Stimulating Drug Rediscovery

Towards a marketing authorisation for new applications of existing medicines

Joris Langedijk
John Lisman
Pieter Stolk
Aukje Mantel-Teeuwisse
Marie-Hélène Schutjens

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***Drs*. J. Langedijk**	*Utrecht University*
***Mr. drs*. J.A. Lisman**	*Lisman Legal Life sciences*
Dr P. Stolk	*Escher project*
Dr A.K. Mantel-Teeuwisse	*Utrecht University*
Prof. M.D.B. Schutjens	*Schutjens de Bruin*

Universiteit Utrecht

Lisman
Legal
Life sciences

project
escher

Schutjens · De Bruin

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Terms

In this report the following terms have the following meanings:

Term	Meaning
Pharmacy preparation:	an officinal or magistral preparation
Drug Rediscovery:	the development and registration of a new application of an existing medicine
Marketing authorisation: *Synonym: registration*	the authorisation to place a medicine on the market
Magistral preparation:	a prescribed pharmacy preparation for a pharmacy's specific patients
New application:	a new indication, a different patient population, a new pharmaceutical form, a new route of administration or a combination thereof
Off-label use: *Synonyms: use for an unregistered application*	the use of an active substance or medicine for an application which is not included in the official product information
Officinal preparation:	a pharmacy preparation which is in stock, and prepared by a pharmacist for his/her own patients
Unregistered medicine:	a medicine for which no marketing authorisation has been issued
Product developer: *Synonyms: manufacturer, authorisation holder, producer*	a party which (further) develops medicines
Registration:	the issue of a marketing authorisation
Variation:	a revision of a marketing authorisation, e.g. the addition of a new indication

Abbreviations

In this report, abbreviations are used as follows:

Abbreviation	Meaning
6-TG	Tioguanine
TAU	Temporary Authorisation for Use (*Autorisations Temporaires d'Utilisation*)
MEB	Medicines Evaluation Board (CBG, College ter Beoordeling van Geneesmiddelen)
CDR	Centre for Drug Rediscovery
CHMP	Committee for Medicinal Products for Human Use
CMDh	Co-ordination Group for Mutual Recognition and Decentralised Procedures - Human
HIB	Healthcare Insurance Board (CVZ, College van Zorgverzekeringen)
DTC	Diagnosis Treatment Combination (DBC, diagnosebehandelcombinatie)
DR	Drug Rediscovery
EMA	European Medicines Agency
ENL	Erythema nodosum laprosum
EPAR	European Public Assessment Report
EU	European Union
GCP	Good Clinical Practices
GMP	Good Manufacturing Practices
MRS	Medicine Reimbursement System (GVS, geneesmiddelenvergoedingssysteem)
HI	Healthcare Inspectorate (IGZ, Inspectie voor de Gezondheidszorg)
RCT	Randomised Controlled (clinical) Trial
R&D	Research and Development
SmPC	Summary of Product Characteristics
SPC	Supplementary protection certificate
HWS	Ministry of Health, Welfare and Sport

1 Introduction

Legislation on the admission of medicines onto the market is intended to ensure that medicines are proven effective, are of high quality and have an acceptable safety profile. In this regard, medicines are evaluated on behalf of the government by authorities such as the *European Medicines Agency* (EMA) and the *Medicines Evaluation Board* (MEB). A marketing authorisation is issued if, based on this evaluation, the benefits of the medicine outweigh the drawbacks: the *benefit-risk ratio* should be favourable. The marketing authorisation also plays an important role in documenting the characteristics of medicines and the provision of information on medicines to patients and practitioners. The assessed data on the medicine are described in the *Summary of Product Characteristics* (SmPC). The SmPC and the corresponding *European Public Assessment Report* (EPAR) set out which applications have been clinically proven, how the evidence was provided and what is known about the safety and safe use of the medicine. This information is accessible to the public. Chapter 3 deals with the development and authorisation of medicines.

The innovation of many types of products - think of cars and medical devices, for example - is an incremental process. A manufacturer makes a prototype of a product. The manufacturer and other parties then continue to improve the product over time. This is an evolutionary process. However, the medicine development process is often characterised as being “intermittent” or revolutionary. If a medicine with an active substance which has not yet been applied medically is allowed onto the market, it will often be the only product with that active substance on the market until the period of patent and dossier protection expires. The *innovator* has made such a significant investment in the new medicine that the given period of protection is needed to recoup the investment. New investments, e.g. the development of new indications or patient populations, are not always rewarded with protection in the form of a patent or market exclusivity.[1] This is why, in general, a manufacturer will significantly scale back its investments in a medicine which has been on the market for some time. At the same time, this protection can to a certain extent impede the further development by other parties.[2]

The indications for which an active substance in a particular dosage (form) is registered therefore only often form a *subset* of the potential applications of the substance in clinical practice.[3] In practice, doctors use medicines for more indications than those for which they have been registered. A particular active substance could have other applications which are not yet known, are not being used in practice or which have not yet been studied further. The actual medical application of an active substance without a marketing authorisation*, off-label* use, is based on evidence from clinical studies, clinical experience or theoretical grounds.[4] The scientific substantiation of unregistered applications differs from case to case.

1 *See Chapter 5.*

2 *See Chapter 5.*

3 *J.A. Lisman, “De toelating van geneesmiddelen: Hoe effectief is ons systeem? [The admission of medicines: How effective is our system?]”, in: Medicines and Law, Association for Health Law, The Hague: SDU uitgevers 2006, p. 106.*

4 *See for example C. Schoonderbeek, J. Lisman, Off-label use of medicinal products: a legal update; PLC Cross-border Handbook, Life Sciences 2007/2008,*

Sometimes, the substantiation for the new application is robust and similar to the substantiation for obtaining a registered indication, but the substantiation is often weaker.[5]

If there is no proper dosage form of a registered medicine (irrespective of the indication) for the necessary active substance, a pharmacy preparation can be used. This may concern a product which is prepared from ingredients (active substance and excipients) or a pharmacy preparation which is based on or derived from a registered medicine.

Disadvantages of Current Practice

Although the use of pharmacy preparations and medicines for unregistered indications can satisfy a clinical need, both have (partly overlapping) disadvantages. We list the following disadvantages:

a. Since the use for unregistered indications has not been assessed based on scientific data, it is not certain whether the advantages of using the product outweigh the disadvantages, i.e. whether the benefit-risk ratio is positive. The medicine might not be effective for the indication for which it is used. There could also be unknown safety risks.[6]
b. The use is often *opinion-based*, not *evidence-based*. A doctor's prescription is often not substantiated by sound clinical evidence; it is often based just on their experience.[7]
c. There is no approved dosage recommendation, based on clinical research, for off-label indications.
d. There is no publicly accessible information on the effectiveness and safety of medicines used for an unregistered indication. This information is lacking for prescribers and patients of pharmacy preparations, while some approved information about the safety of another application is at least available for medicines used for an unregistered indication.
e. The use of medicines for unregistered indications is sometimes not reimbursed. This may prevent a patient from using a medicine or entail great expense for the patient.
f. With respect to pharmacy preparations, there are fewer quality guarantees for the medicine than for a registered product.
g. With respect to pharmacy preparations, a non-standardised product is supplied. Differences in the medicinal products can result in differences in the treatment outcomes, and possibly suboptimal outcomes for the patient.
h. Unregistered medicines are in a regulatory vacuum: there is no registration dossier to fall back on and no one is responsible for the structured collection and reporting of side-effects.

It should be pointed out that different disadvantages may be emphasised for different types of medicines.

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p. 26; and: National Institute for Public Health and the Environment, Off-label gebruik van geneesmiddelen Transparantie gewenst [Off-label use of medicines. Transparency desired]; National Institute for Public Health and the Environment, Bilthoven 2007, p. 69.

5 *Healthcare Insurance Board, Off-label gebruik van innovatieve geneesmiddelen: perspectief van de zorgverzekering [Off-label use of innovative medicines: from the point of view of health insurance], Report No. 29128439, Diemen 21 September 2010.*

6 *R.S. Stafford, "Regulating off-label drug use--rethinking the role of the FDA", N Engl J Med. 2008, pp. 1427-9.*

7 *D.C. Radley, S.N. Finkelstein, R.S. Stafford, "Off-label prescribing among office-based physicians", Arch Intern Med. 2006, pp. 1021-6.*

Objective

This report was commissioned by ZonMw as part of the Rational Pharmacotherapy programme (programma GGG (Goed Gebruik Geneesmiddelen)). This programme aims to promote the effective, safe and efficient use of registered medicines.[8]

Within the context of this objective, this *quickscan* analyses why medicines with known active substances are not (or only to a limited extent) developed further and why this further development does not result in a new marketing authorisation or an extension of the existing marketing authorisation. The focus of this report is on several variants of this further development, referred to as *Drug Rediscovery* (DR). "To stimulate the registration of new indications for an active substance" has been chosen as the desired result. This is accounted for in Chapter 4, which also sets out what we mean by DR.

It should be noted that the inclusion of a new indication for an active substance in a marketing authorisation is a complicated process. The desired endpoint – registration – will therefore not always be achieved. However, the solution pathways in this document can also be used to increase our knowledge of known active substances without having them registered.

This quickscan sets out the hurdles to DR and puts forward possible solution pathways. These are linked wherever possible to the legal and regulatory framework for medicines, such as the regulation of R&D on medicines, the marketing authorisation procedure and the reimbursement/financing of (the use of) medicines.

The criterion for identifying solution pathways was that they (could) fit in with the current legislative system, and that they could actually be implemented.
The focus was therefore more on improvements in procedures, the application of so-called "soft law", and on means for communication and facilitating the exchange of knowledge and experience than on the adjustment of (European) legislation.

Structure of the Report

This report consists of 7 chapters. The emphasis lies on Chapters 6 and 7 in which the identified hurdles and solution pathways are discussed.

Chapters 3, 4 and 5 serve as an introduction. The next chapter sets out how this report came about.
Chapter 3 sets out the process and dynamics of medicine development (*Drug Discovery*). In addition to what was discussed in the introduction, DR is defined in Chapter 4. This is illustrated with examples. Patents and protection systems are intermittently dealt with in this report and therefore briefly discussed in Chapter 5.
The identified hurdles are presented in Chapter 6. The seven solution pathways are set out in Chapter 7. This is followed by a discussion and conclusions regarding the identified hurdles and solution pathways emerging from this quickscan.

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[8] *ZonMw, "Good Use of Medicines programme", http://www.zonmw.nl/nl/programmas/programma-detail/goed-gebruik-geneesmiddelen/, last accessed on 13 January 2012.*

2 Method

This report is an account of a quickscan based on consultations with experts on medicine development and *regulatory science*, the knowledge and experience of the authors and the literature.

Three expert meetings were organised, for which a select number of experts were contacted, based on an overview of relevant parties and the authors' contacts. The experts were given an explanation of the study prior to the meetings. They were also asked to think about cases, hurdles and solution pathways to DR.

At the meetings, the experts were asked in a semi-structured manner about cases, hurdles and solution pathways to research, registration, reimbursement and financing and about other aspects of DR. The hurdles and solution pathways which had emerged from previous expert meetings were discussed at the second and third expert meetings. Reports of the expert meetings were drawn up.

The authors distilled the hurdles given in Figure 3 (see Chapter 6) from these reports and supplemented them with their own knowledge and experience.

In addition, a *search* was carried out of scientific articles on DR. This was done in PubMed using the keywords "*off-label*" and "drug rediscovery". We searched for "off-label" since "off-label" and "DR" were expected to be often interrelated. Additionally, articles and reports suggested by the consulted experts were studied.

An interim report with the identified hurdles and solution pathways was submitted to ZonMw in November 2011. This report was also submitted to several previously consulted experts. A few experts who had not taken part in the expert meetings were asked to make additional suggestions. All the obtained information was used to refine the wording of the solution pathways.

3 Medicine Development

Research & Development

The medicine development process starts with a *lead* for a pharmacologically active substance which may have a positive effect on human health when administered and, ideally, runs until the end of a product's life cycle.

The medicine development process is characterised by significant investments and risks. Estimates of the cost of developing a single new medicine vary.[9] However, when the cost of unsuccessful projects is considered, the cost of the entire development process for a product developer runs into hundreds of millions of euros. Product developers need *incentives* to enter this uncertain and costly process; their investments should yield an adequate return. If the expected *return on investment* is too low, innovation could stall, even if this concerns the further development of medicines which are already on the market. A special juncture is the end of the period of patent or dossier protection of a medicine: generic medicines can then come onto the market and benefit from the investments in and the available knowledge and information on the reference medicine.

The medicine development process is usually represented as a multi-step process (Figure 1). Various parties play an important role in the subsequent steps in the process. In this report, research institutions, product developers and regulatory authorities are the key players.

Basic research and the development of fundamental knowledge usually takes place within (publicly funded) research institutions (such as universities and knowledge institutions). When a project moves on, product developers, such as pharmaceutical companies, usually take the lead. Government regulation applies to the entire medicine development process. This regulation increases in intensity the nearer the medicine is to marketing authorisation application. Relatively little legislation applies to early-stage research. The later stages (e.g. animal and clinical studies) are increasingly regulated. Nuanced legislation and a constructive attitude of the regulatory authorities can stimulate medicine innovation, or at least result in the fewest possible hurdles.

By definition, a representation like the one in Figure 1 is a simplification of reality. In practice, special consideration should be given to two observations which are related to trends in the sector.

