Presenting the bill: a research about the costs and barriers in drug rediscovery

Internship report

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Abstract

INTRODUCTION – Drug rediscovery (DR) provides opportunities for new treatments and patient benefit. However, due to the barriers and the lack of an incentive in the rediscovery process, DR often does not lead to an extension of indications or market authorization. Hence, the patient does not have access to the rediscovered drug, or only off-label with possible safety issues involved. On the other hand, cases of DR that did register and now benefit from regulatory exclusivity are also part of a public debate as there is a perception of low efforts and high prices asked. For a balanced discussion on this topic, it is important to have better insights in the landscape of DR. This will support policymakers to improve the conditions for DR with patient benefit as a focus.

AIM: To examine the efforts needed and barriers of different routes to get drug rediscovery to the patient.

METHODS – 29 experts from different actors were interviewed about specific costs and barriers of DR through one of the following routes: registration, delivered compounding, magistral formulas or off-label use.

RESULTS – Costs of DR fluctuate heavily between projects and routes and must be seen as indicative. Costs of off-label use are almost nihil, while the development of the production of magistral formulas and delivered compounding could reach up to € 10.000 and € 25.000, respectively. Registration of rediscovered drugs is found most expensive, ranging from € 300.000, if no clinical research is needed, to several millions of euros if additional clinical studies are required. One of the barriers to drug rediscovery is the lack of a business case for DR due to the inability to ask a higher price than a generic already on the market. Another barrier is that medical professionals do not value the registration of DR and do not see registration as a necessary goal of DR.

CONCLUSIONS – Paying a fair price for DR is essential for sustainable DR activities and the status-quo causes therapeutic chances to be missed. Registration should be reconsidered as the golden standard of DR, because most of the found barriers are due to the registration process. Also, registering DR can lead to significant regulatory exclusivity, while the costs have shown to be too low to justify such reward. The most important aspect remains that the product itself is of high quality. Under those circumstances, many patients could clinically benefit from wider application and research of medicinal products once on the market. Registration should not always be the desired result of drug rediscovery.

Laymen's summary

Drug rediscovery (DR) is het inzetten van oude geneesmiddelen voor een andere ziekte dan waarvoor ze in eerste instantie ontwikkeld zijn. Hierdoor zijn nieuwe behandelingen nodig die voor een patiënt waardevol kunnen zijn. Maar er zijn barrières om DR soepel te laten verlopen. Het is bijvoorbeeld moeilijk om er geld mee te verdienen. Daardoor worden kansen gemist op nieuwe behandelingen. Ook gaan dokters het 'oude' middel gebruiken voor een nieuwe ziekte terwijl dat niet officieel is goedgekeurd door het College ter Beoordeling van Geneesmiddelen (CBG). Aan de andere kant zijn er geneesmiddelen die al jarenlang gebruikt worden voor een ziekte en nu officieel door een bedrijf geregistreerd zijn. Soms krijgen ze dan een vorm van exclusiviteit of monopoliepositie, waardoor de prijs van het geneesmiddel stijgt. Hier is ophef over, omdat het in die gevallen lijkt alsof het bedrijf weinig moeite heeft hoeven doen om het geneesmiddel te registreren. En vervolgens vraagt het bedrijf er wel een hoge prijs voor.

In dit onderzoek is uitgezocht hoeveel moeite nodig is om DR-geneesmiddelen bij een patiënt te krijgen. Er is gekeken naar welke barrières er zijn voor DR en hoeveel geld het kost. 29 experts, met verschillende achtergronden, zijn geïnterviewd over DR.

De kosten van DR kunnen bijna nihil zijn, maar ook heel hoog. De kosten moeten slechts als een indicatie gezien worden omdat elk ontikkelingstraject anders is. De kosten van de goedkoopste route, het gebruiken van een bestaand middel voor een ziekte waarvoor die niet geregistreerd is, zijn nihil. De kosten van het officieel registreren van een geneesmiddel voor DR zijn minimaal € 300.000, als er geen aanvullende klinische onderzoeken nodig zijn. Als er wel klinisch onderzoek nodig is, dan kan het meer dan enkele miljoenen kosten.

Eén van de grootste barrières voor DR is het terugverdienen van de investering die nodig is om te onderzoeken en aan te tonen dat een geneesmiddel werkt en veilig is voor een ziekte. Dat komt onder andere doordat het vrijwel onmogelijk is om een hogere prijs te vragen voor het geneesmiddel als het patent verlopen is. Een andere grote barrière is dat dokters en medewerkers van het CBG niet hetzelfde denken over de officiële registratie.

De conclusie is dat het betalen van een eerlijke prijs voor DR essentieel is om nieuwe behandelingen te blijven ontwikkelen met oude geneesmiddelen. Op dit moment worden veel kansen gemist om patiënten te helpen. De kosten om DR te registreren en de gevonden barrières geven aanleiding om te heroverwegen of officieel registreren altijd het uitgangspunt moet zijn bij DR. Veel barrières komen namelijk door het registratieproces. Ook kan bijvoorbeeld de hoge prijs die soms gevraagd wordt als een product geregistreerd is en exclusiviteit heeft, niet altijd verklaard worden door de ontwikkelingskosten. Het belangrijkste is dat het geneesmiddel van hoge kwaliteit is. Onder die voorwaarde zijn veel patiënten gebaat bij het breder toepassen en onderzoeken van geregistreerde geneesmiddelen voor andere ziektes dan waarvoor ze geregistreerd zijn. Registratie zou daarvoor niet altijd het uitgangspunt moeten zijn.

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About this research

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Disclaimer

The views expressed in this research are the personal views of the author and may not understood or quoted as being made on behalf of the Dutch Ministry of Health, Welfare and Sport or any of the interviewees.

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List of abbreviations

API	Active Pharmaceutical Ingredient
CBG-MEB	College ter Beoordeling van Geneesmiddelen – Medical Evaluation Board
CHMP	Committee for Medicinal Products for Human Use
CRO	Contract Research Organization
DMF	Drug Master File
EC	European Commission
EMA	European Medicines Agency
GVS	Geneesmiddelenvergoedingssysteem
HTA	Health Technology Assessment
IGJ	Health and Youth Care Inspectorate /Inspectie Gezondheidszorg en Jeugd
MAH	Market Authorization Holder
ODD	Orphan Disease Designation
PIP	Pediatric Investigation Plan
RefMP	Reference Medicinal Product
SPC	Supplementary Protection Certificate

1. Introduction

The societal need for innovative medicine is part of an ever-ongoing call for new therapies. Patients with neglected diseases await first-in-class medicines, patients with genetic diseases await gene therapies and possibly even more innovative treatments will arise in the future. Meanwhile, the World Health Organization publishes the Essential Medicines list with drugs that should be available to all[1] – a list that is probable to keep growing. It is up to the pharmaceutical industry, scientists and other actors to meet the unmet medical need in the world.

Drug rediscovery is one of the activities that is used by several actors to meet this medical need[2,3]. Drug rediscovery has a variety of definitions in literature[4], but is defined in this research as the medical use of an already known active substance for an indication it is not registered for and will focus on off-patent products.

The advantages of drug rediscovery are that it may cost less money and time to develop a treatment than traditional development because existing knowledge, and safety or efficacy studies for the original indication may be used for the application for the second indication[5,6]. Off-patent active substances are often used for drug rediscovery to avoid intellectual property issues. Although drug rediscovery is not a new activity, since the introduction of the term by Ashburn and Thor (2004)[7] the topic has received more attention in literature and in practice[8].

An important principle of the European legislation on medicines is that registration of drugs is the golden standard with the most information for patients and healthcare professionals, the most safety checks, and a benefit/risk assessment by the regulatory body. However, there are other routes that are used in practice to get treatments to patients. These other routes include magistral/officinal formulas (magistrale/officinale bereiding), delivered compounding (doorgeleverde bereiding), and off-label use. These different routes to get a treatment to the patient all have pro's and con's and are being used in daily clinical practice.

Cases of drug rediscovery that have been topic of public debate cover two categories. On the one hand, drugs that have been used in medical practice for a long time are now being registered for that indication. Some of these products benefit from specific incentives (such as the orphan drug regulation) that give the companies a form of exclusivity. The high prices due to these exclusivities in combination with a perception of a low effort that was needed for registration causes public debate. On the other hand, there are numerous opportunities for more drug rediscovery while actors encounter many barriers[6,9,10], for example limited ways to earn back an investment.

Literature gap

It remains unknown what the exact costs of drug rediscovery trajectories are for the different routes and the landscape of drug rediscovery in the Netherlands is unclear. The costs of a single drug rediscovery trajectory will not be generalizable and also be difficult to determine. Therefore, this research focuses on the efforts needed for drug rediscovery. This includes the costs, but also other steps that are needed in a drug rediscovery trajectory. The main question is:

What are the efforts needed to get drug rediscovery to patients?

Next to the efforts needed, expressed in euros where possible, there are barriers to get drug rediscovery to patients. The sub question of this research will focus on that:

What are the barriers that actors experience to get drug rediscovery to patients?

Societal relevance

Several points of societal relevance of this research are highlighted below.

First, there is a debate about drug development, high prices and drug rediscovery. Facts about the efforts needed to bring drug rediscovery to patients will help to bring clarity into the debate. The facts will be a better understanding of the costs of several aspects of drug rediscovery and the other issues regarding the topic.

Second, knowing the costs of the different routes to get drug rediscovery to patients will help the ministry in the discussion about the pricing of such products, especially when there is protection on these products. In the current public debate, the development costs play a role in determining a so-called reasonable price for drugs.

Third, it will become known if it is possible to determine costs of a single drug rediscovery development or that there is not enough transparency to determine these costs. This will be helpful to determine the investment that should go to drug rediscovery projects.

Fourth, by identifying the barriers, certain stages in the drug rediscovery development process could be identified where actors experience problems. A change in policy or legislation could possibly reduce these barriers to bring drug rediscovery to the patient.

Last, drug rediscovery is considered a less risky approach to drug development and may be a promising route to meet the unmet medical need for rare diseases[11]. Therefore, special attention will be given to rare diseases over the course of this report.

Outline of this report

The second chapter describes the background of drug rediscovery and an overview of the literature about efforts needed and costs of drug rediscovery. The third chapter describes the methodology and the results are presented in chapter four. The discussion and conclusion follow in chapters five and six. After the conclusion, in chapter seven four scenarios are presented for the future of drug rediscovery, meant to explore policy directions.

2. Background

The goal of this chapter is to gain understanding of the legal and practical framework in which drug rediscovery takes place, how drug rediscovery is performed and by whom, and what is known about the costs of drug rediscovery.

