijven en regulerende instanties	5%	1	11%	2	63%	12	16%	3	5%	1	19
11	Beperkte toegang tot relevante klinische gegevens en informatie over bestaande geneesmiddelen	26%	5	37%	7	26%	5	11%	2	0%	0	19

ANNEX 4

Drug repurposing GGG projects invited for the survey

This annex provides a list of all drug repurposing projects (N=45), subsidised within the GGG-programme of ZonMw, that were invited to participate in our survey.

Repurposed medicine	Project start year	Originally approved indication	Indication under study (repurposed indication)	Project link (to ZonMw website)
Levothyroxine	2013	Hypothyroidism	Recurrent miscarriage in women with normal thyroid function and positive for TPO-Ab	https://projecten.zonmw.nl/nl/project/levothyroxine-euthyroid-women-recurrent-miscarriage-and-positive-tpo-antibodies-randomized
Dexamethasone	2013	Severe inflammation	Suppressing symptoms in patients with sarcoidosis	https://projecten.zonmw.nl/nl/project/low-dose-dexamethasone-newly-diagnosed-pulmonary-sarcoidosis-low-cost-treatment-favorable
Clonidine	2013	Hypertension	Schizophrenia	https://projecten.zonmw.nl/nl/project/clonidine-als-veelbelovende-aanvulling-op-de-behandeling-van-refractaire-symptomen-van
Rituximab	2014	Various types of cancers and rheumatoid arthritis	Interstitial pneumonitis	https://projecten.zonmw.nl/nl/project/rituximab-life-threatening-therapy-resistant-progressive-interstitial-pneumonitis
Duloxetine	2014	Depression	Osteoarthritis	https://projecten.zonmw.nl/nl/project/duloxetine-chronic-osteoarthritis-pain-important-alternative
Anakinra	2014	Rheumatoid arthritis	Gout	https://projecten.zonmw.nl/nl/project/anakinra-versus-treatament-usual-treatment-acute-gout
Esketamine	2015	Induction of general anaesthesia	Depression	https://projecten.zonmw.nl/nl/project/oral-ketamine-treatment-resistant-depression-new-indication-old-anesthetic-and-analgesic
Morphine	2015	Severe pain	Shortness of breath in people with advanced COPD	https://projecten.zonmw.nl/nl/project/morphine-palliative-treatment-refractory-dyspnea-patients-advanced-copd-benefits-and
Acetylsalicylic acid	2015	Pain	Prevention of recurrent spontaneous preterm birth	https://projecten.zonmw.nl/nl/project/low-dose-aspirin-prevention-recurrent-spontaneous-preterm-labour-april-study

Repurposed medicine	Project start year	Originally approved indication	Indication under study (repurposed indication)	Project link (to ZonMw website)
Raloxifene	2016	Osteoporosis in postmenopausal women	Schizophrenia	https://projecten.zonmw.nl/nl/project/augmentation-raloxifene-towards-better-outcome-patients-schizophrenia-spectrum-disorders
Bumetanide	2016	Oedema in adults due to heart failure, liver cirrhosis, nephrotic syndrome, and medicines	Autism spectrum disorders	https://projecten.zonmw.nl/nl/project/repositioning-bumetanide-treatment-autism-spectrum-disorder
Colchicine	2016	Gout	Secondary prevention of cardiovascular disease	https://projecten.zonmw.nl/nl/project/low-dose-colchicine-secondary-prevention-cardiovascular-disease-lodoco2-trial
Zoledronate	2017	Bone degradation due to cancer, osteoporosis, and Paget's disease	Pain and joint damage in osteoarthritis	https://projecten.zonmw.nl/nl/project/zoledronate-disease-modifier-osteoarthritis
Amitriptyline	2017	Depression	Insomnia	https://projecten.zonmw.nl/nl/project/efficacy-and-safety-label-low-dose-antidepressants-amitriptyline-and-mirtazapine-chronic
Ertapenem	2017	Intra-abdominal infections, community-acquired pneumonia, acute gynaecological infections, skin and soft tissue infections of the foot	Gonorrhoea	https://projecten.zonmw.nl/nl/project/new-antibiotic-treatment-options-uncomplicated-gonorrhoea-nabogo-trial-double-blind
Sirolimus	2017	Prophylaxis of organ rejection in adult patients with a small to moderate immunological risk after a kidney transplant	Treatment of congenital vascular malformations, especially for pain	https://projecten.zonmw.nl/nl/project/treatment-congenital-vascular-malformations-using-sirolimus-improving-quality-life
Insulin nasal spray	2017	Diabetes (not approved in the Netherlands)	Phelan-McDermid syndrome	https://projecten.zonmw.nl/nl/project/implementatie-van-insuline-neusspray-de-behandeling-van-kinderen-met-phelan-mcdermid
Rivastigmine	2017	Symptomatic treatment of mild to moderate Alzheimer's-type dementia, mild to moderate dementia in Parkinson's disease	ECT-induced cognitive adverse effects in late-life depression	https://projecten.zonmw.nl/nl/project/recall-study-rivastigmine-ect-induced-cognitive-adverse-effects-late-life-depressiona
Esomeprazole	2018	Gastroesophageal reflux disease (GERD)	Secondary iron overload	https://projecten.zonmw.nl/nl/project/proton-pump-inhibition-secondary-hemochromatosis-hereditary-anemia-ppi-shine-again-studie