[9] *S. Morgan et al., "The cost of drug development: a systematic review'" Health Policy 2011, pp. 4-17.*

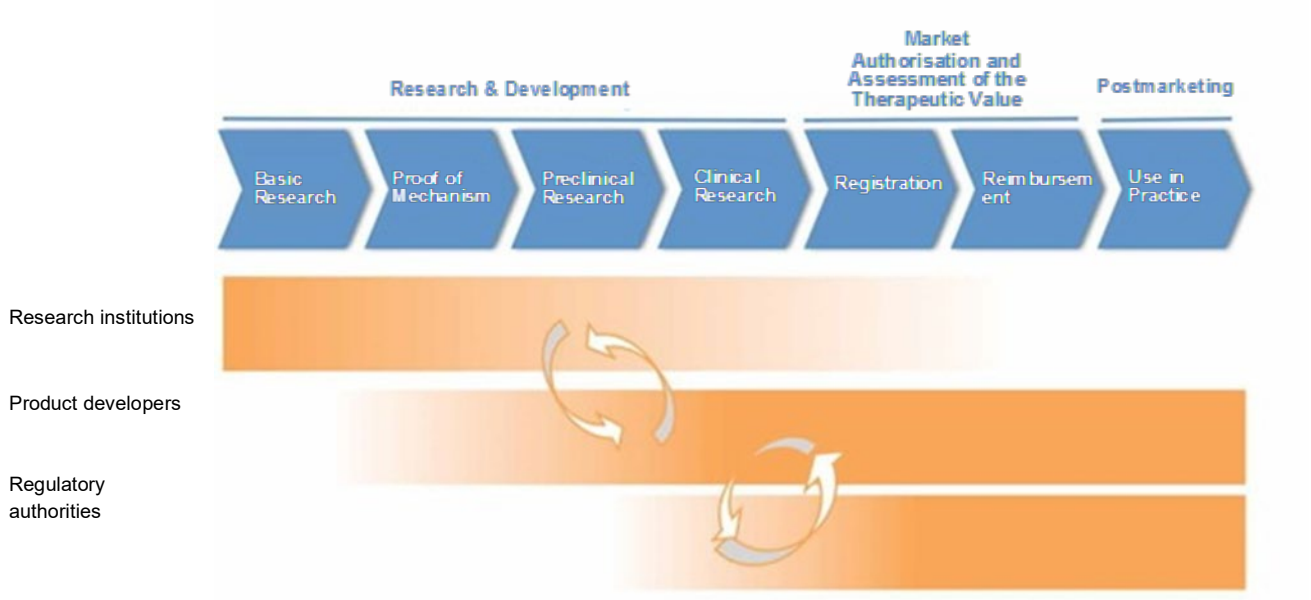

Figure 1: The various steps of the medicine development process, in which all three players (research institutions, product developers and regulatory authorities) play a part.

"Circular" Development Processes

Figure 1 represents medicine development as a linear process. In practice, the medicine development process is often more circular in nature: for instance, further (pre)clinical research (e.g. on new indications or patient groups) is carried out after a medicine has been introduced onto the market.[10] This is reinforced by the various forms of *early access* to medicines which are being developed, whereby some of the research data is collected when a product is already on the market.[11]

New "Business Models" in the Pharmaceutical Industry

Another significant trend is that pharmaceutical companies more and more rarely have the entire development pipeline "in house" and mostly work closely with small companies and universities. This fits in with a trend whereby companies transform themselves from *Research and Development* (R&D) organisations into *Search and Development* organisations. This development can also be seen in the light of the trend towards *open innovation*.[12] Open innovation can best be described as a vision in which companies can and should make use of internal and external ideas to develop new products and broaden their knowledge base. In an open innovation environment, new products are not necessarily introduced onto the market by a single company but in the form of partnerships and joint ventures, for example.

Registration of Medicines

In the European Union (EU), a medicine may only be put on the market after a relevant marketing authorisation is issued. In the EU, the market in medicinal products is supervised and marketing

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[10] *However, in general, this happens less often for medicines than for other products, see also Chapter 1.*

[11] *Price Waterhouse Coopers, "Pharma 2020: The vision which path will you take?" 2007 http://www.pwc.com/en_GX/gx/pharma-life-sciences/pdf/pharma2020final.pdf, last accessed on 13 January 2012.*

[12] *H.W. Chesborough, "Open innovation: the new imperative for creating and profiting from technology", Boston: Harvard Business School Publishing 2003.*

authorisations are issued by a network of competent authorities. All Member States have one or more competent authorities for medicinal products for human use. In the Netherlands, this is the MEB (CBG, College ter Beoordeling van Geneesmiddelen). In addition, there is the European Medicines Agency (EMA), where all European agencies work together in a network system.
The European system provides for coordination by the EMA. Scientific expertise and dossier assessments are primarily carried out by the national competent authorities, such as the pharmacovigilance authorities.

It is a tradition in the European Union that the government (= the competent authority) does not actively interfere with the development of new medicines. Although the quality aspects and ethical principles of research with animal or human subjects are legally enshrined, an opinion on the outcomes is usually not given until after the trials. The European competent authorities nevertheless have a lot of influence on the way medicines are developed and tested. This does not concern direct influence on the work processes but (indirect) influence by drawing up general guidelines and, at the request of applicants, giving so-called "scientific advice". *Guidelines* are adopted by the European Commission or the EMA. Guidelines are about *soft law*. Although the guidelines have binding force, applicants and competent authorities are free to depart from them provided that they give justification. There are guidelines for the chemical pharmaceutical dossier and for preclinical and clinical studies.
Guidelines can be accessed on the websites of the European Commission and the EMA.[13] The format of application dossiers for marketing authorisations is included in Annex I to Directive 2001/83/EC. The dossier requirements are worked out in greater detail in the Commission's *Notice to Applicants*; this contains the main guidelines for the evaluation of medicinal products.

Application Procedures for Marketing Authorisations

The EU has four different application procedures for marketing authorisations: the centralised procedure, the mutual recognition procedure, the decentralised procedure and the national procedure. The centralised procedure, regulated in Regulation (EC) No. 726/2004, leads to a European marketing authorisation. The other procedures lead to one or more national marketing authorisations. The centralised procedure, whereby a European marketing authorisation is obtained after submitting an application to the EMA, is compulsory for many new, innovative medicines.[14] This procedure starts with the submission of an application to the EMA for an authorisation. Medicinal products for human use are evaluated by the *Committee for Medicinal Products for Human Use* (CHMP), which then submits an opinion to the European Commission. The EMA/CHMP has 210 days to form an opinion. If, during this procedure, additional information is considered necessary, the applicant is duly informed, and the evaluation is paused (clock-stop). The actual assessments are carried out by the national competent authorities. The CHMP appoints a rapporteur and co-rapporteur who draw up the draft assessment report with the assistance of reviewers at the national competent authorities (in the case of the Netherlands, the MEB (CBG, College ter Beoordeling van Geneesmiddelen)). After the opinion has been given, the European Commission prepares a draft decision which is submitted to the Permanent Committee, on which the Member States hold a seat, and eventually results in a marketing authorisation which is valid throughout the EU. The official product information (the patient information leaflet and the summary of product characteristics) are appended to this marketing authorisation in all recognised official languages. All marketing authorisations issued by the European Commission are entered in a register.

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[13] *European Commission, "EU Legislation – Eudralex", http://ec.europa.eu/health/documents/eudralex/index_en.htm, last accessed on 13 January 2012; and European Medicines Agency, http://www.ema.europa.eu, last accessed on 13 January 2012.*

[14] *See Article 3(1) and the annex to Regulation (EC) No. 726/2004.*

According to the mutual recognition procedure,[15] Member States are obliged to take over, at the request of the holder, the marketing authorisation for a medicine which was issued in another Member State. If the second Member State objects to this – there must be a potentially serious risk to public health – arbitration proceedings will automatically be initiated by the *Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human* (CMDh).[16] If no agreement is reached in these proceedings, the CHMP must submit an opinion to the European Commission. The judgment which the European Commission gives (based on EMA's recommendation) in arbitration proceedings is binding: if the objections of the second Member State are adopted, the marketing authorisation should also be withdrawn in the first country.

The decentralised procedure[17] is intended for medicines which do not need to be admitted via the centralised procedure and for which no marketing authorisation has been issued in a Member State. In other words, it is actually a combination of the first national procedure and the corresponding mutual recognitions. In this procedure, the competent authorities hold consultations before the initial marketing authorisation is issued. This allows differences of opinion between Member States to be resolved before a marketing authorisation is issued. Arbitration by the CHMP can thus be avoided.

In order to be able to follow the mutual recognition procedure, a national marketing authorisation needs to have been issued in one Member State. There is a national procedure for this initial authorisation and for medicines for which a company wishes to request a marketing authorisation in only one Member State. The procedure is national but is governed by EU law.

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[15] *See Articles 28 and 29 of Directive 2001/83/EC, incorporated in Section 44 of the (Dutch) Medicines Act.*

[16] *Coordination Group for the Mutual Recognition and Decentralised procedures, established by Article 27 of Directive 2001/83/EC.*

[17] *See note 15.*

4 What is “Drug Rediscovery”?

4.1 Drug Rediscovery Defined

The meetings with experts provided an insight into the wide-ranging views on the nature and scope of the problem of development and registration of new applications of an existing medicine. It has also been shown that a proper definition (of the scope) is lacking. This chapter therefore deals with the scope of the research area. The subject of this report is “facilitating the registration of unregistered applications of medicines or active substances”. We give a broad definition to “application”: this may concern a new disease indication, a new patient population, a new pharmaceutical form, a new administration route or a combination thereof. This may therefore concern the conversion of off-label use into *on-label* use, since the unregistered application has been tested and evaluated and included in the marketing authorisation. This may also concern the conversion of pharmacy preparations into registered medicines. For reasons of clarity, we opted for an easy-to-use term for the development and registration of a new application of an existing medicine: Drug Rediscovery (DR).

The term “Drug Rediscovery” can be traced back to the scientific literature on a second Drug Discovery process for a medicine or active substance which has already led to a registered medicine. Grammatically speaking, the term “Drug Rediscovery” can be interpreted more broadly as anything which leads to the “rediscovery” of a medicine, thus anything whereby a medicine is developed into something more. In this regard, a medicine could be a product with a marketing authorisation, an active substance or a pharmacy preparation (large-scale or otherwise).

There is no suitable Dutch definition of “Drug Rediscovery” which fits in with the linguistic meaning. The English term “Drug Rediscovery” is therefore used. Other terms - once again in English - which have a similar meaning are: (*Drug) Repositioning*, *Redirecting*, *Repurposing* and *Reprofiling*.[18] Our interpretation of *Drug Rediscovery* in relation to *Drug Discovery* and *Drug Repositioning*[19] is given in Figure 2. This concerns the development of new applications of a registered medicine which has already been in use but is not limited to adding a “related” indication to the marketing authorisation.[20]

[18] *T.T. Ashburn, K.B. Thor, “Drug repositioning: identifying and developing new uses for existing drugs”, Nat Rev Drug Discov. 2004, pp. 673-83.*
[19] *We consider “Redirecting”, “Repurposing” and “Reprofiling” to be synonymous with “Repositioning”.*
[20] *This is mainly done in oncology.*

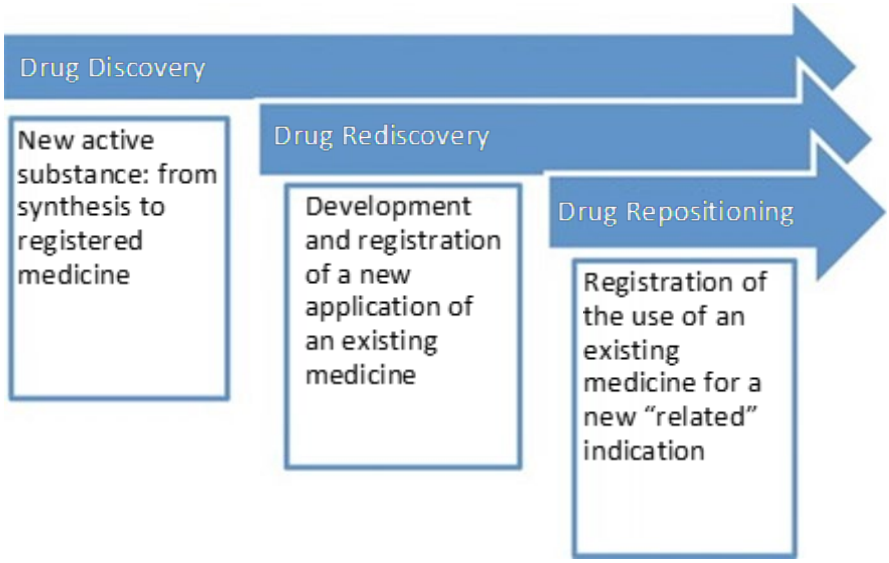

Figure 2: The relationship between Drug Discovery, Drug Rediscovery and Drug Repositioning.

In this light, a variety of development processes can qualify as Drug Rediscovery. For the sake of clarity, the scope of the report was narrowed further.

- The report focuses on unpatented or unprotected medicines.
- The report assumes further development is based on a reasonable amount of existing knowledge. There needs to be a good reason to start the DR project.
- The report is limited to DR projects which aim to increase the practical applicability and wider use of existing active substances. They should therefore lead to the (potential) improvement or advancement of clinical practice.

As such, five different outcomes of DR can be identified in this report:

- Adding a new indication to an existing marketing authorisation based on existing knowledge, whereby a new dosage might be added for the new indication.
- The registration of a new indication for a new pharmaceutical form for an existing medicine based on existing knowledge.
- The registration of a new pharmaceutical form for an existing medicine.
- The registration of a medicine which is available as a pharmacy preparation.
- The registration of a new indication for a medicine which once had a marketing authorisation, possibly with a new pharmaceutical form and dosage.[21]

4.2 Examples of DR Projects

Publications on new indications for existing medicines appear on a regular basis. Sometimes the course is changed during the DR process. Medicines are often developed further for new indications and old medicines are sometimes repurposed. Publications also refer to medicines which have in some way proved to be effective for an unregistered indication: these are candidates for DR.

[21] *J.K. Aronson, "Old drugs – new uses", Br J Clin Pharmacol, 2007, pp. 563-56.*

Medicines with an Indication which differs from the Original Indication

Examples of active substances which can be used in an application other than that for which they were initially tested are duloxetine and sildenafil. Although these were important discoveries for scientific practice, these medicines are not the focus of this report. Duloxetine was initially tested as an antidepressant but turned out to be effective for stress urinary incontinence.[22] The indication envisaged for sildenafil (known under the brand name Viagra) was not for erectile dysfunction. Sildenafil was tested for dilation of the coronary artery. However, male subjects reported an erection as a side-effect in the 1991 and 1992 clinical studies. The indication was changed to erectile dysfunction and a marketing authorisation was issued in 1998.[23] Sildenafil was re-registered many years after the marketing authorisation for Viagra was issued, this time for the indication pulmonary hypertension. If the medicine had not already been registered, pulmonary hypertension would probably have been an insufficient indication for a registration application.[24] The latter extension can be classified as DR.