2.1. Routes to get drug rediscovery to the patient

European legislation (directive 2001/83/EC)[12] has set out registration to be the main route to get drugs to patients. To receive a marketing authorization for a drug, the applicant needs to hand in a drug registration dossier to a competent authority (the CBG-MEB or European Commission, following an EMA-opinion). There is one exception to registration in European legislation and that is the second route: from a compounding pharmacist direct to a patient. This is called a magistral/officinal formula. In the medical practice in the Netherlands, there

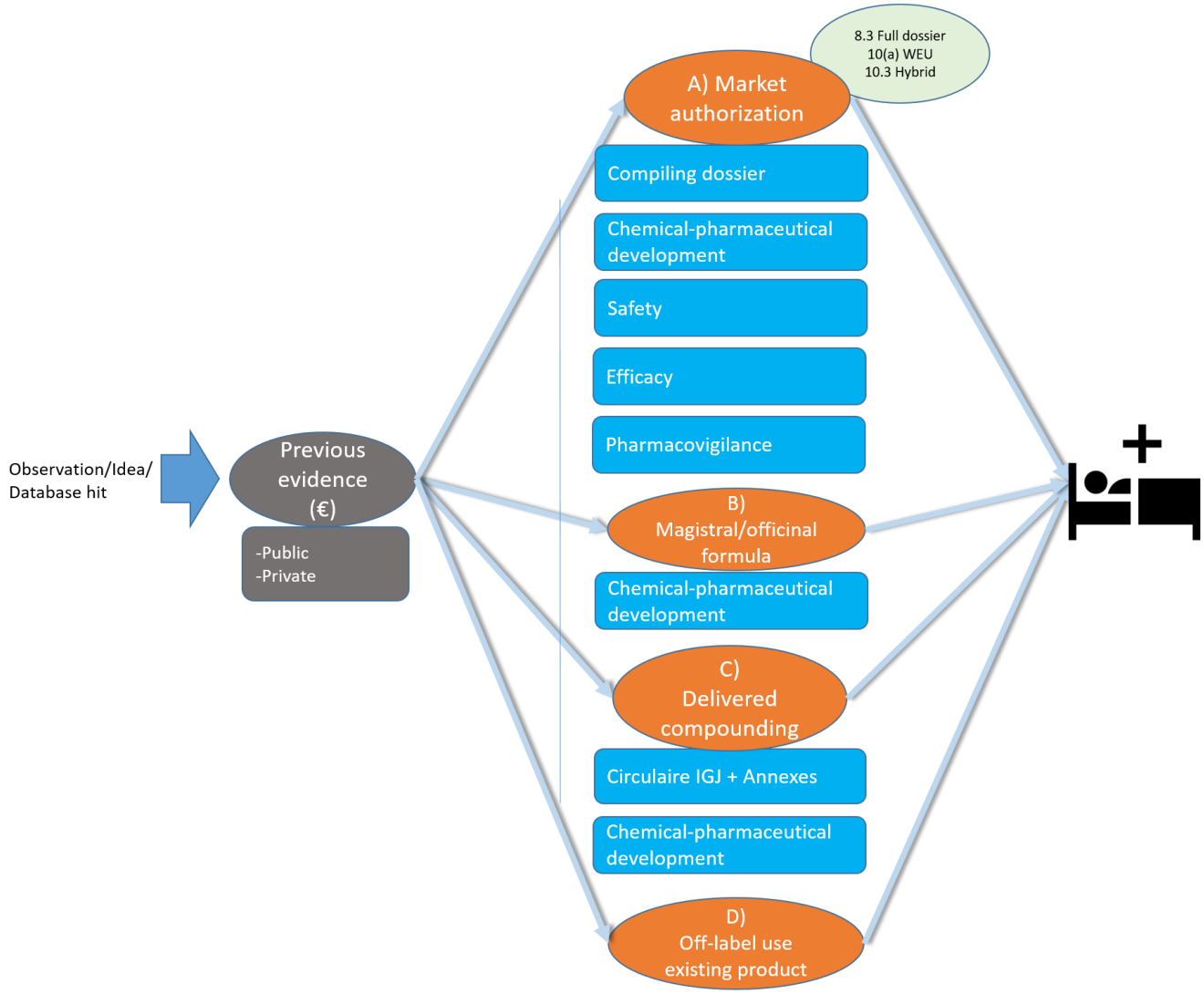

Figure 1: The four identified routes to get drug redisocvery to the patient. At first, there is some previous evidence about the application of a product outside the original registration. Then, route A) is to formally register the use in another indication. Route B) is an exemption in legislation for pharmacists to manufacture products for their own patients. Route C) is a typically Dutch route in which magistral formulas are delivered from one pharmacy to another. Route D) is the off-label use of an existing product.

are two more routes. The third route in the Netherlands is a centralized compounding pharmacy that delivers to other pharmacies, without a registration for that drug (delivered compounding). The fourth route is off-label use, in which a patient gets a registered drug prescribed for an indication although it is not registered for that indication. Off-label use is not limited to the Netherlands[13].

Below, the four routes are discussed in detail (Figure 1Figure 1).

2.1.1. Registration

Organizations can follow different pathways to approval for the marketing of medicines in Europe via different procedures. A company has to choose for a *national* or *centralized* authorization procedure. The *national* authorization procedure can be either the decentralized pathway in which national competent authorities can authorize a medicine simultaneously, or the mutual recognition procedure in which a national competent authority recognizes an existing marketing authorization in another country. The EMA is responsible for the *centralized* procedure. The Committee for Medicinal Products for Human Use (CHMP) carries out the procedures. Several disease areas or drug classes are obliged to follow the centralized procedure, among which orphan drugs.

The directive 2001/83/EC[12] applies to the marketing authorization of medicinal products. This directive is translated into national laws that national competent authorities use in their assessments and is used by the CHMP to assess the dossiers they deal with. Applicants for a new active substance need to hand in the newest data regarding safety and efficacy, while known active substance are allowed to submit dossiers that contain previous data (e.g. without new clinical trials or with references to other dossiers) or refer to another dossier. The directive distinguishes between several pathways that can be followed and criteria that have to be met (Table 1). The pathways are discussed below.

The full dossier pathway (8.3) can be seen as the standard dossier in which data from the applicant can be used or data from the applicant in combination with previously published data from other sources (mixed authorization application).

The well-established use pathway (10(a)) needs to stand on its own (it may not refer to other dossiers), but the non-clinical and clinical data in the dossier need to be exclusively from existing literature. In addition, applicant's own data may be used to prove similarity of the applicant's product to the product used in the literature. To qualify for the 10(a) pathway, an active substance needs to have been used in medical practice for at least 10 years in the European Union.

The hybrid pathway (10.3) is an abbreviated dossier, which means that it can refer to a reference medicinal product (RefMP) for nonclinical and clinical data. This can be supplemented with applicant's own data. The RefMP is an already registered product.

The fixed dose combination pathway (10(b)) can be used to obtain approval for medicines in which previously approved active substances are combined in the doses those active substances already had approval for. This pathway can be used to include therapeutic areas other than the ones mentioned in the approval of the originator's active substances. However,

in practice this pathway seems to be used to obtain approval for the combination of two active substance that both were approved for the same indication as for which the 10(b) application is[14]. Therefore, this pathway will not be topic of this research anymore.

Applications following the generic (10.1 & 10.2), biosimilar (10.4) or informed consent (10(c)) pathway are not allowed to include new indication other than the ones previously authorized for the active substance. Thus, these pathways will also not be topic of this research anymore.

If a product is approved via the CHMP, there is also the Type II variation with which an indication can be added to an existing approval. Because the approval itself would not be changed, the indication added is inherently very close to the original indication. Also, the market authorization holder (MAH) must be the same as the original applicant for a Type II variation. Therefore, this pathway will not be topic of this research.

Table 1: The different application pathways. The green procedures are applicable to this research.

Name	Article
Full dossier	**Directive 2001/83/EC** 8.3
Well-established use	**Directive 2001/83/EC** 10(a)
Hybrid	**Directive 2001/83/EC** 10.3
Fixed dose combination	**Directive 2001/83/EC** 10(b)
Generic	**Directive 2001/83/EC** 10.1, 10.2
Biosimilar	**Directive 2001/83/EC** 10.4
Informed consent	**Directive 2001/83/EC** 10(c)
Type II Variation	**Regulation EC 1234/2008** 4(1)(a) (Guideline paragraph C.1.6)

2.1.1.1. Protection mechanisms

Following marketing authorization, several protection mechanisms apply. The sections below will explain the protection mechanisms and supplementary protection mechanisms for products approved through directive 2001/83/EC articles 8.3, 10(a), and 10.3.

2.1.1.1.1. Data exclusivity & market protection

After the approval of a product via 8.3 or 10(a), the MAH receives 8 years of data exclusivity[12]. During this time, other applicants cannot use the product as a RefMP. After the 8 years, the product has 2 years of market protection, which means that a generic could use the original product as a RefMP but may not enter the market yet. A product approved through article 10.3 does not receive data exclusivity nor market protection.

Extension of indication in the 8 years of data exclusivity provides another 1 year of market protection, leading to a total of 11 years of data exclusivity and market protection combined. Data used for the extension of indication or a change of classification has data exclusivity for 1 year.

2.1.1.1.2. Market exclusivity

A regulation specially designed for rare diseases is the Orphan Regulation 141/2000EC. This regulation states that a medicine that has been designated as an orphan drug by the CHMP receives the market exclusivity for treatment for that disease for 10 years (if no clinical

superior treatments become available) with a possible extension of 2 years if pediatric use is included[12]. One product can have more than one orphan disease designation. The orphan disease designation (ODD) can be assigned to products approved through either the 8.3, 10(a) or 10.3 pathway.

2.1.1.1.3. Supplementary protection certificate

Patent law and regulatory law are distinct mechanisms for protection of intellectual property. However, these two topics come together with the supplementary protection certificate (SPC). The SPC is a prolonging of the patent because of the long time it may take in pharmaceutical development to get from first patent application to the market[15]. The SPC is calculated by taking the time between the filing of the basic patent and the first market authorization minus 5 years, with a maximum of 5 years. A 6-month extension of SPC can be granted if a MAH conducts the studies in the pediatric investigation plan (PIP) after approval. There is no limitation of this mechanism to certain approval pathways. However, it is unlikely that a 10.3 or 10(a) approval has an underlying patent, because products that use these pathways are generally already used in clinical practice for a long time.

2.1.1.2. Actors that register drug rediscovery

For the route of registration, research has been conducted on the actors involved. Research has focused on two aspects. First, one can look at who files a patent that later applies to a repurposed drug. Second, one can look at who files for registration of a repurposed drug. It is interesting to know in both cases what kind of organizations (universities, knowledge institutes, small/medium/big pharma or other organizations) file for patent or a registration and if the applicant for registration or patent is the same as the entity that developed the originator drug.