Repurposed medicine	Project start year	Originally approved indication	Indication under study (repurposed indication)	Project link (to ZonMw website)
Nortriptyline	2018	Depression	Functional dyspepsia	https://projecten.zonmw.nl/nl/project/tailored-treatment-functional-dyspepsia-nortriptyline-multi-center-double-blind-placebo
Ascorbic acid (Vitamin C)	2018	Vitamin C deficiency (scurvy)	Post-cardiac arrest syndrome	https://projecten.zonmw.nl/nl/project/early-high-dose-vitamin-c-post-cardiac-arrest-syndrome
Albendazole	2018	Treatment of hydatid cysts caused by Echinococcus granulosis or Echinococcus multilocularis when surgery is impossible	Crohn's disease: to induce mucosal healing in patients with anti-TNF monotherapy	https://projecten.zonmw.nl/nl/project/efficacy-albendazol-induce-mucosal-healing-patients-anti-tnf-monotherapy-add
Tranexamic acid	2018	Primary hyperfibrinolysis or fibrinogenolysis with bleeding or risk of bleeding, secondary fibrinolysis due to local treatment, hereditary angioedema	Chronic subdural hematoma	https://projecten.zonmw.nl/nl/project/tranexamic-acid-prevent-operation-chronic-subdural-hematoma-torch
Terbinafine	2019	Fungal nails	Chronic hepatitis B	https://projecten.zonmw.nl/nl/project/fungus-virus-investigating-terbinafine-treatment-chronic-hepatitis-b
Pentoxifylline	2019	Peripheral vascular circulation problems	Sepsis	https://projecten.zonmw.nl/nl/project/pentoxifylline-sepsis-preterm-infants-rediscovery-old-drug-new-indication
Doxapram	2019	Respiratory stimulant (not approved in the Netherlands)	Higher survival and better long-term prognosis after extreme preterm birth	https://projecten.zonmw.nl/nl/project/doxapram-protect-preterm-newborns-international-double-blinded-multicenter-randomized
Metformin	2019	Diabetes type 2	Weight gain induced by antipsychotics	https://projecten.zonmw.nl/nl/project/metformin-lifestyle-antipsychotic-users-trial-melia-optimizing-use-metformin-management
Naltrexone	2019	Opioid addiction, alcohol addiction	Crohn's disease	https://projecten.zonmw.nl/nl/project/preliminary-study-low-dose-naltrexone-induction-remission-patients-mild-moderate-crohns
Octreotide	2019	Acromegaly	Rendu-Osler-Weber disease	https://projecten.zonmw.nl/nl/project/effectiveness-somatostatin-analogues-patients-hereditary-hemorrhagic-telangiectasia-and
Allopurinol	2019	Gout	Cerebrum and heart protection in new-borns with duct-dependent congenital	https://projecten.zonmw.nl/nl/project/crucial-trial-cerebrum-and-cardiac-protection-allopurinol-neonates-duct-dependent