"Real" DR projects

A second example of DR is thalidomide. Thalidomide came onto the market in 1957 as a sedative under the name Softenon. It was mainly given to pregnant women. It was discovered in the early sixties that the medicine caused congenital malformations in the babies of users. It was then withdrawn from the market. It was discovered by chance in 1964 that thalidomide can be used to treat erythema nodosum laprosum (ENL). This happened when a doctor prescribed thalidomide to an ENL patient who could not sleep because of the pain.[25] A study confirmed its effect on ENL. In 1998, thalidomide was registered for ENL in the United States.[26] After the discovery of the anti-angiogenetic characteristics, thalidomide came into play as an anti-cancer agent.[27] It has had a marketing authorisation for myeloid leukaemia and the status of orphan medicinal product since 2008.[28]

A third example of DR is nifedipine as a labour suppressant. This off-label indication is generally known but was never included in a marketing authorisation, although the Dutch Society for Obstetrics and Gynaecology regards nifedipine and atosiban as the medicine of first choice in case of impending premature birth. According to the guideline, the non-registration of nifedipine as a labour suppressant is a problem.[29]

A fourth example of a medicine with a DR indication is ibuprofen, which is registered under the name Pedea for patent ductus arteriosus in new-born babies. For this indication, the product has been designated as an orphan medicinal product.[30]

A final example is bevacuzimab, better known under its brand name Avastin. This medicine, which is registered for colorectal cancer, is often used by ophthalmologists to treat age-related blindness.[31]

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22 T.T. Ashburn, K.B. Thor, "Drug repositioning: identifying and developing new uses for existing drugs", Nat Rev Drug Discov. 2004, pp. 673-83.
23 Idem
24 A. Tabarrok, "From off-label prescribing towards a new FDA", Med Hypotheses 2009, pp. 11-3.
25 T.T. Ashburn, K.B. Thor, "Drug repositioning: identifying and developing new uses for existing drugs", Nat Rev Drug Discov. 2004, pp. 673-83.
26 M. Chen, S.D. Doherty, S. Hsu. "Innovative uses of thalidomide", Dermatol Clin. 2010, pp. 577-86.
27 T.T. Ashburn, K.B. Thor, "Drug repositioning: identifying and developing new uses for existing drugs", Nat Rev Drug Discov. 2004, pp. 673-83.
28 Website of the European Medicines Agency, http://www.ema.europa.eu, search for thalidomide, last accessed on 13 January 2012.
29 Dutch Society for Obstetrics and Gynaecology, richtlijn: dreigende vroeggeboorte [guideline: impending premature birth], 2004.
30 Website of the European Medicines Agency, http://www.ema.europa.eu, search for Pedea, last accessed on 13 January 2012.

Ongoing DR Project

A product which is currently in a DR programme is thioguanine (6-TG). This product is being tested for *Irritable Bowel Syndrome* (IBS). Thioguanine, which was introduced onto the market in 1975 under the name Lanvis, is currently registered for certain forms of leukaemia.

DR Candidates

The literature suggests that metformin – a medicine used to treat diabetes – can be used for cancer.[32] This indication still requires a great deal of additional information to qualify for registration. The literature also gives many examples of substances which are promising candidates for DR.
These examples are often included in lists or tables with (possible) new indications, such as in Chong & Sullivan,[33] who attached a table with examples as an appendix to their article, Ashburn & Thor[34] and Gower.[35]

Sources like the children's formularium[36] and clinical practice guidelines of specialist associations may suggest candidates for DR, for example when they recommend off-label use of existing medicines.

Finally, the literature suggests the possibility of developing molecules eliminated in preclinical or clinical studies for other indications. This could be facilitated by setting up large libraries of substances.[37] Better screening techniques for these substances are also suggested.[38]

4.3 Justification for Selecting the Marketing Authorisation as an Objective of DR

This study focuses on encouraging the registration of unregistered applications of a medicine, i.e. obtaining a marketing authorisation for new applications and dosage forms of existing active substances and medicines. The main focus of the system of EU pharmaceutical legislation is the trade in industrially prepared medicines, and not so much the use of medicines in medical practice. There are in fact two separate worlds with little communication between them: the world of the pharmaceutical industry and competent regulatory authorities on the one hand and the world of the practitioners and patients on the other. In the regulatory world, medicines are tested and assessed at population level. The world of medical practice revolves around the treatment of individual patients. Formal communication between the two worlds is through the marketing authorisation and the corresponding official product information.

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[31] *Wet macular degeneration. In this treatment, Avastin is used as an ingredient for a pharmacy preparation. This medicine is seen as a less expensive alternative to Lucentis (ranibizumab), which was developed and registered especially for age-related blindness.*

[32] *C.R. Chong, B.A. Chabner, "Mysterious metformin", Oncologist 2009, pp. 1178-81.*

[33] *C.R. Chong, D.J. Sullivan Jr., "New uses for old drugs", Nature 2007, pp. 645-6.*

[34] *T.T. Ashburn, K.B. Thor, "Drug repositioning: identifying and developing new uses for existing drugs", Nat Rev Drug Discov. 2004, pp. 673-83.*

[35] *T. Gower, "Born again", protomag.com, 2009: protomag.com/assets/drug-repositioning, last accessed on 13 January 2012.*

[36] *Dutch Expertise Centre for Pharmacotherapy in Children, www.kinderformularium.nl, last accessed on 13 January 2012.*

[37] *C.R. Chong, D.J. Sullivan Jr., "New uses for old drugs", Nature 2007, pp. 645-6.*

[38] *L.A. Tartaglia, "Complementary new approaches enable repositioning of failed drug candidates." Expert Opin Investig Drugs 2006, pp. 1295-8.*

To satisfy the requirement that all patients receive the best possible treatment, doctors have a range of options to use medicines outside of the conditions of a marketing authorisation: they can prescribe off-label, i.e. prescribe a registered medicine for a non-registered indication, both in terms of condition and in terms of target group, or at variance with the contra-indications in the official product information, or doctors can prescribe an unregistered medicine, e.g. a pharmacy preparation. The existence of this discretion in the world of medical practice is essential for the quality of medical treatment. With respect to off-label use, the use of the medicine was not approved by the competent authorities, so no scientific assessment was made of the benefit-risk ratio, as is customary for registered applications. The same shortcoming holds for the treatment of patients with unregistered medicines. Moreover, the *design* of the medicine was not assessed, and the medicine was not necessarily prepared under the strict conditions which apply to the preparation of industrially prepared medicines.

Although the inclusion of off-label indications in clinical practice guidelines requires substantiation which goes beyond the experience of an individual practitioner, we assume that a clinical practice guideline cannot and may not replace an assessment by the competent authorities. Assessments based on clinical practice guidelines are less thorough and the assessment authorities have the expertise to assess the benefit-risk balance of an indication. Moreover, the authorities operate within a strict framework, with guarantees for quality, transparency and independence. Off-label prescriptions of unregistered medicines should therefore remain an exception, in cases where there is no suitable registered application of a medicine for a patient. The main objective of the pharmaceutical policy should focus on the inclusion of the indication and pharmaceutical forms in a marketing authorisation.

5 The Function of Patents and Dossier Protection

The roles of patent law, the *Supplementary Protection Certificate* (SPC) and dossier protection are often named as obstructive factors in discussions about DR. This will be dealt with further in various sections of the report. These three forms of protection are briefly described in this chapter. Irrespective of the form, innovation protection is paradoxical in nature: protection encourages innovation but can also constitute a hurdle to other innovations. Both the existence and lack of adequate protection mechanisms are therefore regarded as a hurdle to DR.

Intellectual Property Rights (Including Dossier Protection and DR)

Patent law (and, by extension, the SPC) gives a patent holder a temporary exclusive right to forbid others to use an invention[39] commercially (e.g. to make, import, use, stock, etc. a product).[40] The holder has the exclusive right to exploit the patented invention commercially during the term of the patent (in principle 20 years). In return, the patent is made public. This gives others access to the knowledge which led to the invention and allows them to build on this. Patent law ultimately aims to make knowledge available in order to stimulate innovation. This is achieved by offering a reward in the form of a temporary exclusive right.

It sometimes takes more than ten years to develop and register a medicine based on a new active substance: the patent holder will not benefit from the patent until a new medicine is allowed onto the market.[41] An exclusive right of use is obviously of no value to a patent holder who is not allowed to market a medicine. Due to the long interval between applying for a patent and the actual market introduction, the effective term of a patent for medicines is considerably shorter than 20 years. The European legislator recognised this and therefore made a special provision for medicines:[42] the SPC. The SPC extends the effective term of a patent by a maximum of five years.[43] As such, the patent expires after 20 years. However, if certain conditions are met, the SPC will result in a similar exclusive right.

However, the exclusive right arising from a patent or SPC does not necessarily imply a monopoly. Although the patent prevents exact copies of the medicine from coming onto the market during the term of the patent and SPC, competition in the form of medicines which contain other active substances but have the same

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39 *This invention needs to satisfy several requirements; see Section 3 of the (Dutch) Patents Act 1995: "Inventions that are new, that involve an inventive step and that are susceptible to industrial application shall be patentable."*

40 *Section 53 et seq. of the (Dutch) Patents Act 1995.*

41 *See Chapter 3.*

42 *This concerns extra protection for human and veterinary medicines and crop protection products.*

43 *Regulation (EC) No. 469/2009. This regulation is a recodification of Council Regulation (EEC) No. 1768/92.*

application may obviously occur. Moreover, the success of a medicine on the market also depends to a large extent on the assessment of the usefulness of the medicine for the patient, the question of whether the medicine is included in professional guidelines and standards, the question of whether the medicine is reimbursed or the question of whether its provision is (adequately) financed. Scientific knowledge, regulations and economic conditions are very important in this respect. There are also restrictions on patent law, e.g. for research and pharmacy preparations[44] and licences - the right to make commercial use of the invention, despite the patent - can be obtained and sometimes even enforced.

In addition to patent and SPC-based protection, there is dossier protection and *data exclusivity*. Dossier protection is in fact knowledge protection; it protects the holder of a marketing authorisation for a reference medicine from the use by other parties of the information in the registration dossier during a ten-year period. Other (generic) applicants may not refer to the (pre)clinical data in the dossier of the reference medicine for eight years. This can be done at the end of this period. However, a marketing authorisation thus issued cannot be used to market a (generic) medicine until after ten years.[45] This term can be extended to eleven years if one (or more) new therapeutic indication(s) - considered an important clinical benefit vis-à-vis existing treatments - are added during the first eight years.[46] Nor does dossier protection imply a monopoly since a marketing authorisation can be obtained other than by referring to a registration dossier.[47]

Ultimately, the above-mentioned forms of protection are a political compromise between two public interests: on the one hand, to stimulate innovation and the availability of new medicines by extending the temporary exclusivity to those who invest in a new medicine and, on the other, the disclosure of knowledge and the availability of affordable medicines following a reasonable term of protection.

Since the investments in a new medicine are so substantial, this sector focuses strongly on market exclusivity through patent or dossier protection in order to achieve sufficient *return on investment* . When the period of protection has expired, interest in a certain medicine often wanes. As a result, investments often decrease sharply in the final years of the commercial *life cycle*.

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44 See Section 53(3) of the (Dutch) Patents Act 1995. However, the exception for the pharmacies has not yet come into effect.

45 Section 42(4) of the (Dutch) Medicines Act, based on Article 10, paragraphs 1 and 2 of Directive 2001/83/EC.

46 Added when Article 10 of Directive 2001/83/EC was amended by Directive 2004/27/EC. The possibility to extend the term of protection by one year is intended to compensate for the inability to obtain new dossier protection for improvements of medicines for which a marketing authorisation was already issued. The fact that no new dossier protection is provided is laid down in case law (see CJ EU, 3 December 1998, Medical Jurisprudence 2001/8 (Generics ruling) and CJ EU 29 April 2004, Medical Jurisprudence 2004/25 (Novartis ruling) and was codified in legislation through the introduction of the concept of "global marketing authorisation" in the last subparagraph of Article 6(1) of Directive 2001/83/EC.

47 See J.A. Lisman, "De toelating van geneesmiddelen: Hoe effectief is ons systeem? [The admission of medicines: How effective is our system?]", in: Medicines and Law, Association for Health Law, The Hague: SDU uitgevers 2006, p. 49 et seq.

6 Hurdles

Medicine development is the result of the fruitful interaction between three players: product developers[48], research institutions and the government. This also applies to DR. However, due to its unique nature, DR has its own specific challenges and hurdles. This chapter deals with the identified and perceived hurdles to DR.

Figure 3 shows the main hurdles to DR which emerged from the consultations with experts, the literature and the authors' experiences. The above-mentioned hurdles are divided into three categories according to the type of player (product developer, research institution, regulatory authority) encountering the obstacle. The hurdles will be explained per category.

Figure 3, which should be read from left to right, is intended to clarify the aspects of said hurdles.

- *For product developers*: the hurdles they encounter when they want to develop a product within the domain of DR. This concerns both commercial considerations and practical hurdles.
- *For research institutions*: hurdles to do research relating to DR (including their role as knowledge suppliers for product developers).
- *For the government and regulatory authorities*: hurdles to stimulating DR.

The hurdles shown in Figure 3 are not relevant to all DR development projects and do not affect all projects and players in equal measure. For example, the size of the market will not play a role in some projects. The requirements imposed on the clinical data will be essential, however. This might be completely the other way round in other projects. DR is a diverse and dynamic field, and the mix of hurdles will vary per product.