Mucke & Mucke (2015) have done research on the first aspect (who files for a patent). They found that academia and small sized pharmaceutical companies (not precisely defined) together account for almost 60% of the patent applications for drug rediscovery – although their research also includes products still under patent. Also, 16 of the 20 patents for drug rediscovery filed by big pharmaceutical companies were for additional indications of compounds that those companies had developed and/or launched[16]. This shows that pharmaceutical companies do keep developing new indications for their registered (and possibly patented) products.

Langedijk et al. (2016) have performed research on the second aspect (who files for registration). In this research, one of the conditions for repurposed drugs was to be used in medical practice before 2000. They found that 50% of repurposed drugs that got EMA approval in 2014 or 2015 were filed by a small company (151+ on Scrip's Pharmaceutical Company League Tables 2014) and another 44% by medium-sized companies (21-150 on Scrip's Pharmaceutical Company League Tables 2014).

Outside the measurable scope of patents and registration, Novac (2013) reports contributions of the National Institute of Health to noncommercial drug rediscovery, but also patients that form patient advocacy groups to act as alternative sponsors for clinical development[17,18].

From published literature, is seems that smaller pharmaceutical companies have a relatively big interest in the registering of drug rediscovery. Wilkinson and Pritchard (2015) argue that initially drug rediscovery may be better suited for smaller companies, academic groups and non-for-profit organizations, because these organizations are less constrained to the source of the compound. Cha et al. (2018) add to that the reasoning that small companies have the agility to pursue promising opportunities rapidly and have innovative technologies available to identify candidates for drug rediscovery. From another perspective, Muthyala (2011) argues that drug rediscovery might be suitable for smaller companies because it is relatively less expensive than non-drug rediscovery development.

2.1.1.3. Barriers to registration

There are several hurdles for a business case for the registering of drug rediscovery found in literature, even though a clinical benefit for patients may seem obvious and/or a financial incentive exists. First, drug rediscovery is still a high-risk investment, as there is still a risk for failing the risk/benefit ratio when applying (even though the safety profile may be tested previously)[10,19]. Second, dose determination studies may still have to be done, contributing to higher development costs. Third, regulatory requirements rise over time, so previous data on clinical aspects or starting materials may not be good enough anymore. Fourth, earning back investments does not only rely on market approval, but also on reimbursement and health technology assessment (HTA)[10].

Fifth, there are intellectual property issues. A patent for a second application may be hard to obtain as the knowledge about the use of the medicine for the second application is often already known and/or published about[6]. Then, if an actor would be granted a patent for a second application, a doctor would in practice prescribe the active substance (and not the brand name), and the pharmacist would hand out a generic version if available (instead of the patented medicine). The problem of generics already on the market also applies to data exclusivity: there is no use in keeping data undisclosed when there are already generics on the market[10].

2.1.2. Magistral/Officinal formula

Because there is a clinical need for drugs that are not registered, there is an exemption to the rule that all drugs have to be registered. Pharmacists are allowed to compound a drug if prescribed by a doctor and intended for an individual patient (magistral formula) or for patients later served by the pharmacy in question (officinal formula). In case of the official formula, the pharmacist is allowed to produce and store a batch. Magistral/officinal formulas are daily practice and not all magistral/officinal formulas are drug rediscovery. A magistral/officinal formula is only considered drug rediscovery when the application of the formula is for an indication for which the known active substance is not registered.

There are four criteria that all have to be met for magistral/officinal formulas:

1. The compounding has to take place in the pharmacy
2. In case of drugs that require a recipe: formulation has to be according to the recipe
3. It has to be meant for a determined patient or to be determined patients of the pharmacy

4. It has to be used on a small scale. Recent communication from the Minister of Medical Affairs has set 50 patients for one pharmacy as a maximum in the case of long-term use of medication and 150 patients as a maximum for one pharmacy in the case of short-term use of medication[38].

There is currently a debate going on about these formulas. On the one hand, pharmacists compound patented drugs because the drug is unavailable to the patient because the insurer does not pay the high price. On the other hand, the industry argues that pricing may not be an argument to justify magistral or official formulas, because of the less quality control and the lack of reward for innovation.

For drug rediscovery, magistral and official formulas may be a way to get a treatment to patients when the originator product or active substance is not marketed anymore or not available in the right dosage or method of administration.

2.1.3. Delivered compounding

It is allowed for a pharmacist to produce a batch of a certain drug and to deliver to other pharmacies under strict circumstances in the Netherlands. This has been the result of the closing of many compounding facilities in pharmacies and other pharmacists that have specialized in compounding[20]. Although not legalized, the Ministry of Health, Welfare and Sports has allowed this type of formulas because there is a medical need for these products and specialized pharmacists are better equipped to produce drugs than non-specialized pharmacies. The Health and Youth Care Inspectorate (IGJ) is responsible for this process and has issued a "Circulaire" in which six conditions are explained[20]:

a) It is only allowed when there is no registered adequate alternative commercially available.
b) The authority needs to be notified for every batch that is produced through the *G-standaard* from *Z-index*.
c) There needs to be a product dossier for each batch, consisting of among other a pharmacotherapeutic rationale, production methods, starting materials, information for health care professionals and patients[21].
d) The producing pharmacy needs to comply to GMP-standards.
e) Pharmacovigilance needs to be structurally registered and monitored by the pharmacist.
f) It is not allowed to market the product.

Many delivered compounding products are not drug rediscovery. Delivered compounding is only considered drug rediscovery when the application of the product is for an indication for which the known active substance is not registered.

2.1.4. Off-label use

Off-label use is the use of a registered drug for another indication than what it is registered for.

If the registered dosage and method of administration is suitable for the other indication, this may be an option to get the treatment to the patient. This is the case for drug rediscovery in

which an active substance was already used for an indication in medical practice, after which it has also been used for another indication. Off-label use is common practice and may even be required to fulfill medical needs in areas where no other treatments exist[13]. Important reasons to prescribe off-label are that a doctor finds the available registered treatments not suitable or that there is no registered treatment available at all[22]. Medical guidelines often advise and include off-label prescription[22].

In the Dutch situation, four criteria are considered important for appropriate off-label use[13]:

A) Is the off-label use backed by scientific evidence?
B) Is there no other acceptable treatment available?
C) Are there no known harmful side effects from the off-label treatment?
D) Has the patient been informed about the off-label use and given consent?

Additional legislation (Geneesmiddelenwet 2007) states that off-label use is only permitted in the Netherlands when there are protocols or medical guidelines from the healthcare professionals associations and that pharmacists and doctors need to consult when guidelines are not yet in place[13,22].

There are pro's and con's to off-label prescription[13]. Off-label use can improve (early) access to medicines that under strict prescription of registered drugs would not be available to patients. Off-label prescription may also be cheaper than prescribing a registered product that may be under patent. However, unknown safety issues, adverse events and risk/benefit ratio are important disadvantages for off-label use. Also, responsibility and liability remain unaddressed.

Off-label use is common practice in specific populations and disease areas: children, pregnant women, psychiatry, oncology, dermatology, and new medicines among others[13,22]. Some literature mentions risks of off-label use in the pediatric population because of unknown appropriate doses, side effects, or influence on development[22]. However, this is the case for all off-label use and in most cases, not treating a patient may bring more risks than off-label use of a registered product.

Currently, incentives have been implemented to encourage the registering of off-label use, for example, market protection and data exclusivity extension (section 2.4.1. and 2.4.2.), the pediatric regulation 1901/2006/EC and the orphan medical product regulation 141/2000/EC. Extension of indication of a registered product can currently only be requested by the MAH. The abovementioned measures are meant as additional incentives for MAHs to apply for extension of indication or to apply for the registration of an off-label use[13].

2.2. How drugs for rediscovery are found

Drug rediscovery projects are fueled by different sources. Sardana et al. (2011) describe three sources of drug rediscovery: by serendipity, from informed insights, and from systematic screening[3]. Most repurposed drugs currently on the market originated from serendipity[2,3,6]. However, it is obvious that pursuing a serendipity-based strategy from a company perspective is very hard. From a patient perspective, serendipity is very interesting if you are the first case. Then, you want to know if the use of the drug for your indication is safe and effective.

A step towards systematic approaches for drug rediscovery is development from informed insights. In these cases, a non-profit organization or company may have a sense or reason to believe that a certain drug may work in a disease area.

A fully systematic strategy to drug rediscovery can have different strategies. Several papers highlight the advances in drug rediscovery strategies and methods[2,3,6,9]. Systematic approaches for drug rediscovery can roughly be split up into two groups: experimental approaches and computational approaches[6]. Experimental approaches include phenotypic screening and library/high-throughput screening[2,3,6]. Computational approaches include retrospective clinical analysis, virtual screening and genetic association, amongst others[3,6,9,23].

To foster both strategies, several organizations have developed libraries or tools to screen or to cooperate. Precompetitive public-private partnerships (PPPs) are an example of such an initiative[24]. Precompetitive PPPs have a goal to create scientific contributions by working together. Possible intellectual property can be obtained later in the process. This could for example be a PPP in which organizations can screen compounds in each other's libraries or a PPP that focuses on bringing people together for a breakthrough in a specific disease area. In the Netherlands, Oncode is an example of such a precompetitive PPP.

The risk of not making it through market authorization may differ for projects between these strategies. For drug rediscovery, the risk of failing is considered to be less than non-drug rediscovery in general[2]. This is mostly because side effects may already be known, or clinical efficacy may have been proven. In the case of serendipity findings for drug rediscovery, it is plausible that there is strong evidence for clinical efficacy and/or a safety profile. For drug rediscovery based on informed insight, a strong sense for the application of an active substance is out, but during discovery and development, several setbacks may occur. For a systematic strategy to drug rediscovery, even more risk can be present at the start of the project, as more would probably have to be found out about the active substance in relation to the new indication. One study suggests that drug rediscovery within the same therapeutic area may have a higher approval rate than outside the therapeutic area of the originator drug[11].

2.3. Literature about costs

Literature on the costs of development of drugs differs in order of magnitude. Some literature assesses the costs of development by taking into account failed projects, and others don't. No literature has been found on the specific costs of drug rediscovery. So, to come to a literature-based view on the costs of drug rediscovery, the different cost aspects of drug rediscovery were looked for.

The total costs for registering are initially based on the type of dossier that has to be handed in by the applicant. The fees that competent authorities charge differ per country and per dossier type (Table 2). The fees charged by the EMA are the highest. The dossier has roughly three topics: quality, safety, and efficacy. After that, there is the pharmacovigilance. Quality relates to the costs of research for the final compound, setting up the manufacturing process, the quality assurance of the compound and the development of tests. Safety relates to the research to assess patient safety, for example during *in vitro* research, non-clinical trials and

clinical trials. Efficacy relates to whether the compound has a clinical effect on patients, for example researched during *in vitro* research, non-clinical trials and clinical trials. The costs for safety and efficacy will vary between drug rediscovery, as for some projects previous data can be used and for other projects, new data has to be generated.