Repurposed medicine	Project start year	Originally approved indication	Indication under study (repurposed indication)	Project link (to ZonMw website)
			heart disease requiring cardiac surgery with cardiopulmonary bypass	
Metformin	2019	Diabetes type 2	Non-muscle invasive bladder cancer	https://projecten.zonmw.nl/nl/project/oral-metformin-intravesical-treatment-non-muscle-invasive-bladder-cancer
Metronidazole and ciproxin	2021	Bacterial infections	Abscess	https://projecten.zonmw.nl/nl/project/antibiotic-treatment-following-surgical-drainage-perianal-abscess-double-blind-placebo
Leuprorelin	2021	Hormone-sensitive cancers	Endometriosis, Polycystic liver disease	https://projecten.zonmw.nl/nl/project/against-pld-gnrh-agonist-pre-menopausal-women-study-treat-severe-polycystic-liver-disease
Guanabenz	2021	Hypertension (not approved in the Netherlands)	Vanishing white matter	https://projecten.zonmw.nl/nl/project/repurposing-guanabenz-vanishing-white-matter
Rivastigmine	2021	Symptomatic treatment of mild to moderate Alzheimer's-type dementia	Reducing cognitive side effects of ECT in patients with depression	https://projecten.zonmw.nl/nl/project/fewer-cognitive-side-effects-electroconvulsive-therapy-rivastigmine-patches
Clonazepam	2021	Epilepsy	Intellectual disability caused by mutations in the ARID1B gene (Coffin-Siris syndrome)	https://projecten.zonmw.nl/nl/project/randomized-double-blind-placebo-controlled-two-way-crossover-single-centre-study-evaluating
Metformin (added on top of standard doxycycline therapy)	2021	Diabetes type 2	Hidradenitis suppurativa	https://projecten.zonmw.nl/nl/project/rediscovery-metformin-chronic-disabling-auto-inflammatory-disease-hidradenitis-suppurativa
Mycophenolate mofetil and tacrolimus	2021	Prophylaxis of rejection of an allogeneic liver, kidney, or heart transplant	Autoimmune hepatitis	https://projecten.zonmw.nl/nl/project/tacrolimus-or-mycophenolate-autoimmune-hepatitis-patients-incomplete-response-first-line
Rituximab	2022	Various types of cancer and rheumatoid arthritis	Polymyalgia rheumatica	https://projecten.zonmw.nl/nl/project/reduce-pmr-rituximab-effect-decreasing-glucocorticoid-exposition-polymyalgia-rheumatica-2

Repurposed medicine	Project start year	Originally approved indication	Indication under study (repurposed indication)	Project link (to ZonMw website)
Lysergic acid diethylamide (LSD)	2022	Not approved for a disease/indication	Chronic cluster headache	https://projecten.zonmw.nl/nl/project/lysergzuurdiethylamide-lsd-als-preventieve-behandeling-bij-chronische-clusterhoofdpijn
Dexamphetamine	2022	ADHD	Cocaine addiction with comorbid opioid addiction	https://projecten.zonmw.nl/nl/project/efficacy-and-safety-24-weeks-sustained-release-dexamphetamine-patients-moderate-severe
Allopurinol	2022	Gout	Treatment of atherosclerosis in patients with hyperuricemia	https://projecten.zonmw.nl/nl/project/impact-allopurinol-cardiovascular-morbidity-and-mortality-randomized-double-blind-placebo
Injection in the middle ear with adrenal cortex hormone	2023	Primary and secondary (acute) adrenal cortex insufficiency and (potential) adrenal crisis; COPD, Asthma	Meniere's disease (against dizzy attacks)	https://projecten.zonmw.nl/nl/project/multicentre-double-blinded-randomized-placebo-controlled-trial-compare-effectiveness
Amifampridine	2023	Symptomatic treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults	Myasthenia gravis	https://projecten.zonmw.nl/nl/project/impact-mg-improving-symptomatic-treatment-amifampridine-randomized-double-blinded-placebo
Senolytics	2023	Not yet approved; new drug class	Non-alcoholic fatty liver disease	https://projecten.zonmw.nl/nl/project/therapeutical-efficacy-senolytic-drugs-treatment-non-alcoholic-fatty-liver-disease-fibrosis

Acknowledgments and list of consulted experts

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