The identification of the hurdles shown in Figure 3 is not intended to provide an exhaustive list of all the obstacles which need to (or can) be overcome in order to stimulate DR. They are aspects of the current system of medicine development which, as shown by this study, may constitute a hurdle to DR. In practice, the level of threat of a hurdle cannot be determined objectively since this depends strongly on the specific situation and party.

[48] *"Product developers" include large pharmaceutical companies (international or not) and small businesses.*

Figure 3: Hurdles to Drug Rediscovery.

6.1 Hurdles for Product Developers

Return on Investment (ROI)

The main incentive to market a medicine is the expectation of a high return on the investments which have been made, usually referred to as *return on investment*. This is not unique to DR since the expected returns should also exceed the investments for a new medicine. The expected return on investment therefore plays a very important role in the question of whether the medicine will be developed (further) and registered.

Cost of Research

Medicines research, in particular the clinical trials which aim to provide evidence for the efficacy and benefit-risk ratio, is often expensive. Because it is bound by strict European and national rules, this research requires a professional organisation and significant investments. In clinical research, the rights of human subjects require a high level of protection. In the Netherlands, the Medical Research (Human Subjects) Act (WMO, Wet medisch-wetenschappelijk onderzoek met mensen)[49] applies to carrying out medicine research.
As a result of the implementation of Directive 2001/20/EC,[50] the Clinical Trials Directive, this act was extended with a chapter dealing specifically with medicine research. The main changes are the introduction of *Good Clinical Practices* (GCP), as a result of which clinical research is bound by strict requirements regarding the protection of human subjects and data integrity.[51]

This legislation stipulates that a "sponsor" needs to be available for all clinical research. A sponsor is subject to i.a. the following obligations:

- The sponsor should appoint a doctor (not involved in the research) as contact person for the human subjects.[52]
- The sponsor should take out insurance for research subjects according to the requirements set out in the Medical Research (Human Subjects) Compulsory Insurance Decree (Bvvmo, Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen)[53]. The sponsor should also take out third-party insurance which covers any damage which might result from the clinical research.[54]
- The investigational medicinal product is subject to high requirements: an *Investigational Medicinal Product Dossier* should be compiled. The investigational medicinal product should be manufactured according to GMP. [55]
- A system for identifying and evaluating side-effects should be set up.[56]

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[49] *Act of 26 February 1998 regulating medical scientific research involving human subjects (Medical Research (Human Subjects) Act), Bulletin of Acts and Decrees 1998, 161.*

[50] *Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use, Official Journal 1 May 2001, L 121-134.*

[51] *See subsection 5(a) of the (Dutch) Medical Research (Human Subjects) Act.*

[52] *Section 9 of the (Dutch) Medical Research (Human Subjects) Act.*

[53] *Decree of 23 June 2003 containing rules for compulsory insurance in medical research involving human subjects (Medical Research (Human Subjects) Compulsory Insurance Decree), Bulletin of Acts and Decrees 2003, 266.*

[54] *Section 7(6) of the (Dutch|) Medical Research (Human Subjects) Act.*

[55] *GMP stands for: Good Manufacturing Practices. This means that the preparation should be in accordance with Commission Directive 2003/94/EC of 8 October 2003 laying down the principles and guidelines of good manufacturing practice in respect of medicinal products for human use and investigational medicinal products for human use, Official Journal L 262 of 14 October 2003, pp. 22-26. There are also applicable guidelines. These have been included in Volume 4 of the Rules governing medicinal products in the EU, which can be accessed on: http://ec.europa.eu/health/documents/eudralex/vol-4/index_en.htm, last accessed on 13 January 2012.*

[56] *See for example: ICH guideline E2F Note for guidance on development safety update reports, EMA/CHMP/ICH/309348/2008.*

The EMA and ICH guidelines imposed further strict requirements regarding the methodological aspects of clinical research.[57] Controlled, randomised clinical trials are often required (often referred to as Randomised Controlled (clinical) Trials (RCTs) ; less complicated research, e.g. observational or retrospective research, does not suffice. RCTs are not easy to carry out. Such research is actually difficult to carry out without the involvement of large professional organisations (*Contract Research Organisations* or *CROs*). This makes it very expensive to do clinical research. The high cost of carrying out the necessary clinical research has a negative effect on the expected ROI.

Cost of Compiling a Registration Dossier

An application for an (extension of a) marketing authorisation should include a large amount of formatted information (the *Common Technical Document*).[58] Paragraph 6.1 also deals with practical hurdles to registration procedures and the information required for these procedures. It is not easy to obtain and pool all the information required for an application; this usually requires significant investments. The high cost of compiling a registration dossier has a negative effect on the expected ROI.

Payment Registration Authorities

The submission of an application for an (extension of a) marketing authorisation to the competent authorities involves costs. The maintenance of a marketing authorisation leads to an annual cost item consisting of the payment to the registration authorities. The rates for medicines admitted via the centralised procedure are included in Regulation (EC) No. 297/95. These rates apply to marketing authorisations which are valid within the EU. The rates for registering with the MEB (CBG, College ter Beoordeling van Geneesmiddelen) – are set by the (Dutch) Minister of *Health, Welfare and Sport* .
Table 1 gives an overview of the rates for applying for a new marketing authorisation with a known active substance and for a so-called *type-II variation*,[59] the procedure which a marketing authorisation holder needs to follow to register a new indication or user population.[60] It is notable that neither the EMA nor the MEB (CBG, College ter Beoordeling van Geneesmiddelen) apply an adjusted rate for applications for marketing authorisations for medicines with a known active substance which do not fall under the generic application. As a result, there are usually no reduced rates for DR-related applications; the highest rates are charged.[61]
These costs can result in a negative expected *return on investment* for products which, due to the addition of a new indication, might generate a small (increase in) sales.

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[57] *Product-specific guidelines are posted on the website of the EMA, http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000043.jsp&mid=WC0b01ac05800240cb, last accessed on 13 January 2012.*

[58] *See Annex 1 to Directive 2001/83/EC, Part I and the Notice to Applicants, Volume 2 of the Rules governing medicinal products in the EU, http:// ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm, last accessed on 13 January 2012.*

[59] *The procedure for amending and expanding marketing authorisations is laid down in Regulation (EC) No. 2008/1234.*

[60] *The amounts are given in order to give an idea of the cost involved. The exact amount will depend on the specific details of an application. Both the EMA and MEB (CBG, College ter Beoordeling van Geneesmiddelen) also charge an annual fee. Although this cost item is less relevant to an application, it does have an effect on the eventual ROI.*

[61] *However, Regulation (EC) No. 726/2004 includes the potential to give a discount on EMA's rates. The EMA has set up a special SME office for this.*

Type of Application	EMA	MEB
New marketing authorisation	at *259,400*	at *43,900*
Generic marketing authorisation	at *100,700*	at *23,060*
Extension type-II variation	at *77,900*	-
Annual fee	at *93,000*	at *1,050*

Table 1: rates for new marketing authorisation applications with a known active substance and type-II variation applications.

Low Price

The price which a product developer expects to get for their product plays an important part in their decision on whether or not to launch a DR programme. However, the manufacturer is not completely free to set the price of a medicine. Under the (Dutch) Pharmaceutical Pricing Act (WGP, Wet geneesmiddelenprijzen), the Minister of Health, Welfare and Sport can set a maximum price for a medicine.[62] The system of the Pharmaceutical Pricing Act links the price in the Netherlands to the prices of the same and similar medicines in France, Belgium, Germany and the United Kingdom. The maximum price may be set so low that it is not commercially responsible for a company to market the medicine.

Limited Reimbursement (outpatient setting)

It is very important for the manufacturer of a medicine to know whether and, if yes, to what amount health insurers will reimburse the medicine. The medicine reimbursement system (GVS, geneesmiddelenvergoedingssysteem) is particularly relevant here.[63] The prospect that a medicine will not be included in the system or will be included in a cluster with a (relatively low) reimbursement limit constitutes a hurdle to DR. In the first case, the patient bears the full cost of the medicine (and the care provided by the pharmacy). In the second case, the limit determines the amount of the reimbursement. If the price of a medicine exceeds the limit, the patient needs to make an additional payment. Additional payment (or payment in full) by the patient could be a reason for a doctor not to prescribe the medicine. This can be avoided by decreasing the price of the medicine (e.g. to the reimbursement limit). This will obviously have an effect on the expected ROI. The restriction of claims for compensation by the Minister[64] and health insurers[65] may also constitute a hurdle. Moreover, the procedure for receiving optimal payment is time-consuming and costly (due to compulsory investigations and dossiers and (often) the involvement of consultants and (legal) experts), while the outcome cannot always be predicted. This also constitutes a hurdle.

Limited Financing (hospital setting)

The financing and reimbursement system in a hospital setting differs from that in an outpatient setting. In a hospital setting, the entitlement to medicines forms part of the entitlement to medical care.[66] Medicines are financed from the hospital budget.

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62 Act of 25 January 1996 containing rules for setting maximum prices for medicines (Pharmaceutical Pricing Act), Bulletin of Acts and Decrees 1994, 837.

63 Under the (Dutch) Healthcare Insurance Act, not all medicines are (fully) reimbursed by health insurers. For medicines used in an outpatient setting, the reimbursement depends on the answer to the question of whether the medicine is included in the medicine reimbursement system and, if yes, whether the medicine will be included in a cluster or in Annex Ib. A reimbursement limit is set per cluster. Reimbursement may also be subject to conditions. In the Healthcare Insurance Decree, the entitlement to (compensation for) pharmaceutical care is set out in Article 2.8. This has been worked out in the Healthcare Insurance Regulations (Articles 2.5, 2.39-2.50).

64 Article 2.5 of the Healthcare Insurance Regulations and Annex 2 to this decree.

65 Article 2.8, paragraphs 1 and 3 of the Healthcare Insurance Decree.

66 Article 2.4 of the Healthcare Insurance Decree. The medicine reimbursement system does not apply here.

The level of the hospital budget is based on the "care services" it provides. Care services are defined as *diagnosis treatment combinations* (DTCs) and linked to rates. Hospitals can decide which medicines they wish to use. The quality of care is obviously the criterion (and assessment framework)[67] and the budget sets limits on the financial possibilities. Budgetary scope and possibly additional financing are particularly important for expensive medicines which weigh relatively heavily on the budget. Medicines are covered by the system of DTCs but expensive medicines may be financed in the form of *add-ons*.[68] The qualification procedure and criteria for add-ons may constitute a hurdle to DR. For instance, it may be difficult, time-consuming and expensive to collect the necessary information, e.g. when research needs to be done or advisers and (legal) experts need to be consulted.

Small Market

Some illnesses and conditions are relatively rare; by definition, their market is small. The decision to invest in these small markets involves a high risk. The likelihood of recouping an investment and making some profit is small. Incentives have been developed to stimulate the development of medicines which are intended for the treatment of rare conditions[69] . This concerns the Regulation on Orphan Medicinal Products.[70] It goes without saying that if the criteria for an orphan medicinal product are not satisfied, the incentives do not apply. For instance, the designation as orphan medicinal product as defined in the Regulation on Orphan Medicinal Products can be refused if a medicine with the relevant active substance is, or has already been, on the market for the treatment of the rare condition. In that case, the criterion that a treatment for the relevant indication is not yet available will not be satisfied. If an application of a medicine which has not been registered for a rare condition is actually being used for the condition, the designation as orphan medicinal product may be refused. This also applies if the requested indication is very similar to that for a previously registered application. EMA's authorised committee, the *Committee for Orphan Medicinal Products*, uses the term *salami slicing*.

The regulation offers the recipient – in addition to assistance in R&D[71] and other regulatory assistance – special protection of the marketing authorisation, namely a 10-year period of *market exclusivity*. This market exclusivity forbids the competent authorities from processing an application for a marketing authorisation for another medicine for the same condition, unless the new medicine is clinically superior. Market exclusivity is not a strong *incentive* since the market – even if it is exclusive – is a small one. Moreover, the exclusivity loses its effect when a better medicine is developed. In the case of rare conditions, it remains to be seen whether these *incentives* stimulate DR to a sufficient extent.

No or Insufficient Protection

The development and market introduction of a medicine requires investment; this also applies to DR. If there is no adequate patent, SPC and/or dossier protection, investments may not be (adequately) recouped[72] since there will be no legal hurdles for third parties to copy the medicine, to register the medicine and to compete on price with the innovative product. The prospect that this protection is not provided or inadequate, i.e. that the medicine may soon face competition from generic medicines, may constitute a hurdle to investing in DR.

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67 Section 2 of the (Dutch) Care Institutions (Quality) Act.

68 Until 1 January 2012, pursuant to the Policy Regulation on Expensive Medicines (Policy Regulation BR/CU-2017, Expensive Medicines), hospitals could obtain additional financing for certain expensive medicines. The Dutch Healthcare Authority's Policy Regulation on "Services and Rates for Specialist Medical Care", www.nza.nl search for "Services and Rates for Specialist Medical Care", last accessed on 13 January 2012.

69 Medicines for a condition which affects fewer than 1:2,000 EU residents.

70 Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products, Official Journal No. L 018 of 22 January 2000, p. 1.

71 Protocol Assistance. Protocol Assistance goes beyond EMA's standard scientific advice. If they so desire, orphan designation holders can receive guidance and assistance from the EMA during the clinical development of their medicine.

The hurdle may take two different forms: (1) there are insufficient possibilities for legal protection or (2) protection is provided but the rights arising therefrom are difficult to enforce in practice (expensive,[73] time-consuming, damaging to one's image).

On-label Use of Generic Medicines

A manufacturer can submit an application for an additional indication. He will then need to make the necessary investments in order to compile the dossier, possibly based on existing knowledge. If there is no protection, other parties can take advantage of the investment by the initial authorisation holder by copying the medicine and submitting a generic application, referring to the information from the original dossier. This assures these parties that the indication for the active substance is accepted and gives them a competitive lead since they had to invest considerably less and will be able to factor this into their price. The prospect of no or a very *low return on investment* is a hurdle to DR.