Table 2: The fees for applying at the CBG-MEB and the EMA. The fees are subject to change. The annual fee for the CBG-MEB was not found. Several discounts may apply for small-medium enterprises or for drugs with an orphan disease designation.

	CBG-MEB[35]	EMA[36]
Full dossier (8.3)	€ 49.390	€ 291,800
Well-established use (10(a))	€ 25.940	€ 291,800
Hybrid (10.3)	€ 25.940	€ 291,800
Annual fee	N/A	€ 104,600

Below, recent literature on the costs of drug development in general and literature on the costs of clinical trials is discussed. DiMasi et al. (2016) is a highly-cited paper that estimates the R&D costs of new approved drugs[25]. They estimate the mean R&D-costs of a new approved drug to be $2.588B (capitalized at 10.5%). DiMasi et al. (2016) consider failed projects in the price of a new approved drug. Prasad & Mailankody (2017)[26] challenge this study because of a lack of transparency. Pharmaceutical companies were asked to deliver data and neither the sources nor the exact data is provided in the DiMasi et al. (2016) article. In their article, Prasad & Mailankody use a different approach to calculate mean drug development costs for ten oncology products (of which 9 are orphan drugs). They looked only at firms with one compound approved and used public filings from the US Securities and Exchange Commission from the time of discovery to the approval of the compound to calculate the R&D costs. All firms in this research were developing multiple drugs, so this article also considers the costs of failed projects. The mean R&D costs were $905.6M (capitalized at 7%). These are just two examples of studies in the costs of pharmaceutical R&D to show the difference in approaches and outcomes. An important aspect is that stakeholders have an interest in the outcomes of these studies, as they might influence the public debate on drug prices and thus the profit companies can make. Estimations that do not take failures into account and look at the out-of-pocket costs of a single successful product range from $0,2B to $0,5B[25-27].

The next studies zoom in on the costs of clinical trials.

Sertkaya et al. (2016)[28] and Moore et al. (2018)[29] have used tools and databases from contract research organizations (CROs) to calculate clinical trial costs. The results of Sertkaya et al. (2016) present a great variety of costs, differentiated by therapeutic area and phase of the study. The main cost drivers of clinical trials are clinical procedures, administrative staff, and site monitoring, respectively. Moore et al. (2018) focused on pivotal trials (generally phase III). They also found that the therapeutic area is a big influence on the costs of a clinical trial. In addition, a clinical outcome is more expensive than a surrogate endpoint and a placebo-controlled or active comparator clinical trial is more expensive than an active drug only clinical trial. Last, a small number of patients (≤100) and a short treatment duration

(≤26 weeks) cost least. These are not surprising results, though the significance and the size of the difference in price has been calculated for the first time.

Sinha et al. (2018) have researched the pediatric exclusivity extension in the US, including the costs of clinical trials associated. They use data from a March 2015 report by Phrma, the branch organization of the pharmaceutical industry in the US, in which the per patient costs of clinical trials per disease area and per phase are presented, based on an industry survey[30].

Overall, there is little literature on the costs of drug rediscovery and the literature that is available is focused on specific areas.

3. Methodology

3.1. Research design

The effort needed for the registration of drug rediscovery for rare diseases was researched by conducting interviews with 29 experts from different actors in the field of drug rediscovery. The goal was to establish an overview of the efforts needed for the four routes to get drug rediscovery to the patient, where possible with an indication of the exact costs. The method has a quantitative aspect regarding the costs and a qualitative aspect regarding barriers and other efforts that interviewees encounter.

3.2. Interviewees

29 experts were interviewed, some of which were conducted in the same interview. The type of actors of their affiliations and the interviewees are listed in table 3. The interviewees have either experienced drug rediscovery first-hand or work for an organization that is involved in drug rediscovery.

Table 3: The list of interviewees, alphabetically ordered on type of actor.

Type of actor	Interviewees
Delivering compounding & registering company	Hans Waals, Wouter de Vries, Roselinda van der Vlugt – Meijer, Jan Willem Popma
Delivering compounding company	Reinout Schellekens, Bart Claassen, Louwrien Buisman
Doctor-researcher	Louisa Hoes, 3 other doctors involved in drug rediscovery projects
CBG-MEB	Max Polano
IGJ	Nico Kijlstra
Hospital pharmacist	Mirjam Crul
Industry Association for innovative pharmaceutical companies - VIG	Jan Oltvoort, Peter Bertens
Non-profit organizations	Ciska Verbaanderd, Ton Rijnders, Wilbert Bannenberg
Pharmaceutical startup	Tom Manussen, Simon van der Schans, Frans-Joseph Sinorgo, Hein Coolen, Vincent van der Wel
Pharmaceutical supplier	Mina Al Fartousi
Public pharmacist	Paul Lebbink
Registering company	Hennie Henrichs
Subsidy organization for medical research - ZonMw	Martin Favié, Jasmijn Timp

3.3. Data collection

The interviews were semi-structured. A list with questions was sent on beforehand. The full list of questions can be found in appendix A. The list of questions was adapted to each

interviewee according to the affiliation and/or experience. First, each interviewee was asked about the costs of the different routes and specifically for the part they had experience with, if applicable. Second, each interviewee was asked about their experiences with drug rediscovery and what efforts they had to make and what efforts they see for the different routes of drug rediscovery.

3.4. Data analysis

The analysis was done in two steps. First, the costs mentioned in the interviews are presented. The costs are purposely not presented in figure or tables, as this could suggest a validated outcome. However, for some costs only one or two interviewees provided input. Second, insights from the expert interviews were analyzed as an addition to the quantitative calculations of the effort needed for drug rediscovery and to discuss the different viewpoints on drug rediscovery. Results from the study are presented without a direct reference to the interviewee to ensure the free speech during the interviews. The role of the researcher has been to provide a coherent overview of the costs (4.1.) and to put any given arguments in perspective (4.2.) without subjective judgement.

3.5. Reliability and validity

The reliability and validity will be discussed using three concepts: reliability, construct validity, and internal validity[31].

Reliability is about whether it is possible to conduct the same research and have the same results. Conducting the same interviews with the same interviewees would yield a similar result, although the costs of drug rediscovery vary over time and may have changed already since this report. Regarding all barriers and efforts, policy changes and/or the public debate have influence on the landscape of drug rediscovery. For all results, one should consider if it is a structural or temporal outcome.

Construct validity is about whether the research is a realistic view of the actual situation. As many different stakeholders were consulted and interviewed, this report is believed to approach the actual situation. However, it is important to realize that each drug rediscovery trajectory is different and encounters other costs and barriers. The results in this report are therefore not necessarily generalizable to all cases of drug rediscovery. Also, from some type of actors, less than three interviewees were interviewed. For triangulation between people from the same type of actor, three interviewees are desirable.

Internal validity is about whether the causal conclusions of a research are right. The conclusions of this research are meant to give an overview of drug rediscovery and not to steer in a certain direction. However, chapter 7. is more prospective and not traceable to the results. This is clearly indicated in the introduction of the section.

4. Results

The results are provided in two sections. In the first section, the outcomes about the efforts needed and the costs from interviews will be presented. In the second section, the barriers to get to patients that were mentioned in the interviews will be presented.

4.1. Efforts needed (costs)

There are some costs aspects that apply to all routes but are not unique to drug rediscovery. These aspects are production costs of product, obtaining reimbursement (HTA), marketing & sales costs, and distribution. These costs apply after the four routes in figure 1. It is important to realize that these costs do differ between actors and routes. For example, a smaller company may have higher costs for distribution than a big company due to economies of scale and obtaining reimbursement may be more expensive for a registered product than for off-label use.

The specific costs for the four routes will be discussed separately.

4.1.1. Market registration

Not all registering companies have given specific numbers on different aspects. Below, the numbers that were mentioned will be discussed.

Previous evidence

Most interviewees note that the previous evidence available is in most cases not enough to obtain a registration. Most previous evidence is available for free. Several non-profit interviewees mention that their policy is open-science or based on open-science principles (FAIR). A registering company gathers previous evidence by providing clinical trial medication and then in return getting the data. This costs € 100.000 to € 700.000 per project. They use this method to test a new product and to wait for its proof of concept, before stepping in and deciding on registering.

Another interviewee mentions that an Investigational Medicinal Product Dossier – a dossier containing information on a product that is being developed – may cost € 200.000 to buy. A non-profit organization mentions that for shelved compounds it may cost money to get information from commercial organizations and they will never give all available information.

One interviewee says: "You need to change more about the system than on subsidies at this moment [the early stage]. … Investments at the early stage are not the rate-limiting step."

Following this quote, the costs of previous evidence are an investment for any organization that steps into drug rediscovery. However, the costs are not that high that it limits organizations in performing drug rediscovery activities.

Total costs

Estimation of the total costs of an average drug rediscovery project have been: € 4 million, € 5-10 million euros, 'several millions of euros'. These prices were for DR projects that included clinical trials and are out-of-pocket costs.

If we break down the total costs, the aspects below were mentioned.

Active pharmaceutical ingredient

If there is no certified active pharmaceutical ingredient (API) available, a supplier has to be found that will do the certification. This project involves risk and costs money. Several interviewees mention a cost of about 1 million euros for the development of the API. One registering company and a startup say several hundred thousand of euros. Another aspect is the amount of the active pharmaceutical ingredient. Suppliers may have the condition to sell at least a certain amount of the ingredient.

Compiling the dossier

Compiling the dossier is an activity that has to be done by professionals, most of the time academic scholars. The regulatory field and writing the dossier is a high-skilled job that is done by well-trained and experienced people.

A registering company mentions € 200.000 to € 300.000 euros to compile the dossier, including the validation batches and the clinical literature part of the application, while another registering company mentions several millions of euros, including chemical-pharmaceutical development.

A pharmacy estimates € 100.000 to € 200.000 for making the dossier, excluding fees. A delivering compounding company is exploring registering and is looking at € 500.000 euros for making the dossier and filing out-of-pocket costs, including fees.

One interviewee estimates the costs of compiling the dossier at € 700.000 to € 800.000 euros.

Chemical-pharmaceutical development

There is a basic infrastructure on which the companies rely. On top of that, a registering company mentions € 50.000 for development and € 100.000 for product validation. Another company mentions € 100.000 euro.

The companies indicate that the chemical-pharmaceutical development is usually not very difficult, as they already have experience with the compounds they choose to register.

Safety and efficacy

Most companies take these costs together. It depends a lot on if clinical trials are needed. If not, the clinical (literature) part costs € 100.000 to € 150.000 euros according to a registering company, in an average 'simple' case. For 6TG (Thiosix), it was about € 450.000 to € 500.000 euros to pay for the scientists that were involved.