Off-label Use of Generic Medicines

Medicines may face competition from medicines which have not been registered for a certain indication but are prescribed (off-label) for it. This may also be the case in DR, especially where new applications of existing medicines are concerned. In practice, medicines are often protected by several patents (e.g. on the substance, on the method of preparing the medicine and on the various subsequently developed applications). These patents can expire at different times. The patent on the substance usually lapses first, and patents on subsequently developed applications will remain valid. This means that third parties may manufacture and register the medicine. However, the patented applications are not included in the official user information. Although the scope of application in the official product information of a generic medicine should normally be identical to that of the reference medicine, the registration authorities are obliged to depart from this for patented applications.
However, this does not stop generic versions of the applications (which are still covered by a patent and therefore not included in the authorisation) being prescribed and supplied in practice. The prescriber and pharmacist are often not aware that the generic versions have not been registered for certain indications. Brand name medicines are automatically replaced by generic versions. In theory, the pharmacist could be aware of the differences between the medicines. However, since the indication is usually not stated on the prescription, the pharmacist will not know if the indication for the version they supply has been registered. The use of the generic version for the unregistered indication is also encouraged by MEB's policy to include a standard passage in the patient information leaflet for the generic variant.

This may encourage doctors and pharmacists to prescribe or supply the medicine for a patented indication. The protection of patents for new applications of existing medicines thus becomes an illusion. This may constitute a hurdle to the further development of medicines.

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[72] *See Chapter 4.*

[73] *In practice, the cost of defending a patent is very high, i.a. due to the high cost of legal procedures. It should be taken into account here that the party found to be in the wrong in a legal action regarding intellectual property rights not only has to pay their own legal expenses but those of the other party as well.*

Pharmacy Preparations - Non-Enforcement of Large-Scale Preparation and Pharmacy-to-Pharmacy Supply

Medicines which qualify for DR may face competition from pharmacy preparations. A marketing authorisation must be obtained before a medicine can be introduced onto the market. There are a limited number of exceptions. One of these exceptions is the pharmacy preparation. This exception is subject to the following conditions: the medicine must be prepared in a pharmacy by or at the request of a pharmacist, the medicine must be prepared on a small scale and the pharmacy preparation must be supplied to the pharmacy's own patients. If this exception is applied to other practical cases (e.g. large-scale preparation and onward supply to other pharmacies when there is a registered alternative (see below)), this in-house preparation competes with the registered medicine. The prospect that pharmacy preparations are produced on a large scale and compete with registered medicines may constitute a hurdle to investing in the procurement of a marketing authorisation or registering a new application. A complicating factor here is that the quality requirements imposed on pharmacy preparations are considerably less strict than those imposed on the products of the pharmaceutical industry: this makes it even less interesting for manufacturers to compete with compounding pharmacies.

Additionally, the (Dutch) *Healthcare Inspectorate (IGZ, Inspectie voor de Gezondheidszorg)* implemented a non-enforcement policy for pharmacy-to-pharmacy preparation and supply in 2007. A pharmacist may – under strict conditions – prepare and supply medicines to other pharmacies without having a marketing and manufacturing authorisation.

However, in principle, this is limited to medicines for which there is no registered alternative. As long as this possibility exists, pharmacies have no incentive to apply for marketing authorisations for their preparations and others may be prevented from applying for a marketing authorisation since they may soon face competition from so-called *own preparers* (who might also supply elsewhere).

Other Newcomers and Market Threats

Third parties could quickly introduce another competitive medicine onto the market. This may concern generic variants (if there is no or insufficient protection), as well as the further development of existing medicines. Although generic competition may be somewhat limited by patent law, SPC or dossier protection, the further development of a medicine could, provided that it is new and innovative, obtain protection. In such cases, the party which uses the patented medicine to find a new application requests a licence and, if necessary, even opts for a compulsory licence due to interdependence. Although, strictly speaking, it is a threat to DR, DR can also take advantage of the opportunity to obtain a (compulsory) licence if a patented medicine is used or developed further.

The Long Interval Between Investment and Return on Investment

The medicine development process is complex and requires an investment of time and money. This also applies – sometimes to a lesser extent – to developments relating to existing medicines

(new application, other pharmaceutical forms or dosages).[74] The regulatory hurdles which need to be overcome before a (revision of the) marketing authorisation can be obtained and the medicine can be introduced onto the market have already been set out in Chapter 3. There is often an additional procedure for reimbursement or financing (see paragraph 6.1 (Limited reimbursement (outpatient setting) and Limited reimbursement (hospital setting)). These are lengthy procedures and their outcome is not at all certain. The legal environment, policies and market change on a regular basis. International developments are increasingly important; the euro crisis and the measures taken or imposed at European level are illustrative. The prospect of a long and uncertain procedure can also constitute a hurdle to DR.

Difficult Access to Capital

What also counts for product developers involved in DR: nothing ventured, nothing gained. Because of the (actual and perceived) risks of not making an adequate return on investment in a DR project, it is not easy to raise the necessary funds for a project. This is reinforced by the current financial and economic situation, as a result of which investors are even less inclined to invest in DR under reasonable conditions.

Practical Hurdles

In addition to the above-mentioned hurdles to recouping investments for DR, or at least the expectation of being able to recoup them, product developers also encounter practical hurdles to DR. These hurdles are partly related to the hurdles with respect to returns on investment, because practical hurdles often push up costs. However, there are also hurdles which high investments cannot remove. The practical hurdles mentioned in the consultations with experts and the literature and gleaned from the authors' personal experiences will be dealt with below.

Data is Difficult to Obtain and the Existing Data is not Useful

Various forms of clinical research can be used to produce evidence for the efficacy and safety of medicines and their applications. To date, the randomised placebo or comparator-controlled clinical study, where the inclusion and exclusion criteria, primary and secondary endpoints and stop criteria are laid down in advance, is the golden standard for clinical research. The need to adhere to this golden standard is not laid down by law but in ICH and CHMP*guidelines*.[75] These guidelines were drawn up in order to be applied to *New Chemical Entities*, but will also be used for older molecules.
These kinds of studies are difficult to set up for testing new applications of known active substances. The idea to develop a new application for a known active substance often springs from the off-label treatment of patients (often in an academic setting). The starting point is then treating patients rather than investigating medicines. In this situation, it is still possible to collect information on the efficacy and risks of the new application. In practice,

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[74] *See Chapter 3.*

[75] *ICH: The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. This organisation lays down guidelines which are used in i.a. the EU, the US and Japan; CHMP: Committee on Human Medicinal Products. This is the scientific committee of the EMA which is responsible for medicines for human use. The committee's working groups lay down guidelines for the evaluation of medicines.*

setting up prospective controlled trials creates major problems since it is difficult to interest human subjects in taking part in research when inclusion means that there is a likelihood of them being treated with a placebo or reference medicine. Moreover, the medical ethics committee, which needs to give an opinion on a RCT on a well-known application of a known medicine, could refrain from giving a favourable opinion since the requirement that clinical research makes a contribution to science is not met.[76] Research "for the sake of research" does not satisfy the legal requirements.
Holding on to the golden standard of RCTs also leads to the non-acceptance of the knowledge which is already available but which was obtained from retrospective or observational research.

No Suitable Procedure for DR

The procedures for applying for a marketing authorisation are regulated in Directive 2001/83/EC and Annex 1 to this directive. Supplementary rules are laid down in the *Notice to Applicants*[77] which – although it has the status of soft law – is considered binding by the Court of Justice.
A marketing authorisation application (or type-II variation) can be based on four legal grounds: full dossier,[78] generic application,[79] *informed consent*[80] and *well-established use*.[81] These grounds are not geared towards applications relating to the clinical dossier; assessments are based on previously submitted dossiers. This means that there is no separate procedure for DR.
Submitting a full dossier within the context of a DR project ignores the fact that much is already known about the relevant medicine. The core of generic applications is that generic medicines are - in every respect - copies of reference medicines. This therefore also applies to the official product information. And to informed consent applications. Thus these procedures are also not suitable for submitting a DR project. With regard to well-established use applications, the European Commission has set out that a bibliographic application should be based entirely on data in the literature and that it is therefore not possible to supplement this data with one's own data: if one's own data is also used, the application is regarded as a *mixed application* ; a full dossier needs to be submitted.[82]
A procedure geared towards the further use of known medicines (DR) is therefore lacking.

High Requirements Imposed on the Registration Dossier

The legislation imposes high requirements on the dossier which needs to accompany a marketing authorisation or type-II variation application. The expert meetings have shown that sometimes information needs to be submitted which is not relevant to the assessment of the benefit-risk ratio. For example,

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76 Cf. e.g. the Declaration of Helsinki; Article 21: Medical research involving human subjects may only be carried out if the importance of the objective outweighs the inherent risks and burdens to the research subjects.

77 Volume 2A of the Rules governing medicinal products in the EU, http://ec.europa.eu/health/documents/eudralex/index_en.htm, last accessed on 13 January 2012.

78 Article 8(3) of Directive 2001/83/EC, implemented in Dutch law in Section 42(2) of the Medicines Act juncto Article 3.7 of the Medicines Act Regulations.

79 Article 10(1-2) of Directive 2001/83/EC, implemented in Dutch law in Section 42(5)(a) of the Medicines Act.

80 Article 10(c) of Directive 2001/83/EC, implemented in Dutch law in Section 42(5)(c) of the Medicines Act.

81 Article 10(a) of Directive 2001/83/EC, implemented in Dutch law in Section 42(5)(b) of the (Dutch) Medicines Act.

82 See paragraph 7 of Part II of Annex 1 to Directive 2001/83/EC.

preclinical data: in fact, research with animal subjects is (often) nonsensical (and unethical) if a medicine is already being used for humans. Also, information on the risks of side-effects will often be available since the medicine has already been used in practice. In a general sense, one has the impression that some of the requirements of the regulatory guidelines are superfluous or too strict for medicines being tested in the context of a DR project.

Third Parties do not Have Access to the Existing Marketing Authorisation

The marketing authorisation holder is free to market the corresponding medicine or to withdraw the marketing authorisation so that the medicine will no longer be available for the treatment of patients.[83] The marketing authorisation holder is also free to register or not register a new application of a medicine. However, if third parties collected the data in order to be able to register a new application, this will require the cooperation of the marketing authorisation holder. Other parties cannot influence the existing marketing authorisation.
If a third party – another pharmaceutical company or a patients' or practitioners' organisation – wishes to register a new application, it will have to prepare its own dossier so that the new indication or dosage can be included therein.

Ingredients Not Available

Some medical ingredients are manufactured exclusively for the marketing authorisation holder. It may be difficult for third parties to buy an active substance which is manufactured according to the GMP. The new legislation, aimed at controlling falsified medicines, can exacerbate this problem since the ingredients imported from third countries will need to satisfy strict requirements.[84]

6.2 Hurdles for Research Institutions

As set out in Chapter 3, research institutions such as universities play a role in generating basic knowledge, which (pharmaceutical) companies can then use to devise practical applications. A great deal of clinical research is also being carried out at university medical centres. In general, in the context of DR, there is a need for practical research, such as (non-interventional) clinical research with (the data of) patients. The consultations with experts from the field have shown that little practical research is currently being carried out. Two reasons have been identified for this: the lack of targeted funding and the relatively poor scientific image of such research. Both reasons are explained below.

No or Insufficient Financing

The research which is being carried out at universities needs to be financed. Universities have limited funds for research which they can earmark themselves, the so-called "first flow of funds". In addition to the first flow of funds, universities obtain financing from the second and third flows of funds. These are subsidies from government institutions such as the Dutch Research Council (NWO, Nederlandse Organisatie voor Wetenschappelijk Onderzoek),

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[83] *Notwithstanding the obligation to market a medicine within 3 years of the renewal of the marketing authorisation: the so-called "Sunset clause" (Article 24(4-6) of Directive 2001/83/EC, worked out in Sections 47(4) and 49(5-6) of the (Dutch) Medicines Act.*

[84] *Directive 2011/62/EU of the European Parliament and of the Council of 8 June 2011 amending Directive 2001/83/EC on the Community code relating to medicinal products for human use, as regards the prevention of the entry into the legal supply chain of falsified medicinal products.*

ZonMw, the European Commission and companies. Since much research is often financed from the second and third flows of funds, this financing is usually linked to a specific research objective. There are still not many funds for conducting fundamental and practical research focused on DR. In clinical research, DR needs to compete with clinical research on new medicines, whereby the sponsors often make substantial payments to the researchers and research institution.

Low Scientific Status

It has also been said that DR is not scientifically interesting enough for research. Research on old active substances has a low scientific status, and is less likely to result in oft-cited publications in journals more prestigious than Drug Discovery. Finding a revolutionary new indication for an existing medicine is scientifically interesting. However, the focus of DR is often on further research after the major "discoveries" have already been made.

6.3 Hurdles for the Government/Regulatory Authorities

As a player, the government also encounters hurdles when stimulating DR. The government lacks the incentive to act proactively for DR. On the other hand, the government is limited by the rigidity of the existing system, which is not easily changed.

No agenda setting due to significant latitude of off-label use by practitioners Practitioners (doctors) have a high degree of freedom of action. Their professional autonomy is only circumscribed by the obligation to provide good-quality care.[85]

As stated in paragraph 4.3, doctors are not obliged to use medicines for registered indications. Because prescribers can prescribe any medicines they want (on-label or off-label, commercial or pharmacy preparation), and the profession thinks it is capable of assessing the suitability of prescribed products, marketing authorisations for new applications are not often called for. This has a limiting effect on setting the agenda for DR for the government.

If stricter requirements for prescribing off-label and pharmacy preparations were imposed on prescribers, there would probably be a stronger call for the registration of new applications.

"Applicant-Driven" Medicine Registration System

As the competent authority for the admission of medicines in the Netherlands, the MEB (CBG, College ter Beoordeling van Geneesmiddelen) feels responsible for the use of medicines. However, the MEB (CBG, College ter Beoordeling van Geneesmiddelen) essentially plays a passive role.[86] In principle, only a marketing authorisation holder can suggest changes to the marketing authorisation. The MEB then accepts them or not. In other words, the system is *applicant-driven*.[87] The MEB (CBG, College ter Beoordeling van Geneesmiddelen) sometimes thinks it would be in the interest of public health to add a specific application (indication or patient group) to the official product information. However, it is not authorised to take such an initiative. The competent authorities can nevertheless take measures when the interest of public health is at stake.

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85 *Within the scope of the (Dutch) Medical Treatment Contracts Act, the (Dutch) Individual Healthcare Professions Act and the (Dutch) Care Institutions (Quality) Act.*

86 *J.A. Lisman, "De toelating van geneesmiddelen: Hoe effectief is ons systeem? [The admission of medicines: How effective is our system?]", in: Medicines and Law, Association for Health Law, The Hague: SDU uitgevers 2006, pp. 32 - 33.*

87 *Presentation by S. Krüger in the workshop "Blijvend investeren in oude producten [Continued investment in old products]", 10 June 2011, Utrecht, http://www.cbg-meb.nl/CBG/nl/over-ons/bijeen komsten/20110616watisbesprokentijdensdecollegedag2011/default.htm, last accessed on 13 January 2012.*

However, this is limited to negative decisions resulting in the suspension or cancellation of the marketing authorisation, the deletion of an indication from the marketing authorisation or the inclusion of a warning in the official product information. These do not result in more (broadly) registered medicines becoming available.

No Toolbox with Incentives for Drug Rediscovery

The fact that the Ministry of Health, Welfare and Sport and ZonMw commissioned this research shows that ways are being sought to stimulate the registration of unregistered applications of medicines, or at least that there is a will to encourage more effective use of (existing) medicines. However, it also shows that it is not known how this use can best be improved.

Limitations (to Change) as a result of the Regulatory/Legal System

The Dutch regulatory system for the quality and provision of medicines is to a large extent based on European law. Various EU directives, regulations, guidelines and further implementing regulations have been introduced which have a direct effect or have been incorporated into national legislation. The Dutch legislator is only occasionally free to make divergent or additional regulations. In other words, the Dutch government can only revise regulations based on European law with the cooperation of the EU institutions and other Member States. This is a lengthy process which is usually followed by a national implementation procedure.

Moreover, primary legislation requires political decision-making. Different priorities, political agendas and interests often make the process – at both national and international level – quite difficult and time-consuming.

6.4 NB - Perception of Hurdles

Although during the consultations, the experts mentioned the (aspects of) hurdles discussed in this chapter, it became clear that there is no consensus regarding the relevance and influence of the various factors. Not everyone encounters or acknowledges all the above-mentioned hurdles or gives the same weight to the hurdles. This seems to depend strongly on a party's position in relation to DR, e.g. whether the party is involved as product developer, practitioner or government.

They have different opinions about whether all the identified hurdles are equally realistic, and some have the impression that it is about the *perceptions* of hurdles. These perceptions could result from unfamiliarity with DR, a lack of knowledge of the possibilities provided by the present legislation, inadequate communication and "cold feet".

7 Solution Pathways

Although several real and perceived hurdles to DR are identified in Chapter 6, not all of the given solution pathways can be directly linked to one or more specific hurdle. We therefore decided to put forward a number of solution pathways without specifying the hurdle which would be removed by putting a proposed solution into effect. Our decision to take this approach is based on the conviction that stimulating DR is best served by a comprehensive approach.

7.1 Reviewing the Regulatory Requirements Imposed on Clinical Research and Setting Up a Clinical Trial Service for DR

The golden standard for clinical research for registration purposes is the randomised placebo or *comparator* controlled clinical study where the inclusion and exclusion criteria, primary and secondary endpoints and stop criteria are laid down in advance. The competent authorities should reassess clinical data which is not obtained according to the golden standard and give industry and the scientific community the opportunity to use data obtained from other sources in a dossier. It is important to create support for this and to lay down rules which provide the proper basis and safeguards for it.

The establishment of a scientific committee which investigates the usefulness of observational and other, non-standard medical scientific research within the context of DR can be useful here. The results of such research can be discussed at EMA (European) level. This may lead to the formulation of specific guidelines for DR. These guidelines should stipulate that data obtained from non-interventional or retrospective research can also be used to apply for registration. It is also recommended that scientific research (e.g. in the field of *Regulatory Science*) be carried out on ways to generate clinical data for DR in a more rational manner.

The Dutch authority has a relatively high profile and good name within the community of European assessment authorities. This is shown by i.a. the number of applications for which the MEB acts as a "guide",[88] and by the fact that the MEB (CBG, College ter Beoordeling van Geneesmiddelen) holds numerous relatively important scientific positions, including the chairmanship of the *Efficacy Working Party* (until 2010). The MEB should make optimal use of its authoritative position to stimulate DR – also within the European forums – by creating support for said solutions and initiating regulatory changes.

[88] *The mutual recognition and decentralised procedures are about the role of the reference Member State (RMS); the centralised procedure is about the role of the rapporteur.*

High demands are imposed on clinical research. When doing the necessary research, the complexity of the regulations and the requirement to comply with GCP result in relatively high costs and practical problems, particularly for smaller product developers. To address the hurdles referred to in paragraph 6.1, we propose setting up a Clinical Trial Service for DR so that appropriate research can be carried out. Costs could be shared and expertise could be centralised by means of a public-private partnership. We also propose raising finance for useful clinical research within the context of DR from designated public funds. The Clinical Trial Service should form part of the Centre for Drug Rediscovery (see paragraph 7.7) and focus on giving practical support to product developers.

As with other forms of government support for clinical research, when a Clinical Trial Service is set up with the cooperation of the government, a great deal of attention should be paid to preventing unfair competition and unlawful state aid.
ZonMw and the MEB (CBG, College ter Beoordeling van Geneesmiddelen) could jointly explore the possibility of reviewing the requirements imposed on clinical research. ZonMw could also – e.g. by consulting the parties concerned – examine what is and what is not possible as far as setting up a Clinical Trial Service is concerned.

7.2 Introducing a Special Procedure for Drug Rediscovery

The European system for the authorisation of medicines lacks a procedure geared towards the further use of known active substances. The new medicine application (*full dossier*) and generic application procedures are less suitable for DR projects. We think the question of whether a specific procedure should be introduced for DR should be looked into.

Of the four existing application procedures, those for well-established use and/or mixed application are the most closely aligned. It should be investigated whether there is scope for a revised interpretation and practical implementation of European legislation and the implementing texts so that research on off-label applications of existing medicines and completely new applications of known medicines can be regulated. This can be brought up for discussion at the various European forums in which the Ministry of Health, Welfare and Sport and the MEB (CBG, College ter Beoordeling van Geneesmiddelen)take part.

The objective could be to introduce such a degree of flexibility in legislation that all available data – whether from one's own studies, from third-party studies or from the scientific literature – can be used to assess the benefit-risk ratio. Together with the MEB (CBG, College ter Beoordeling van Geneesmiddelen), ZonMw should support embarking on a dialogue about creating more flexibility in the application of the law on clinical research within the context of DR.

7.3 International Comparison of Initiatives to Stimulate Drug Rediscovery

The hurdles and solution pathways set out in this report are formulated from a Dutch perspective. Although this report is also based on European legislation, the focus was primarily on the situation in the Netherlands. This cannot be offset by literature research since little has been published on the regulatory aspects of, and actual hurdles to, DR.
Initiatives might nevertheless exist in other countries, both inside and outside the EU, which have a positive

effect on DR, e.g. specific incentive measures or reimbursement systems which stimulate DR. An example of such an initiative is France's *Temporary Authorisation for Use* , which will be discussed in greater detail in paragraph 7.3. Knowledge and experience from other countries could contribute to a better understanding of DR in the Netherlands and/or the EU. Since thorough knowledge of, and insight into, the legislation of other countries regarding research on and registration and reimbursement of medicines is essential, this needs to be investigated further.

Initiatives in other countries are not likely to result from legislation on the registration of medicines, since the competent authorities in the European countries are bound by the same European laws and guidelines. Possible differences in interpretation are discussed in committees such as the Pharmaceutical Committee, the CHMP, the CMDh, EMACOLEX and Heads of Medicines Agencies (HMA).

However, the reimbursement of medicines and the financing of medicines research are national matters. Different systems with different outcomes are possible here, some of which might be more favourable for DR than others.

Information on the initiatives in other countries can be obtained in different ways. The first option is to discuss the possibilities for DR at international forums. This could be done as part of a promotional campaign for DR, as proposed in paragraph 7.6. Alternatively, ZonMw could ask product developers (e.g. via Nefarma) to report initiatives in other countries. If they operate internationally, product developers will encounter all the aspects of the laws and regulations of various countries. They know like no other what initiatives can make a positive contribution to DR. Finally, ZonMw could conduct a survey among e.g. the ministries of public health in the EU Member States to identify the existing DR initiatives.

7.4 Limiting Off-Label Use and Pharmacy Preparations to Situations of Medical Necessity

Section 68(1) of the (Dutch) Medicines Act (GMW, Geneesmiddelenwet) relates to off-label use of medicines: prescribing non-registered applications. Medicines can be prescribed by doctors - and then supplied by pharmacists - for conditions for which they are not registered. They can also be prescribed to patient groups other than those for which registration was obtained (e.g. to children, while the medicine is only registered for use in adults). Under the law (Section 40 of the Medicines Act (GMW, Geneesmiddelenwet)), a pharmacist who does not have a relevant manufacturing and marketing authorisation is allowed to prepare medicines which are not registered and for which no commercial preparations are therefore available.[89]

In short, negatively put, off-label use and pharmacy preparation make it possible to bypass the registration of (new applications of) medicines. Obviously, if doctors and pharmacists can thus supply unregistered (applications of) medicines, there is no need and thus no

[89] *See Article 3(1)(2) of Directive 2001/83/EC, which stipulates that the guideline does not apply to magistral and officinal preparations. The directive describes officinal preparations as "medicines which are prepared in a pharmacy in accordance with the prescriptions of the pharmacopeia and which are intended to be supplied directly to the patients of the pharmacy." In the directive, magistral preparations are understood to mean "medicines which are prepared in a pharmacy in accordance with a medical prescription for a particular patient."*

incentive for further research, let alone registration. Restricting off-label use or pharmacy preparations can change this.

Off-label Prescriptions

Section 68(1) of the (Dutch) Medicines Act (GMW, Geneesmiddelenwet) limits the prescription of medicines for unregistered indications to situations where (in short) professional guidelines or protocols are available or, if these are not (yet) available, consultations have been held between the doctor and pharmacist. The motion, which prompted the inclusion of Section 68(1) in the (Dutch) Medicines Act (GMW, Geneesmiddelenwet) (tabled by i.a. the current Minister of Health, Welfare and Sport (Schippers)), listed a number of prerequisites by which off-label prescriptions would be assessed, including the prerequisite that there should be a *medical necessity*.[90] This stipulation was not included in the Act, however, although the then Minister of Health, Welfare and Sport did acknowledge that off-label prescriptions should be limited to situations in which "no alternative treatment options are available".[91]

Since the requirement of medical necessity was not included in the Act, the Act does not offer an incentive to apply for the registration of the unregistered application. Moreover, in principle, the pharmacist does not have the ability to check whether the prescription conforms to the medicine's registered applications. The introduction of the requirement for the indication to be stated on the prescription for medicines designated by ministerial regulation has since partially provided for this.[92] Allowing off-label prescriptions when there is no medical necessity not only constitutes a hurdle to DR but also undermines the marketing authorisation system and discourages investments in research on new medicines or new applications thereof.

This could be resolved by inserting the stipulation in Section 68(1) of the (Dutch) Medicines Act (GMW, Geneesmiddelenwet) that off-label prescriptions are only permitted if they are medically necessary. This medical necessity lies in the fact that there is no adequate registered alternative, i.e. that the doctor has no choice but to prescribe off-label since adequate treatment is not possible with the registered range of medicines.

This can be achieved by inserting the stipulation in Section 68(1) that the prescription of medicines for unregistered indications may only be allowed if, in addition to the existing conditions, the condition that there is no registered alternative with which the patient can be adequately treated is also met. Use could be made of the requirement which the Healthcare Inspectorate (IGZ, Inspectie voor de Gezondheidszorg) currently imposes on large-scale preparation with pharmacy-to-pharmacy supply: pharmacy-to-pharmacy supply is not permitted if there a registered therapeutic equivalent on the Dutch market or on that of another EU Member State.[93]

To support this new legal framework, the scope of Section 68(2) can be further broadened by obliging the prescriber to state the reason for prescribing (the indication) on the prescription in more cases.

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[90] *Parliamentary Documents II 2005/06, 29359, No. 57.*

[91] *Parliamentary Documents II 2005/06, 29359, No 62, pp. 14-15.*

[92] *New second subsection of Section 68 of the (Dutch) Medicines Act.*

[93] *Healthcare Inspectorate Circular 2007-02-IGZ of 22 August 2007, http://www.igz.nl/onderwerpen/curatieve-gezondheidszorg/apotheken/gmpz/ (at the bottom of this page), last accessed on 13 January 2012.*

Pharmacy Preparations

The above also applies to pharmacy preparations. Section 40(3)(a) of the (Dutch) Medicines Act (GMW, Geneesmiddelenwet) stipulates that the ban on preparing medicines without a marketing authorisation does not apply to medicines supplied by a pharmacist (on request) which have been prepared on a small scale in their pharmacy.[94] This exception is warranted by the fact that situations may occur in which the registered range of medicines does not provide an adequate solution. A pharmacist may therefore be required to prepare a medicine for a patient himself/herself or to prepare a suitable application based on a commercial preparation. If the system of compulsory marketing authorisations were to be applied too strictly, this could interfere with patient care.