When clinical trials are needed, the costs rise enormously as discussed in section 2.2.

Registry

Setting up and maintaining a registry after marketing is a big cost. Among others, doctors need to be trained, an IT-system needs to be built and nurses have to be paid. Estimations range from € 1 million to € 1,5 million. A big company says about € 20.000 per patient for rare diseases.

Pharmacovigilance

These costs are insignificant according to already established companies, because they have an active pharmacovigilance department. One extra product does not cost a lot. Estimations

range from € 5.000 when there are no issues with the product. Costs can rise if there are important issues. For a startup, the costs can be € 50.000 – 100.000 per year or a couple of tons to set up and a smaller annual cost. However, industry says that the costs of pharmacovigilance might be a barrier for them to take on an extra indication because they have to rely on someone else's research. The annual fees for maintaining a market authorization are also mentioned. These costs differ between the CBG-MEB, EMA and other countries.

4.1.2. Magistral/officinal formulas

The costs of magistral/officinal formulas in general consist of the aspects below. The exact costs of these aspects differ significantly between products. The costs between magistral/officinal formulas in general and for drug rediscovery do not differ in essence.

1) Resources. The costs of the resource include the active pharmaceutical ingredient and excipients. These costs are reimbursed by the health insurance in the Netherlands.
2) Labor costs. The labor costs depend for example on the difficulty of the compounding and the duration of the compounding, which can vary between a couple of hours and multiple days.
3) Costs of analysis (if applicable). Pharmacies can have the products tested before they distribute them to patients. This is not obligatory in all cases.
4) Packaging. The packaging in pharmacy compounding is mostly a manual process, because some tubes cannot be handled by machinery and because it is performed on a small scale.

Apart from these costs for each product, there are fixed costs. The fixed costs are the following.

1) Investments in production facility. Depending on the kind of product, nature of the pharmacy and the size of the facility, significant investments may be needed.
2) Investment in the development of a new product. This is the research that the pharmacists do before production of a single product can start and the test batches. The costs of these investments may reach €10.000 in exceptional cases.

4.1.3. Delivered compounding

Most of the costs for delivered compounding are spent on meeting the criteria in the "Circulaire" of the IGJ. Different delivering compounding pharmacies mention different costs. Some pharmacies also register products. These pharmacies spend more money on the preparation of the product dossier than pharmacies that don't register, because the registering companies prepare at the same time for a market authorization application. The companies that also register may spend up to € 25.000 on a product dossier before it is ready to be produced. During the product life cycle, the product dossier may even become bigger and more extended when the sales volume grows in preparation of a market authorization application. The higher costs for the product dossier are not necessarily reflected in the price asked, because the higher costs are seen as an investment in the possible registration of the product. The market for delivered compounding product is generally very competitive.

The pharmacies that do not register indicate to spend several thousands of euros up to € 10.000 on a product dossier before it is ready to be produced.

The chemical-pharmaceutical development is the costliest part of preparing the product dossier. These costs depend a lot on the kind of preparation (capsule, drink, pill) and the nature of the specific product. The price of the ingredients also plays a role. When the active pharmaceutical ingredient is expensive, the production is adapted; a test batch may cost a lot when it is done on a large scale. Several test batches are needed. So, for a delivered compounding, smaller batches are chosen to save costs.

4.1.4. Off-label use

The costs of off-label use of an existing product are relatively low, as there is generally no research performed and the health insurance covers most of these costs in the Netherlands. One interviewee pointed out that there may be significant costs to society for off-label use. As there is limited research about dosing, patients may be getting too less or too much of the drug. The first can mean that the treatment is not optimal for the patient's disease. The second can mean that the patient is exposed to unnecessary high doses, with accompanying adverse events or side effects. The societal benefit of research performed under the PIP-regulation was pointed out. The PIP-regulation has helped the research in off-label use for pediatric indications forward.

4.2. Barriers

The barriers mentioned during all interviews are presented in a chronological way following a possible drug rediscovery pathway, using a small introduction in each paragraph below.

4.2.1. Off-label use

Drug rediscovery often starts with a researcher from a company or research organization, doctor, or pharmacist that observes an effect on another indication than a product is registered for or deducts a possible effect. The first option is then off-label use of an existing product, when possible.

It is considered easy to use products off-label in the Netherlands. There are rules, including informed consent for each off-label use and rational pharmacotherapy, but there is no strict enforcement. One interviewee points out the importance of off-label use, for example for pediatric use. Another interviewee suggests that the easy off-label use creates a disincentive to register more indications.

Healthcare professionals do often not know whether they are prescribing off-label and are also not interested in knowing if something is off-label or on-label. Doctors in the Netherlands use 3 main sources for their treatment decisions: the "Farmacotherapeutisch Kompas", scientific literature and guidelines when available. The Farmacotherapeutisch Kompas and guidelines have considered all available evidence, but individual scientific articles may not provide a balanced point of view.

Some doctors also do not seem to want to know about off-label use as that means that they have to comply to the rules about off-label use: *ignorance is bliss*. For most doctors, the goal

is to get drug rediscovery in a guideline, because then the use will become widespread and patients will be treated. The registration is something they have not heard of, or do not care for. Doctors say that pharmacists and regulators live in a different world than doctors.

Companies point out that it is important that patients can find information about their indication in the label of a product. However, doctors mentioned during the interviews that they have never heard of a patient that complains about the absence of an indication in a label. This may be explained by the effort of pharmacists. Although pharmacists often do not know if a drug is prescribed off-label or on-label, there are drugs that are commonly used off-label. A pharmacist will spend more time with those patients to inform them about the off-label use of the drug.

In the experience of interviewees, pharmaceutical companies do not want to get involved in official research in off-label use of their products, as they could be held responsible for safety issues regarding the off-label use when they acknowledge a potential use. In practice, pharmaceutical companies stay in touch with the healthcare professionals, but only get involved when the research in another indication is in a later stage. In current legislation, a company is also forced to follow-up on pharmacovigilance notifications on off-label use.

An important aspect of off-label use mentioned by several interviewees is that it is not systematically registered, and it is hard to research.

Companies also stress that off-label use, compounding and delivered compounding may seem cheaper, but the risk of safety issues – with accompanying costs – is higher for those routes.

4.2.2. Magistral/officinal and delivered compounding

When off-label use is not an option, for example because a product is withdrawn by a market authorization holder or the existing product is not suitable for the other indication because of method of administration or dosing, compounding of the product is a way to get the treatment to the patient.

Multiple interviewees agree that compounding and delivered compounding is not a sustainable way to get drug rediscovery products to patients on a large international scale and on the long term. These interviewees also mention that the rules of compounding differ per country. Some of these interviewees say that compounding is necessary when registration fails or when registration is not an option for a specific product but amplify that a registered product is safer in terms of a higher product quality because it has to adhere to higher manufacturing standards. It is considered unfair by some interviewees that compounding pharmacists and delivered compounding companies have lower manufacturing standards to comply to than companies with registered products.

Also, interviewees warn that compounding may prevent pharmaceutical companies to bring drugs to the Dutch market in the long run because the market becomes smaller and they will have negative publicity because of the public debate about high drug prices. However, this is only the case if there is competition between a compounded product and a registered product. If a product is unavailable to a patient because of a high price and then a compounded product is made, it is the question if this should be seen as direct competition.

On the other hand, interviewees argued that compounded products are tailor-made for each patient and thus more patient-specific. This may increase the proper use of medicines for that patient. Another interviewee says that delivered compounding products "are already really safe and will only become more expensive when registered".

4.2.3. Clinical aspects

Researchers or doctors then might want to research the use of the product. Several aspects are important when they consider research.

Doctors have to take on drug rediscovery projects in their own time in some cases as the hospital does not support drug rediscovery. These doctors act as pioneers. Their goal is usually to prove that a treatment works and to get it in a guideline.

Doctors also indicate that they are hesitating to take drug rediscovery projects further, because they are afraid a pharmaceutical company will 'hijack' the product. By 'hijacking', they mean that a pharmaceutical company registers the products and increases the price dramatically.

Also, doctors foresee problems with rules and regulations about clinical research that they will encounter. This prevents them from taking research further.

Hospitals, especially academic hospitals, earn money by conducting clinical trials for CROs and pharmaceutical companies. Any effort they put in doctors that pursue their own drug rediscovery projects is a risky investment, while the money for conducting clinical trials is a risk-free activity.

4.2.4. Active pharmaceutical ingredient

When a drug rediscovery project is taken further, they may be additional issues with the active pharmaceutical ingredient.

The API needs to comply to all current rules and standards of today to be eligible for registration. However, the originating product of the drug rediscovery project may have been developed years ago when rules and standards were less strict. This might also result in big costs of the development of a certified API and the associated risk. Another aspect is that updating an old drug master file (DMF) dossier may have impact on other products that use the same DMF. This has also a cost implication which may keep the supplier from updating the DMF to current rules and standards.

Another issue may be that the originator company does not want to sell the Drug master file or at a very expensive price. It also happens that suppliers make exclusive deals with pharmaceutical companies, which limits the availability of the API.

For rare diseases there is an additional issue. When the supplier has to develop an API and can only sell a small amount each year because of the small population, the business case for the development of the API is even harder.

4.2.5. Commercially driven

Until now, the drug rediscovery project has been in hands of researchers that do not necessarily have registration in mind. But for registration, a market authorization holder has to step in. Another possibility is that a company discovered a potential use of an existing product. There are several aspects that might explain why companies are not enthusiastic about registering drug rediscovery.

There are some aspects that are related to the fact that companies are commercially driven mentioned by the interviewees.

First, when a pharmaceutical company invests in research in off-label use, potentially discovered side effects may backfire on the original indication and thus cost a lot of money. If a researcher would conduct a research and find out the side effects, it would still be discovered. But when a pharmaceutical company steps in and accelerates the research, it may be found earlier.

Second, a new indication may be out of the scope of the therapeutic areas that a company focuses on.

Third, companies will always look for ways to make money from new regulations and laws. The Netherlands cannot prevent unintended effects of for example the orphan drug designation on their own and should cooperate with other European countries.

Fourth, companies have a lot of shelved compounds they would prefer to explore first, before investing in potential drug rediscovery projects. Compounds with possible intellectual property are more interesting for the pharmaceutical company. The pharmaceutical companies don't publish the data about those shelved compounds.

Last, an interviewee argues that the market is more important to companies than a patient or researchers and the market does not solve all medical needs.

4.2.6. Lack of a business case

So, it is commercially driven. But when it is possible to make money, companies will step in. However, making money can be hard in drug rediscovery.

The lack of a business case for drug rediscovery in general was mentioned in almost every interview. Several reasons for the lack of a business case to register have been put forward, which will be discussed below.