It is therefore relevant that the Healthcare Inspectorate (IGZ, Inspectie voor de Gezondheidszorg) attached strict conditions to *large-scale preparation* by pharmacists in 2007. The existing practice of large-scale preparation and onward supply by pharmacies without a marketing (and manufacturing) authorisation prescribed by the (Dutch) Medicines Act (GMW, Geneesmiddelenwet), which had not been enforced by the Healthcare Inspectorate (IGZ, Inspectie voor de Gezondheidszorg) until that point, was therefore brought to an end. The Healthcare Inspectorate made up for this by drafting a revised non-enforcement policy for large-scale preparation and pharmacy-to-pharmacy supply shortly after the Medicines Act (GMW, Geneesmiddelenwet) came into force. This non-enforcement policy was implemented in the interest of patients, in order to avoid a gap which would have existed if the law had been strictly applied. It was also implemented in order to allow for tailor-made solutions when necessary. Following a strong decline (in favour of industrially prepared and registered medicines) which extended into the nineties, pharmacy preparations are once again in demand by prescribers and patients.[95]
This demand is reflected in the fact that the Healthcare Inspectorate's non-enforcement policy is based on the assumption that pharmacy-to-pharmacy supply is only possible without authorisation if there is no registered therapeutic equivalent. A pharmacist should demonstrably investigate the existence/absence of therapeutic alternatives before preparing an unregistered medicine.

Attaching this condition to pharmacy preparations which are *not* supplied onwards could be an incentive for DR. For example, Section 40(3)(a) of the (Dutch) Medicines Act (GMW, Geneesmiddelenwet) could be amended in such a way that the preparation of medicines by a pharmacy is subject to the condition that there is no registered alternative with which a patient can be adequately treated. The text can be based on the previously mentioned Healthcare Inspectorate Circular and the policies of other EU countries. The need to tighten the non-enforcement policy on pharmacy preparations was recently confirmed by the District Court of Breda.[96]

There are also other reasons – in addition to stimulating DR – for such an amendment. If there is a medicine made by a manufacturing authorisation holder according to GMP and evaluated and approved by the competent authorities, allowing a pharmacy preparation would disregard the fact that users of medicines are entitled to the best possible product, which is closely monitored by the competent authorities.[97]

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[94] *See also Section 18 (5) of the (Dutch) Medicines Act (GMW, Geneesmiddelenwet) which makes the following exception for the compulsory manufacturing authorisation: the small-scale preparation of medicines supplied in a pharmacy by or at the request of a pharmacist or dispensing doctor.*

[95] *The number of onward supplied preparations has increased from 589,000 to 1,445,000 since 2009. The number of products offered as onward supplied preparation increased from 161 in 2009 to 390 in 2010. By mid-2011, the supply had increased to over 500 different products; see polls of the Medicines and Medical Devices Information Project Healthcare Insurance Board October 2011.*

[96] *District Court of Breda, 23 December 2011, National Case-Law Number BV0199.*

[97] *Cf. the preamble of the Regulation on Orphan Medicinal Products (Regulation (EC) No. 141/2000), recital 7: persons (…) are entitled to medicines of the same quality, safety and efficacy level as other patients. Orphan medicinal products should therefore be subject to the standard assessment procedure (…).*

In both situations (off-label prescriptions and pharmacy preparations), an amendment of the relevant sections of the (Dutch) Medicines Act (GMW, Geneesmiddelenwet) is advisable but not necessary.
We believe that the underlying European legislation provides (scope) for strictly limiting pharmacy preparations and off-label use to situations where this is necessary for a patient from a medical viewpoint.

It is conceivable that the Healthcare Inspectorate (IGZ, Inspectie voor de Gezondheidszorg) will declare its policy on pharmacy-to-pharmacy supply to apply mutatis mutandis to pharmacy preparations and that the Minister of Health, Welfare and Sport and/or the Healthcare Inspectorate (IGZ, Inspectie voor de Gezondheidszorg) will (when asked) openly speak out for an interpretation of Section 68(1) of the (Dutch) Medicines Act (GMW, Geneesmiddelenwet) which does justice to the basic premise that registration is preferable. Unregistered applications of medicines or unregistered medicines should only be allowed in cases of medical necessity.

The advantage of an adjustment in the Healthcare Inspectorate's policy and the further interpretation of the above-mentioned sections by the Minister of Health, Welfare and Sport or Healthcare Inspectorate (IGZ, Inspectie voor de Gezondheidszorg) is that a lengthy legislative amendment process can be avoided. This applies even more now that an amendment to the Medicines Act (GMW, Geneesmiddelenwet) has become effective.[98]

ZonMw could investigate (or have investigated) how and in what form policy can be formulated and embedded and play a catalysing role in this process.

7.5 Accelerated Assessment and Market Authorisation

One of the issues raised at the expert meetings is that it takes a long time for a DR project to result in a marketing authorisation and thus to the possibility of financing and reimbursement. This makes it difficult and risky to finance this process. This could be overcome by making the medicine available to the patient and reimbursable before the new application is registered.

The system of European pharmaceutical legislation provides patients and practitioners with various options for early access to innovative, life-saving medicines. A new medicine which is being developed can be made available provisionally before the registration dossier is completed and/or the marketing authorisation is issued.
The (European) competent authorities can issue a provisional marketing authorisation for medicines which are in great demand and still under investigation. An exception to the marketing authorisation requirement can also be made in national legislation: such exceptions are usually referred to as *compassionate use* .

The consulted experts suggested making it possible to grant such medicines provisional admission, based on the model of the French system of Temporary Authorisation for Use. The Temporary Authorisation for Use is an example of early access for compassionate use. Early marketing authorisation or accelerated assessment and conditional inclusion in the basic healthcare package are dealt with below.

Early Marketing Authorisation

The current legislation provides for various ways to make a medicine available sooner: *Early Access*).

[98] *Act of 7 November 2011, Bulletin of Acts and Decrees 572.*

In the first place, a request for accelerated assessment of the application can be submitted to the EMA.[99] If the CHMP accepts the request, the assessment period will be shortened by 60 days. This is subject to the prerequisite that the application will result in an important innovation for patient care.
If there are practical hurdles to submitting a full dossier, a marketing authorisation may be issued *under exceptional circumstances* .[100] This special marketing authorisation may only be issued if the following conditions are met:[101]

- The indication is so rare that the applicant cannot be expected to submit all the data; or
- The state of knowledge prevents the submission of the full data set; or
- The data collection would be medically unethical.

Within the context of DR, these conditions will rarely apply. We will therefore not give any further consideration to this marketing authorisation *under exceptional circumstances*.

If a new medicine is so important that there is not enough time to complete the dossier, a conditional marketing authorisation can be issued. In such cases – a new medicine is tested for the treatment of a serious, life-threatening or otherwise irreversible condition, and there is no alternative treatment – the European Commission can issue a conditional marketing authorisation before the requirements for extending a marketing authorisation have been fully met.[102]

However, a conditional marketing authorisation can only be issued within the context of the centralised procedure. Such an application should – in summary – concern:

- a medicine used to treat a seriously debilitating or life-threatening condition; or
- a medicine which needs to be used in emergencies; or
- an orphan medicinal product.

It should also be possible to assess the risks and benefits based on the available data. *unmet medical needs* should be addressed and the benefits of having the medicine available should outweigh the risks of marketing the medicine.

The conditional marketing authorisation is therefore largely intended for so-called *break-through* medicines, medicines which are important innovations but take too long to develop in relation to the interests of untreated patients. A conditional marketing authorisation can only be issued if the dossier has largely been completed to enable the competent authorities to form a reasonably substantiated opinion on the benefit-risk ratio of the application.[103] This situation is not very likely to occur in DR projects.

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[99] Article 14(9) of Regulation (EC) No. 726/2004.

[100] This procedure is not about temporary rules: in general, the special circumstances will be permanent. See Article 22 of Directive 2001/83/EC. This provision is included in Section 45(4) of the (Dutch) Medicines Act.

[101] See Annex 1 to Directive 2001/83/EC, Part II, paragraph 6.

[102] See Article 14(8) of Regulation (EC) No. 726/2004 in conjunction with Regulation (EC) No. 507/2006. The application of this provision is dealt with in Article 3.18 of the (Dutch) Medicines Act Regulations.

[103] Article 4(1)(a) of Regulation (EC) No. 507/2006.

Compassionate Use

The term "compassionate use" refers to the situation where a medicine is made available before a marketing authorisation is issued. In principle, this falls outside the scope of European legislation which focuses on the trade in medicines and not on situations where a medicine is made available, usually free of charge or at cost price.[104] Compassionate use is based on national legislation which provides for the supply of a medicine without a marketing authorisation. Article 5(1) of Directive 2001/83/EC forms the legal basis for compassionate use.[105]

There are two forms of compassionate use: individual consent (*Named Patient*) and cohort-based consent. The consent should in any case be based on an unmet medical need: the competent authorities only allow unregistered medicines to be supplied if there is no alternative. The authority to admit unregistered medicines in the Netherlands is vested in the Healthcare Inspectorate (IGZ, Inspectie voor de Gezondheidszorg). The conditions under which (still) unregistered medicines can be supplied are set down in Article 3.17 of the (Dutch) Medicines Act Regulations (Regeling Geneesmiddelenwet). This article includes the explicit condition that no adequate medicinal alternative is on the market or otherwise available in the Netherlands.

Section 3.18 of the (Dutch) Medicines Act Regulations (Regeling Geneesmiddelenwet) concerns the specific situation in which a marketing authorisation application has been submitted for a medicine within the context of the centralised procedure. In accordance with Article 83 of Regulation (EC) No. 726/2004, if a compassionate use programme is recommended for such a medicine, consultations should be held at the level of the EMA.

In general, it may be said that compassionate use situations will not occur within the context of DR.

Reimbursement and Financing of DR

It may be important for the development of DR that a medicine is reimbursable, also if the application is still under (further) investigation.[106] Since DR usually concerns the further development of existing medicines, reimbursement will often depend on the medicine's reimbursement status.

Outpatient Setting

Medicines used in an outpatient setting are reimbursed if they are included in Annex 1 to the Healthcare Insurance Regulations (Rzv, Regeling zorgverzekering), irrespective of the person and reason for being prescribed. To encourage the rational use of medicines, medicines can be included in Annex 2. The Minister of Health, Welfare and Sport can attach conditions to the right to compensation.[107] This has not been worked out in greater detail in legislation. The Minister therefore has a wide margin of discretion.[108] This usually concerns limiting the entitlement to (one or more) specific registered indication(s).

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[104] *Cf. Article 2 of Directive 2001/83/EC.*

[105] *Compassionate use is also referred to in Article 83 of Regulation (EC) No. 726/2004. This article states explicitly that the authority to permit compassionate use is vested in the Member States. If this concerns medicines which are admitted via the centralised procedure, the relevant Member State should report programmes to the EMA and the Member States should coordinate their policies. This specific situation is included in Article 3.18 of the Medicines Act Regulations.*

[106] *Article 19 of Directive 2001/20/EC stipulates that the sponsor should make investigational medicinal products available free of charge, unless the Member States allow reimbursement in exceptional circumstances.*

[107] *Article 2.5(2) of the (Dutch) Healthcare Insurance Regulations.*

[108] *M.F. van der Mersch, C. Velink, "Het recht op geneesmiddelen [The right to medicines]", in: Medicines and Law, Association for Health Law, The Hague: SDU uitgevers 2006, p. 180.*

If the medicine is not being used in accordance with the indications specified in Annex 2, reimbursement may be refused.
It is explicitly stipulated for some Annex 2 medicines that unregistered indications may also qualify for reimbursement, provided that the following criteria are satisfied: [109]

- the insured person suffers from an illness which affects fewer than 1/150,000 residents in the Netherlands;
- and the effectiveness of the medicine for that indication is scientifically substantiated;
- and the condition cannot be treated with any other medicine in the Netherlands.

Since the manner in which the conditions (and their wording) for inclusion in Annex 2 should be laid down has not been worked out in greater detail in legislation, the current legal framework provides scope for taking into account the interest of DR. For example, if reimbursement of the medicine to which the DR relates is subject to restrictive conditions, the conditions set out in Annex 2 could be revised.
This does not require adjustment of the legislation. However, it is important that relevant parties at the Ministry of Health, Welfare and Sport and the Healthcare Insurance Board (CVZ, College voor Zorgverzekeringen) are prepared to extend the reimbursement. Any fear of misuse could be offset by setting certain requirements and conditions.
A reimbursement scheme could also be set up for situations where a new medicine with the same active substance is being developed for the purpose of DR. This scheme would be an exception to the rule that investigational medicinal products should be made available free of charge. However, if specific rules apply, Member States are authorised to make such an exception.

Hospital Setting

Medicines used in a hospital setting form part of the "medical care" service. This includes care which practitioners "tend to provide". This is defined more specifically by the state of medical science and practice. If a patient is being treated in a hospital with a registered medicine, that medicine will be reimbursed. The system has no restrictions within a hospital setting, such as Annex 2 conditions in an outpatient setting.
Medicines used in a hospital setting are not reimbursed separately; they are factored into the price of treatment (from 1 January 2012, the DTC care services). In that regard, it is not relevant whether or not a medicine is used for a registered indication or whether or not it concerns an indication which is being developed within the context of DR. However, it is conceivable that, as far as expensive medicines which are the subject of DR are concerned, wider use of the medicine will have budgetary consequences for the hospital. From 1 January 2012, pursuant to the Policy Regulation on *Services and Rates for Specialist Medical Care (Beleidsregel Prestaties en tarieven medisch specialistische zorg)*, expensive medicines used in hospitals can be financed in the form of add-ons .[110] The medicines which can be claimed as add-ons are included in an exhaustive list (Annex 5) which is apparently based on the old substances list of the Policy Regulation on Expensive Medicines (Beleidsregel Dure Geneesmiddelen). The indication for which the add-on and thus additional financing applies is specified for some medicines.