First, there is little exclusivity or intellectual property possible for most drug rediscovery projects, except for rare diseases where there is a 10-year market exclusivity. The one year extra data-exclusivity you get for an extension of indication is considered too low. In general, margins on generics are small, which reduces the incentive to invest, even when a 10-year data exclusivity is possible.

Second, it may be hard to ask a higher price because some products can be bought in the drug store or a cheap generic available will be prescribed off-label anyway (even though some sort of exclusivity may apply). If there are generics on the market, these could easily copy the indication to their label if there is no data exclusivity and if a product is already prescribed off-label, the population to sell a product to does not necessarily increase when an indication is brought on-label.

Third, the current system does not reward an innovating company for long-term cost saving, for example when hospitalization can be avoided in the long run. It was said that insurers do not want to be involved in such projects but rather increase the prices of their insurances each year. Multiple interviewees see a role for the payers or insurers in drug rediscovery.

Fifth, the compensation system for medicines in the Netherlands (GVS) clusters medicines that are interchangeable by active substance and not by indication. When a product is clustered, there is maximum reimbursement. So, when an indication is added to a product, the price cannot go above the maximum price, creating a price cap. One interviewee describes as follows: "Even if we want – or need to earn our investment back – to set a higher but 'reasonable' price for the second indication, we are simple not able to do that!"

Last, a business case would make a sustainable model for drug rediscovery possible. What you earn as a profit is used to pay for future investments. At this moment, a lot of possible medical advantages are lost.

The topics below relate to some extent to the lack of a business case but are more specific to another topic.

Capital

The dose finding and efficacy trials are the costliest part of the development and a lot of capital is needed, with the accompanying costs of capital. Smaller pharmaceutical companies don't have the capital to invest. Another issue with the big capital needed and the costs of capital is mentioned by an interviewee. The interviewee claims that as money is spend on costly clinical trials for one drug rediscovery project, less money is available for the development of other products. Because those other products are not developed, the price of the one project that is funded, stays high as the interviewee believes that competition will eventually lead to the lowering of price.

One interviewee summarizes the issue of capital as: "if I would have enough money, I would register everything".

Another aspect is that the costs of clinical trials and development differ between therapeutic areas. This may favor the development of one therapeutic area over another.

Patents & HTA

There are a few more constraints in patents and HTA.

First, TTOs that want to engage with pharmaceutical companies are put on hold by pharmaceutical companies because of potential patent infringes. The patents on a substance are also very hard to find, as there are multiple patents to one drug. Finding out the IP status

of one drug is therefore difficult. Progress has been made on this aspect, for example the WHO/EFPMA database Pat-INFORMED and the Medicines Patent Pool[3233].

Second, second-medical-use patents are applied and used in different ways in different countries, which makes them less attractive. Second-medical-use patents are part of the TRIPs Plus, that are not enforced by all countries.

The next constraints below are not unique to drug rediscovery. In general, it is hard to get a patent for an indication because there might be data or publications about the use already. Also, dossier exclusivity differs between the EU, Canada, the US and Japan and HTA and pricing is even different all across the EU. Although these aspects also constrain non drug rediscovery development, these aspects also apply to drug rediscovery.

4.2.7. Registration

The lack of a business case is related to the conditions that have to be met to get a market authorization (registration)

Registrations has multiple times been described as the 'golden route' or 'golden standard' to achieve because of the pharmacovigilance and the safety for the patients. Also, it is appreciated because it is a clear system to all involved that has strict boundaries.

The *registration light* has come up in several interviews. Interviewees point at the existing evidence about safety in drug rediscovery and argue that an abbreviated dossier should be possible for all of these products. They say that the barriers and costs of a dossier that has to meet current standers are too high to foster innovation. One interviewee says: "Even if we know a compound A to Z, still the same rules apply as it were a new molecule." Another interviewee argues that "saying everything should go in the systems makes that we lose valuable leads." Another interviewee: "95% of the pharmaceuticals can go through the system. But for the other 5% we have a choice: forcing them through the system and lose them or finding another way to gain value from them." These interviewees seem to argue that not only an abbreviated dossier should be possible, but that registration for drug rediscovery should have lower standards than 'regular' applications.

One reported issue is that regulatory authorities ask for prospective and placebo-controlled studies. An interviewee mentions that these are not only costly, but also the medical-ethical committees may not accept these studies when the treatment is already standard-of-care. In fact, regulatory authorities to not always ask for prospective and placebo-controlled studies but do ask for *controlled* studies. These studies may also be hard to conduct when the treatment is standard-of-care.

Only the current MAH can extend an existing market authorization and a willing MAH is needed to register. One interviewee argues that companies already have to follow-up on 'negative' side effects, and that a follow-up on 'positive' side effects (effect in another indication), may also be needed.

Then, a national registration procedure does not make a product worldwide available. It is only a step in the right direction. A national registration in a country such as the Netherlands where the MEB is highly valued, does open doors to registration in other countries more easily.

Several interviewees have mentioned that it is not possible to register all products. Especially rare diseases and pediatric use create both a monetary (registration is expensive in comparison to the number of patients) and practical issues (finding subjects, scientifically proving safety and efficacy, distribution, presence across multiple countries). Also, they mention that there are so many delivered compounding products that it would cost a fortune to register all.

An interviewee told that in one case, a drug rediscovery product was registered. However, the original product was an acid and the company chose to register the product as a base. Every time the product is now prescribed, doctors and pharmacists have to do calculations to prescribe the right dose and double-check their calculations with others. The take home message from this is that registration is not always in the interest of all parties involved.

Doctors or researchers do not know the system of registering drugs. They do not know where to begin and how to find their way in the regulatory world. ZonMw recently started to include advice of the Dutch CBG-MEB in the Drug Rediscovery program. However, ZonMw cannot force a research group to take a project to registering. The "Advies op Maat", regulatory help from the Dutch CBG-MEB, may help to solve this issue, but doctors still have no incentive to spend money on that.

Interviewees that say that the scientific evidence (previous evidence) that is available, in most cases is not usable for the registration dossier also amplify the lack of knowledge about registration with doctors or researchers.

Smaller pharmaceutical companies and/or pharmacists do not have the knowledge to register a product. Smaller companies but also other actors pointed this out. They need partners to get to registering a product.

Several interviewees point out that the CBG-MEB is willing to think along with research groups or doctors that want to take a drug rediscovery project to registering in informal conversations or on a personal note. However, the formal advice is still "stubborn" and does not divert much from the formal regulations, as described by an interviewee. Interviewees describe a mismatch between the opinions of individual CBG-MEB-employees and the formal advice that is given.

One interviewee points out that safety is a S-curve in which we are already at the plateau. Every rule more will cost thousands of dollars and bring none or a little extra safety, because there will always be the weakest link.

For some drug rediscovery projects, a registry is launched to serve as evidence for the registration. One interviewee points out that from a risk mitigation point of view a clinical trial is actually preferred over a clinical trial, because the possible outcomes of a clinical trials are easier to predict and monitor.

Insurers may see a rise in the price of a product when it is registered after a period of off-label use. In the CDCA case, this made the insurer actively looking for a compounding pharmacist to make the product. This shows that the insurer is not always happy with the registering of a new indication. This can only happen when there is no competition, for example because of market exclusivity. Some interviewees point out that it is important to introduce a way to reduce market exclusivity, similar to compulsory licensing.

5. Discussion

In the first part of the results, an overview has been provided of the efforts need that are possibly associated with different routes to get drug rediscovery to the patient. These insights are new, as earlier research in the costs of drug development has not specifically focused on drug rediscovery. In a first attempt in this research, four companies were approached to give insight in the efforts in the development of a single drug rediscovery product for a rare disease. Two of the companies rejected and two never responded after repeated attempts.

The difficulties of finding out the costs of specific cases may be illustrative for drug rediscovery or even drug discovery in general. The development of each product is very specific and may not be generalizable. Also, companies do not seem to keep track of the costs of a development associated to one product. As a result, the costs and numbers found are strict indicative and meant to give a feeling for the costs involved in drug rediscovery.

The problem of 'known unknowns' applies to more aspects of drug rediscovery. There is off-label use, but we do not know on what scale and in what therapeutic areas. Sources on off-label use are scarce and outdated. There is magistral/officinal compounding, but we do not know the order of magnitude and the risks and benefits that it brings. There is delivered compounding, but it is very typical for the Dutch situation. More research in these topics from a system point-of-view will help to understand the relative importance of these issues for drug rediscovery.

The costs that are found in this research can help to bring the dialogue about drug rediscovery to the next stage. While the costs of development in drug rediscovery are not linked in any way to the price asked, it is important for the public debate that the order of magnitude is clear on all sides. Especially the big difference in costs between delivered compounding and registration is a useful insight, as there are many delivered compounding products. Also, an important note is that clinical trials or a patient registry dramatically increase the costs of drug rediscovery. Registering all those products would probably cost billions of euros. There are almost 1.600 delivered compounding products identified[37], registering following the cheapest out-of-pocket costs as found in this study would cost 1.600 * € 0,3M = € 480M. But the average costs to register will probably be higher. One may therefore question the current registering system in which the costs of registering seem to hinder the registering of many products.

The costs of registering a product may also vary between actors. A company that registered for the first time may spend more money on the process because it still has to learn several aspects. An incumbent with experience may develop at lower costs.

The second part of the results shows the variety of barriers and the complexity surrounding drug rediscovery.

A lot of barriers come down to the absence of a way to earn money with drug rediscovery. The absence of some sort of exclusivity, for example with patents, may hinder innovation in that sense. But there are more reasons for the absence of a business case. Unforeseen effects of prescribing methods and the compensation system in the Netherlands, combined with large scale off-label use make drug rediscovery a hard and risky project.

Another important barrier is the role of doctors and researchers who seem not to know about registrations and not to care about whether an indication is off-label or on-label. This could make the doctors even more skeptical about companies that approach them to register

indications as the doctors and researchers may suspect the companies to 'only want to make money out of it'. The fact that long-term availability is ensured by registering could make the doctors think otherwise, but as long as the CBG-MEB and doctors do not find a common ground on the importance of registration, these worlds will continue to live apart. Off-label use also plays a role, because a product that is deemed not ready for registration is common to be used off-label on a large scale. By tolerating this widespread off-label use, the medical society implies that the use of drugs for indications for which the balance between efficacy and safety has not been established by the CBG-MEB, is permitted. There is a role for the ministry of health in this matter to engage in conversation with all parties, find a common ground and start teaching doctors based on this common ground in their medical training.

A new insight is the potential problems with APIs in drug rediscovery, as the API has to comply to current standards and rules. These practical issues may cost a lot of energy from doctors and researchers that decide to get involved in drug rediscovery.

Issues may arise when pharmacists manufacture a magistral/officinal formula of a drug rediscovery product and after some years, the product is registered. A price rise is usually the next step after registering, but in the public opinion, this price rise can be found outrageous. Each case should be looked at individually, but an unconditional rejection of any price rise is unjustified as long as we consider registration as the golden route for all applications of medicines.

The magistral/officinal formula is currently a widely discussed topic. There are cases in which pharmacists manufacture magistral formulas of registered products because the registered product is unavailable to the patient due to a high price. Considering this research, a company has taken the effort to register a product, even though there are several barriers, after which the product is manufactured as a magistral formula. This could be interpreted as a disincentive to registering drug rediscovery, because it strengthens the lack of a business case after registering.

Rare diseases are an interesting category of drug rediscovery. While the efforts may be lower to get a drug rediscovery project for a rare disease to registration[27], there are important barriers, as the small patient population causes issues with finding subjects for clinical trials and with significantly proving and effect. Also, developing an API for a rare disease may be hard because the amount needed per year is relatively low. On the other hand, the orphan drug designation does provide an incentive for registering drug rediscovery for rare diseases. The incentive is however thought to be too high in specific cases. This research shows that the costs of the development of drug rediscovery for rare diseases is indeed not necessarily as high as the revenues made with products that did get the orphan drug designation, although a link between development costs and a price has never been shown.

The barriers discussed above have been mentioned before in literature[9,10] and in a report by Langedijk et al. (2012) about stimulating drug rediscovery in the Netherlands[34]. However, the solutions in that report as an advice to the Dutch ministry of health have been only partly addressed and a comprehensive approach to drug rediscovery is missing. This research shows that the barriers are still present and have only become more urgent.

The strengths of this research lie in the comprehensiveness of the approach, in which not only registration but also other routes for drug rediscovery have been studied and the range of interviewees from different actors. The combination of studying both the efforts needed and the barriers for drug rediscovery also has led to a perspective for both. The limitations include

that the found efforts needed are not generalizable and may differ heavily between drug rediscovery projects. Also, the costs are subject of change due to changes in fees, regulations or the economy. The relative importance of each barrier is also debatable, since the interviewees have an interest in a change in policy.

6. Conclusion

This research has investigated the effort needed to get drug rediscovery to patients. Four routes were identified to drug rediscovery to the patients: registration, delivered compounding, magistral/officinal formulas, and off-label use. An indication of the effort needed for these four routes was found and expressed in the costs in euros ranging from up to € 10.000 for magistral formulas to several millions of euros for a market authorization. Next, the barriers to drug rediscovery were identified. In the public debate about drug rediscovery, many arguments are used about the costs of registering and the barriers to drug rediscovery. The results of this report can help to put those arguments into perspective.

This report shows that in some cases the incentive for drug rediscovery is too high, while in many cases there is no incentive at all. On one side of the public debate, there is discussion about a perceived difference between the effort needed for development and a high price. The results support that it is possible that in some of these cases, the prices asked for drug rediscovery product are very high in relation to the efforts needed. Regarding these 'hijacked' drug rediscovery projects, exclusivity as an incentive to stimulate the registration of medicines seems, also in the case of drug rediscovery, seems to work. The orphan drug designation and supplementary protection certificates have caused more registrations in those areas and stimulated development. But the exclusivity causes public debate about the prices of those medicines. It is important to realize that the price of medicinal products and the development costs are not necessarily linked, but objections to the claims that development costs for drug rediscovery are high may be justified as shown by the data in this research. People objecting to the price rises of drug rediscovery projects should ask themselves the question what they find a registration worth, while companies that register drug rediscovery projects could prevent the public debate by explaining the difficulties of drug rediscovery. In the end, all regulations will be utilized by companies to the full extent.

On the other side of the public debate, there are products that are not developed and missed opportunities for patients that could benefit from known active substances. The multiple reasons for the lack of a business case underline this problem. It is important to realize that drug rediscovery is not free and is not a gift that will present itself. Paying a price for drug rediscovery is essential for sustainable drug rediscovery activity and the status-quo causes therapeutic chances to be missed.

The concepts *effort needed* and *barriers* may interact. Some barriers mentioned in the results section have a direct effect on the efforts needed. For example, the requirement of a new dossier for the active pharmaceutical ingredient or the need of clinical trials for registration will increase the effort needed. Other barriers exist without having a direct effect on the effort needed, for example the absence of exclusivity, off-label use or a lack of knowledge about registration with doctors. These barriers however may prevent an organization from taking the effort to get drug rediscovery to patients. When policymakers want to encourage drug rediscovery, they should consider whether they want to focus on decreasing the effort needed or other barriers and what the impact is of those barriers.

Registration should be reconsidered as the golden standard for drug rediscovery, because most efforts and barriers relate to the registering of drug rediscovery and public debate is caused by the regulatory exclusivity after registration. Also, the deemed acceptance of widespread off-label use is reason to reconsider the role of the registration and regulatory authorities in drug rediscovery. The most important aspect remains that the product itself is of high quality. Under those circumstances, many patients could clinically benefit from wider

application and research of medicinal products once on the market. Registration should not always be the desired result of drug rediscovery.

Chapter 7 explores four scenarios for the future of drug rediscovery. Two of these scenarios do not have registration as the *golden standard* for drug rediscovery.

7. Future scenarios of drug rediscovery

It remains important to discuss what an ideal situation for drug rediscovery would be. Discussion is needed on to what extent we want unregistered use of drugs to be registered, and the price we are willing to pay. Given all the found costs and barriers, four scenarios will be presented below using the quadrant in figure 2. The scenario's stretch across two axes. The horizontal axis represents whether the principle of registration as the *golden standard* is upheld or there is a change in legislation. The vertical axis represents what we think should be the main source of financing for drug rediscovery. The four scenarios will be discussed with advantages and disadvantages. These scenarios are prospective and meant to stimulate the debate.

General remark about the scenarios

Most scenarios imply a policy or legislation change. It is important to realize that any industry benefits from a stable ecosystem and predictability. Policy makers need to announce and explain any changes years before the implementation. A period of ten years would be appropriate in the case of drug rediscovery, as the standard period of data exclusivity + market protection is 10 years (8+2 years).

Some of the scenarios also will lead to increase costs. This is not considered a disadvantage in the analysis of the scenarios, because all costs need to be evaluated in light of its health and economic benefits.

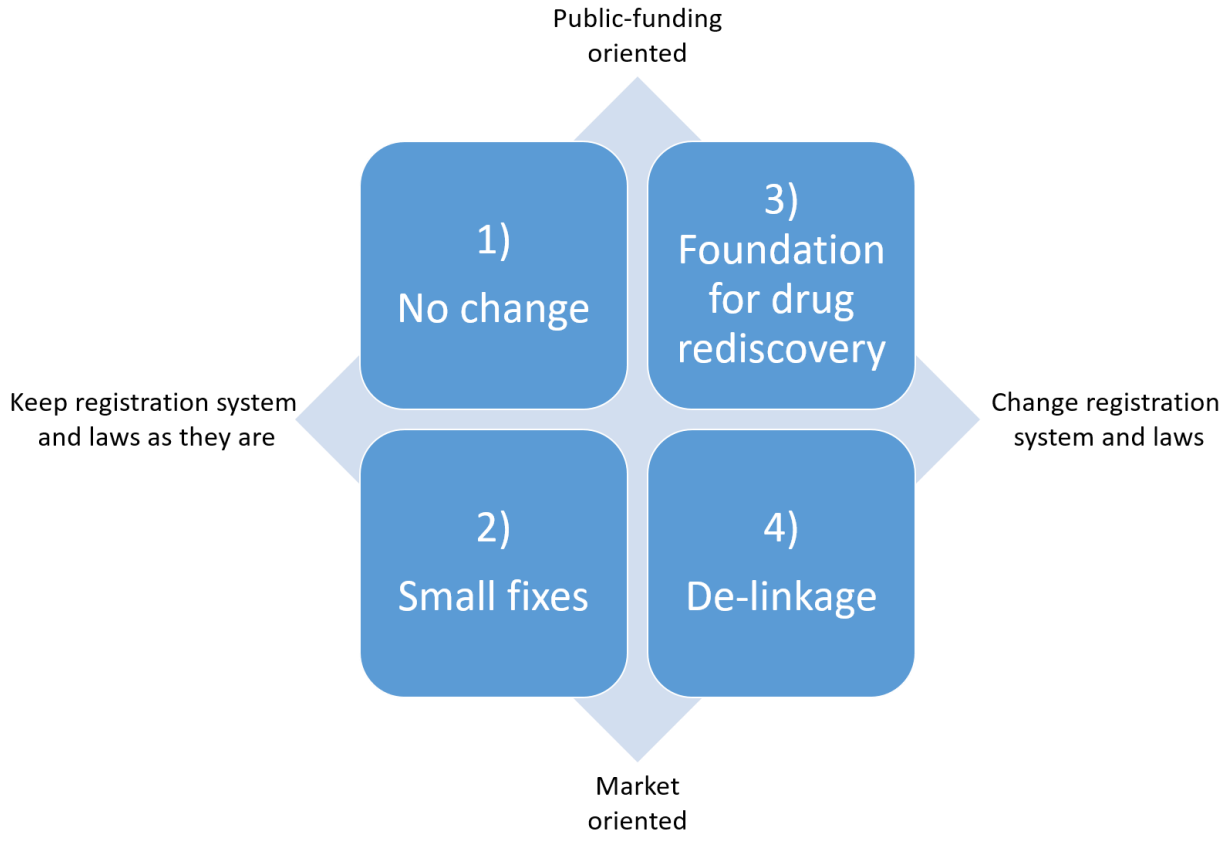

Figure 2: The four scenarios represented in a matrix.

7.1. Scenario 1: No change

If no rules were to be changed, drug rediscovery for off-patent products in general will not be a sustainable market activity. All efforts and constraints mentioned in section 4.2. will continue to exist. There will be drug rediscovery projects that succeed, but mostly because individuals (doctors, researchers or pioneers) pursue a project, supported with public funding. For specific niches where there are incentives, for example rare diseases, there will be more successful drug rediscovery. However, these incentives may be too high or disproportionate, causing a price-rise for drugs that may make the treatment unavailable to patients. This causes public debate. Hypothesizing, if companies would from now on only set so called reasonable prices, this public debate would likely disappear. However, still a lot of opportunities for drug rediscovery are missed because of the lack of a business case.

With the contribution of non-profit organizations and subsidies like ZonMw, some drug rediscovery projects will be launched, but rarely make it to registration. Overall, few indications will be added to labels or new registrations with known active substances will be filed.

An advantage of this scenario is that everything can stay the same. A disadvantage is that possible treatments are not explored or will stay in the proof-of-concept phase, while patients could gain clinical benefit from it. Also, off-label use will be widespread and there will be more public debate on cases where old drugs are registered using the orphan drug designation.

7.2. Scenario 2: Small fixes

Within the current registration system and legislation, there is room for improvement. This scenario explores a market-driven approach to make it possible to earn back investments on drug rediscovery. Three measures are described below.

Prescribing for specific indication

Doctors will need to write down the indication for which a product is prescribed. Then, the pharmacist must hand out the product with a registration for that indication, when applicable. This will create a way for companies to earn on protection. This measure will probably be unwanted by doctors and pharmacists as this requires more work from them and an active role in finding out the protection status of a drug. Also, doctors are not always sure about the indication of the patients and prescribe based on a differential diagnosis. Writing down an indication may give the false impression that the doctor is certain about the indication of a patient. However, using modern IT applications, it must be possible to link the prescribing method to a database with protection status.

Changing the GVS and preference policy

The GVS and preference policy will need to be based on indication (instead of active substance) or to be removed. This will allow for more differentiation in price for an extension of indication of a product. Right now, when there are similar products (generics) and only one of the generics has a registration for a certain indication, the maximum reimbursement in the GVS is the same as for the generics that do not have a registration for that indication. The same applies to the preference policy where insurers buy based on an active substance.

Involving the payers (insurers) in drug rediscovery

The health insurers will need to participate in drug rediscovery to take advantage of health benefits and possible contributing to a way of earning money for the companies that carry out drug rediscovery. Their contributions may be financial or by putting drug rediscovery on the agenda in their network.

All in all, this scenario creates possibilities for financially sustainable drug rediscovery. An advantage is that drug rediscovery will be a market activity, as is all the whole system of drug development. Also, treatments will be developed that patients will benefit from. A disadvantage may be extra work that needs to be done by doctors when prescribing. Also, this scenario does not allow for steering in for example therapeutic areas.

7.3. Scenario 3: Foundation for drug rediscovery

This scenario puts the necessity of registering all drug rediscovery aside. Drug rediscovery is a valuable activity in which treatments can be found with active substances about which we already have knowledge and data. This system is focused on stimulating and rewarding the added value of an authorized drug for multiple uses. Several measures are explained below.

A foundation for drug rediscovery research

A foundation or other organization is responsible for coordinating off-patent drug rediscovery research with no outlook of ever gaining IP or another sort of exclusivity and no competition on this development with other actors. The foundation is only meant for applications and indications that would otherwise not be researched. The foundation is also involved in an international network that will prevent the same research in the Netherlands and elsewhere. This organization tries to take the research to the level for registering and then sells the 'dossier' to any party interested or takes it to the CBG-MEB itself. During the process, there is a lot of contact with the CBG-MEB. The foundation's role is also to communicate with involved company to prevent competition between research groups or organizations and the market authorization holder. Rare diseases could be chosen as a manageable focus area as a start. With the help of the results of this research, it can be determined how big the funding for the foundation should be.

An organization such as the foundation for drug rediscovery research as suggested above has already been presented to the Dutch authorities in the report of Langedijk et al. (2012)[34]. The "Center for Drug Rediscovery" in the report has several activities such as *Regulatory Cooperation, Development Coordination,* and *Research Coordination.*

Once a product has a market authorization, use in other indication is tolerated but monitored with registers for all off-label use

A more hybrid approach to drug rediscovery will enable more research which leads to better healthcare. This could also lead to 'just' the implementation in a guideline. The goal of all use of a product once it is on the market is to research the best use of the drug, including the use for other indications than the one(s) it is registered for. The goal is not necessarily to register all uses but to provide the best care possible. Doctors should be involved in this research and it should be made as easy as possible for doctors to research off-label use and other indications for an existing product. The foundation can play a role in helping the doctors/researchers. The most important condition is that the quality of the product is high and adheres to the MA.

A more advisory role for the CBG-MEB during research

The CBG-MEB has a monitoring and advising role that is more hybrid. The CBG-MEB can identify off-label use or other drug rediscovery projects and decide to give its opinion about it. This allows drug rediscovery projects for which there seems to be no interested MAH to be implemented in clinical practice. This requires the CBG-MEB to look at all available data from a new perspective and could include moving some of the evidence from phase 3 to phase 4 for drug rediscovery.

Don't rely on the willingness of the MAH

In the current system, the label of an authorized drug is property of the market authorization holder. To change that, legislation needs to be changed. This scenario proposes to give the CBG-MEB the authority to force a MAH to add an indication and information to a label after the 10-year period of data exclusivity. An application or variation can also be done by another organization than the MAH.

All in all, this scenario has a public role in drug rediscovery as a starting point. By centralizing drug rediscovery research, it will gain attention and more products will be both used more appropriately and be developed for other indications. The advantages include the possibility to focus on specific niches, such as therapeutic areas and/or rare diseases. Also, the gap between the registration authorities and the medical practice will become smaller as there will be more interaction. Another advantage is that even the outcomes of research that shows that an application of a known active substance is not beneficial for the patient can be spread by the foundation, whereas commercial organization don't have the incentive to publish such research. The foundation would be the organization that A disadvantage may be that there could be that the scenario only favors the business model of drug rediscovery for one actor: the foundation. This could mean that companies will wait for the foundation to research a second indication or that the foundation registers the use of a competitor's product for an indication of a product of a company. That could decrease the market size of the first company.

7.4. Scenario 4: De-linkage

The last scenario is market-driven and has 'de-linkage' as a starting point, in which the reward for the development of a drug is de-linked from the manufacturing and selling of the drug. Similar as in scenario 3 is the market authorization no longer property of the authorization holder and is any organization or the CBG-MEB itself allowed to apply for a registration. Also, the CBG-MEB will need to look at the available data for drug rediscovery from a new perspective and be involved in off-label use. Off-label use needs to be accepted as common practice and incorporated in the system of drug use, although the importance of registering is upheld.

An important aspect of this scenario is that the subsequent manufacturing and selling of a drug can be cheap, as there is no investment that needs to be earned back. De-linkage can be used as a policy instrument for a focus on specific niches or therapeutic areas.

Lump sum

The reward for registering a drug rediscovery project can be implemented in different forms of which two will be discussed: the *lump sum* and the *reimburse+*. The *lump sum* is a pre-determined amount of money available after the successful registering of drug rediscovery for an indication for which the drug is best-in-class. The advantage is that the policy maker knows that the maximum budget impact will be as they set out the rules. Also, efficient drug development will be rewarded and stimulated because every saving in the development process has a direct influence on the profit of the development. A difficult aspect will be to set the reward. As illustrated in this research, every drug rediscovery project is very different, and the necessity of clinical trials has a big impact on the development costs. The lump sum will probably attract the low hanging fruit first, e.g. projects of which the development costs are considered low. This is not necessarily bad as it also stimulates competition but may cause public debate on the perception of low development costs versus a high lump sum.

Reimburse+

The *reimburse+* is a model in which a company needs to show the development costs of drug rediscovery and gets a reward on top of that. This can be a fixed amount or a percentage of the development costs. The advantage of this model is that the reward will likely never cause a public debate on the perception of low development costs versus a high reward, because these two have a clear relationship and are transparent. A disadvantage is that there is little incentive to companies or other organizations to work efficient or at low costs.

All in all, the de-linkage model provides possibilities for a market-driven approach to drug rediscovery but will be difficult to implement. A specific niche may be a good opportunity to use de-linkage in a policy experiment. It can be considered to have not only registration as an 'endpoint' for the reward, as registration is not necessarily the optimal outcome for all drug use. More research in off-label use and application of drugs for drug rediscovery may also be worth a reward in that sense.

Appendix A – All questions (Dutch)

The question list was adapted to the type of actor.

Inleiding

Dit is een onderzoek naar de effort/moeite die nodig is voor registratie van drug rediscovery voor zeldzame ziekten. Het gaat uit van een scenario waarin een onderzoeker een idee heeft of iets tegenkomt. Dan wordt daar ("initieel") onderzoek naar gedaan en het ziet er veelbelovend uit. Dan kan het middel op verschillende manieren bij de patiënt komen: A) marktregistratie B) doorgeleverde bereiding, C) magistrale/officinale bereiding, D) off-label use van een bestaand geregistreerd product.

*Zie ook model (Figure 1)

Vragen algemeen

Welke rol vervult WCN in het geschetste model?

Wat is uw visie op het model? Is A) altijd de meest wenselijke route?

Wat is uw visie op de verschillende routes om een product voor een andere indicatie dan waarvoor het geregistreerd is bij de patiënt te krijgen?

Wanneer gaat een product van C) magistraal/officinaal naar B) doorgeleverd en van B) doorgeleverd naar A) marktregistratie ? Hoe gaat dat proces? Zijn artsen/onderzoekers daarbij betrokken of is dat een (ziekenhuis)apotheker of fabrikant?

Op basis waarvan maakt u de keuze tussen A) en B)?

Hoe verhouden de kosten van de onderdelen in A) zich tot elkaar?

Wat kost het opzetten van GMP-productie voor een product bij A)?

Hoeveel kost een literatuurstudie om te gebruiken bij A)?

Hoe verhouden de kosten van de onderdelen in B) zich tot elkaar?

Wat kost het opzetten van GMP-productie voor een product bij B)?

Hoeveel kost een literatuurstudie om te gebruiken bij B)?

Hoe verhouden de kosten van A) tov B) zich?

Bent u bereid om een schatting te geven van de kosten van de onderdelen van A) en B)?

Vragen previous evidence

Is previous evidence doorgaans publieke data of kan het geval zijn dat daarvoor betaald moet worden?

Hoe verhouden de kosten van previous evidence zich tot de kosten die gepaard gaan met de registratie of een andere route?

Gat onderzoeker > registratie. Hoe heeft u dit ervaren?

Vragen specifiek B) doorgeleverde bereiding

Op basis waarvan maakt u de keuze om een product te ontwikkelen voor uw portfolio?

Speelt pharmacovigilance een rol in het beslisproces om een product te ontwikkelen?

Hoe schat u de verhoudingen van de kosten van de onderdelen in B)?

Bent u bereid om een schatting te geven van de kosten van B)?

Tegen welke zaken loopt u aan bij B)?

Vragen specifiek A) marktregistratie

Hoe verhouden de kosten van de onderdelen in A) zich tot elkaar bij drug rediscovery?

Bent u bereid om een schatting te geven van de kosten van de onderdelen van A) bij drug rediscovery?

Speelt preklinisch onderzoek een grote rol bij drug rediscovery?

In het geval er geen klinisch onderzoek meer nodig is (well established use), hoeveel kost dan nog het samenstellen van een dossier?

Speelt P4 / pharmacovigilance en de overige kosten voor het onderhouden van een handelsvergunning dat registratie is verkregen nog een rol in het beslisproces?

Vragen overig

Wat zijn volgens u barrières voor drug rediscovery?

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