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[109] *Healthcare Insurance Board, Evaluation of medicines for unregistered indications, unregistered medicines and pharmacy preparations, position of the Committee for the Reimbursement of Medicines of 4 June 2007, www.cvz.nl, search for "Evaluation of medicines for unregistered indications, unregistered medicines and pharmacy preparations, position of the Committee for the Reimbursement of Medicines", last accessed on 13 January 2012.*

[110] *Policy Regulation BR/CU-2045 "'Services and Rates for Specialist Medical Care", www.nza.nl search for "Services and Rates for Specialist Medical Care", last accessed on 13 January 2012.*

The criteria for inclusion in Annex 5 and the continuation of inclusion in this list were not yet known at the start of 2012. It is conceivable that DR will also be taken into account here, e.g. by extending the potential indications to which the add-on applies.
Primary legislation will not have to be adjusted. At the instruction of the Minister, the criteria can be set by the Healthcare Insurance Board (CVZ, College voor Zorgverzekeringen), possibly with the involvement of the Dutch Healthcare Authority (NZa, Nederlandse Zorgautoriteit). However, in the case of DR, the relevant parties at the Ministry of Health, Welfare and Sport and Healthcare Insurance Board (CVZ, College voor Zorgverzekeringen) should then be prepared to broaden the scope for add-ons. Any fear of misuse could also be offset by setting further requirements and conditions.
ZonMw could put the solutions for the outpatient and hospital settings on the agenda of the Ministry of Health, Welfare and Sport and, together with the field and (in particular) the Healthcare Insurance Board (CVZ, College voor Zorgverzekeringen), stimulate the development of criteria for reimbursement or additional financing. Since the criteria for inclusion in Annex 5 to the above-mentioned policy regulation have yet to be set, this point can be raised at the same time.

7.6 Promotional Campaign for Drug Rediscovery

The solution pathway “promotional campaign” intends to encourage familiarity with and awareness of DR among product developers – pharmaceutical companies – and government agencies such as the MEB (CBG, College ter Beoordeling van Geneesmiddelen) and the Healthcare Inspectorate (IGZ, Inspectie voor de Gezondheidszorg)). As previously indicated, the image of the opportunities and possibilities for registering unregistered applications of medicines is too negative; the hurdles are not so much real as perceived. This could be one of the reasons for the low number of DR initiatives. By providing more general information on (the perceived hurdles to) DR and highlighting the benefits, more product developers could be encouraged to engage in DR and more DR initiatives could be taken.

Knowledge of the context and the importance of DR also apply to the competent authorities: the EMA and MEB (CBG, College ter Beoordeling van Geneesmiddelen). Assessment authorities can support product developers in DR projects. This also applies to the Healthcare Inspectorate as supervisory authority and to the Ministry of Health, Welfare and Sport, the Dutch Healthcare Authority (NZa, Nederlandse Zorgautoriteit) and the Healthcare Insurance Board (CVZ, College voor Zorgverzekeringen), which are involved in i.a. the reimbursement and financing of medicines.

This study is the first step towards positioning and promoting DR. In addition to this, familiarity with and consideration and awareness of DR can be stimulated by paying attention to the opportunities and possibilities of DR in various forums. For example:

- Giving presentations at meetings and conferences of (scientific) associations and sector organisations;[111]
- Placing it on the agenda of meetings of the competent authorities;[112]
- Placing it on the agenda of meetings regarding national and international policy;[113]
- Contacting professional organisations such as the Royal Dutch Society for the Advancement of Pharmacy (KNMP, Koninklijke Nederlandse Maatschappij ter bevordering der Pharmacie), the Royal Dutch Medical Association (KNMG, Koninklijke Nederlandsche Maatschappij tot bevordering der Geneeskunst),

[111] *For example, a session on Drug Rediscovery will be held at the Annual Meeting of the Drug Information Association (June 2012, Philadelphia). Presentations on DR could be given at the annual regulatory conferences of the European umbrella organisations EFPIA and EGA.*
[112] *The issue of DR could be addressed (through the MEB) in EMA’s scientific committees and in the Heads of Medicines Agencies and EMACOLEX.*
[113] *For example, EU’s Council for Public Health.*

the Dutch Association of Medical Specialists and patient organisations (Orde van Medisch Specialisten). The members of these organisations might benefit from concrete DR projects.

Following on from this, a scientific association for DR could be formed or an alliance could be formed with an existing international association. A long-term goal could be to launch a scientific journal for DR.

ZonMw could ask the above-mentioned organisations to give consideration to this report and to DR in general. This could be initiated by a roundtable or conference. There is also a role for the *Centre for Drug Rediscovery* (CDR) here, which will be discussed below.

7.7 Centre for Drug Rediscovery

Many hurdles to DR are related to the lack of know-how on the one hand and inadequate communication between various players involved in DR on the other. The competent authorities believe that some of the hurdles are less insurmountable than potential applicants might think. On the other hand, the competent authorities don't always fully understand the backgrounds and reasons for not submitting applications or requesting their assistance. The parties involved appear to have different perceptions and expectations; communication may resolve this.

It is clear that there is a range of issues which the competent authorities and other parties involved need to discuss. This, and the communication between various companies and scientific institutions, could bring the perception of the hurdles to a realistic level,

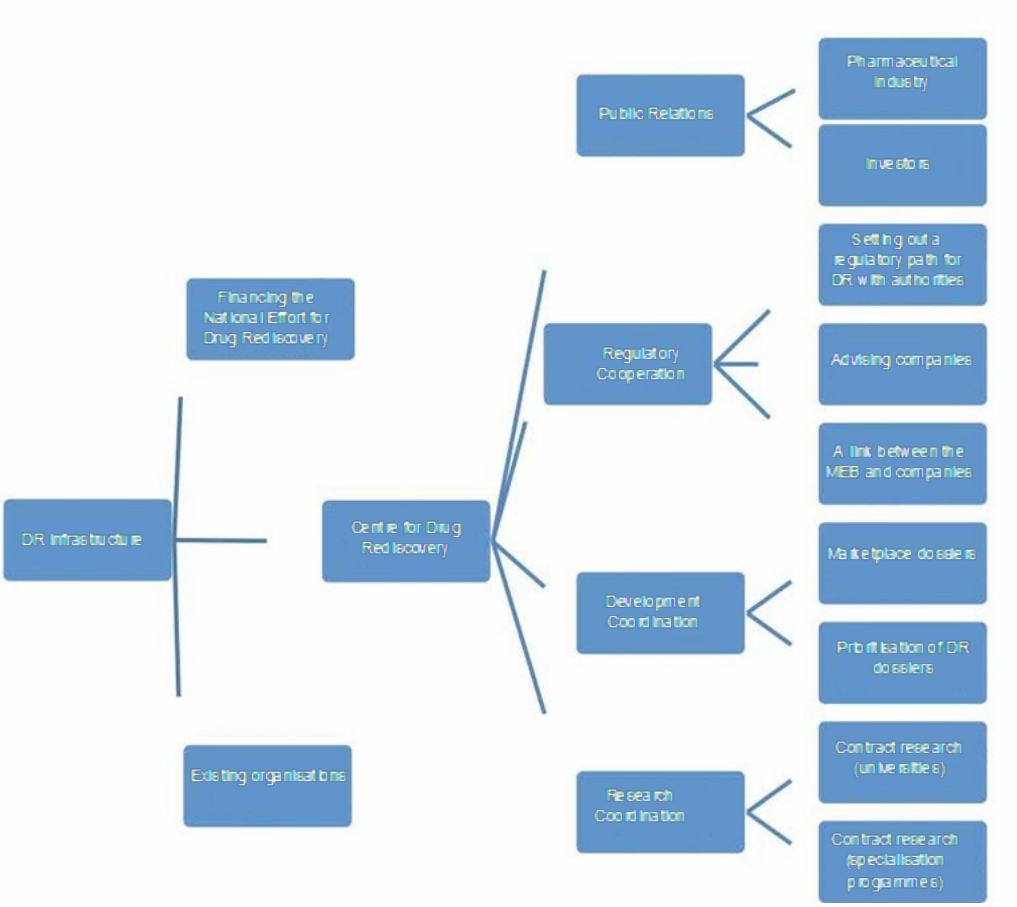

Figure 4: Drug Rediscovery Infrastructure.

provide greater insight into and better understanding of the positions of the various parties and, on that basis, lead to joint solutions for removing actual hurdles. To achieve this, we propose setting up a CDR which will position itself between the parties and act as a centre of expertise and communication hub.

The CDR would therefore be a platform and helpdesk for all those involved in the development and registration of unregistered indications of medicines. It could close the (perceived) gap between the government and the field, remove the existing misperceptions of possibilities and hurdles, both on the part of the government and on the part of potential applicants for marketing authorisations or revisions thereof, and help to remove actual hurdles. Finally, the CDR could set up a campaign to encourage all parties involved to take appropriate action, as discussed in paragraph 7.6.

A second important role of the CDR is that of marketplace: the CDR brings together the parties in the market for DR projects. We expect the interaction between presenting and requesting parties to encourage activities in the area of DR. The CDR will carry out a range of activities in order to stimulate DR. The functions of the CDR are shown in the figure below.

The CDR makes an important contribution to the Dutch infrastructure for DR by – together with existing organisations which play a role here – bringing the parties into contact with each other. The roles of the CDR are briefly summarised below.

Public Relations

Within the context of the CDR, *Public Relations* is understood to mean providing information on DR to businesses, patient organisations and potential investors. This could, for example, make it easier to raise investment capital and stimulate research.

Regulatory Cooperation

Within the function of *Regulatory Cooperation* , the CDR can act as a link between the applicants and the competent authorities (the MEB (CBG, College ter Beoordeling van Geneesmiddelen) and, through the MEB, the EMA and other (supervisory) authorities, such as the Healthcare Inspectorate (IGZ, Inspectie voor de Gezondheidszorg). The CDR will initially be able to focus on improving the *Regulatory Pathway* for old medicines and on improving the coordination of the necessary data and the evaluation of medicines based on these data.

The CDR will also be able to profile itself as a helpdesk for companies considering or undertaking a DR project.

Development Coordination

Development Coordination refers to the possibility for interested parties to create a marketplace within the CDR for selecting new DR projects. To this end, the CDR, in collaboration with international partners, is going to create a database of DR opportunities. An example of such a database is RedB or Red Bee.[114] A second, extremely important element is organising the availability of medicine dossiers as a basis for new products with added new applications. These dossiers are often in the hands of companies which first developed the medicine. This is why the input of the (innovative) pharmaceutical industry is very important. Pharmaceutical companies can consider situations in which one of their products could qualify for a Drug Rediscovery project. They should then ask themselves whether they want to sponsor a Drug Rediscovery Project and, if not, whether, by making a dossier available – whether or not for payment – they want to cooperate in extending the applications of the relevant products.

Research Coordination

Under the flag of *Research Coordination* , a marketplace can be created for researchers, research institutions and potential applicants where the research for Drug Rediscovery projects can be contracted out. In addition to the regular *Contract Research Organisations* , one might think of university medical centres, research by pharmacists and doctors in their specialisation phase and the CDR's own research.

Also, registers could be set up for information on off-label use which might be important for the documentation of DR projects. The main success factor of this solution pathway is the desire to take part and work with the other parties involved. It has already been pointed out at the expert meetings that this is extremely important for DR since the margins are small and parties cannot afford to have the same initiatives taken in different locations at the same time.

In terms of investments, these can be limited by joining organisations which are already active in the area of DR, such as ZonMw and the MEB (CBG, College ter Beoordeling van Geneesmiddelen). Funding will nevertheless be necessary, especially in the start-up phase of the CDR. One could think of a joint venture between the Ministry of Health, Welfare and Sport and the Ministry of Economic Affairs, Agriculture and Innovation.

Formalisation is important for a well-functioning CDR. One could consider establishing a foundation, using the experience acquired in organisations which are similar in some respects, such as the Orphan Drugs Steering Group (Stuurgroep Weesgeneesmiddelen). Before doing so, a conference should be held to which all interested parties can make a contribution. The foundation should be staffed by at least one person who is expert in the area of DR. Over time, it can develop into an organisation which achieves the above-mentioned objectives.

ZonMw can bring together parties involved in DR in order to set up a Centre for Drug Rediscovery.

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[114] *Rediscovery Database, http://rediscovery.bioinformatics.ucdavis.edu/, last accessed on 13 January 2012.*

8 Conclusion and Summary

Problem Definition

Doctors have a wide range of medicines for treating patients. However, it is not certain whether these medicines are always being optimally used; many existing medicines are suspected of having other unknown but medically relevant applications. This report was therefore prompted by the assumption that there are new applications of well established (generic) medicines which are not or insufficiently translated into new marketing authorisations or revisions of existing ones. Two questions are central to this report:

- What are the practical hurdles to this further development?
- How can the further development of medicines be stimulated?

In this report, the term “Drug Rediscovery” (DR) is used for the further development of existing medicines.

Contents of the Report

The report contains the results of a quickscan on possible hurdles to registering new DR applications and an overview of ways to remove these hurdles. The focus was mainly on regulatory hurdles.

The first chapters cover a number of issues which are important for a proper understanding of the problem, such as an outline of the development of medicines (Chapter 3), the background of Drug Rediscovery (Chapter 4) and the legal and practical aspects of patents and protection of innovation (Chapter 5).

The essence of the report can be found in Chapters 6 and 7. Chapter 6 contains an overview of the hurdles to DR referred to by experts and in the literature. The hurdles are classified according to their relevance for the three *stakeholder groups* in DR: product developers, research institutions and the government. Some of the identified hurdles are not equally relevant for all players and it is not always clear whether these are actual or perceived hurdles, based on e.g. a lack of knowledge or communication. Nevertheless, both cases (actual and perceived hurdles) have an effect on DR.

The main hurdle for product developers is the lack of a prospect of *return on investment*. This prospect depends on a large number of factors, such as the potential to obtain protection from competition in (whatever form) and inclusion in the basic health insurance package. A second category of hurdles for product developers is more practical in nature. These hurdles often involve high costs and therefore a decrease in the expected *return on investment*. Research institutions are faced with other hurdles, such as lack of funding and the low scientific status of DR-related research. The government largely sees itself bound hand and foot by the strict regulatory framework (dictated by European law) in which the competent authorities (e.g. the MEB (CBG, College ter Beoordeling van Geneesmiddelen) and EMA) play a passive role, as a result of which the registration of new applications cannot – as much as this is desired – be enforced.

Our findings show that there are very few concrete examples of ongoing DR projects which encounter the hurdles referred to in this report and therefore cannot be registered. This may suggest that the assumption that there is a problem is incorrect or should be nuanced. It should be noted here that DR projects which encounter problems might not always be made public and that mainly successful registrations of new applications are cited in the literature. In any case, many opportunities for DR still seem to have been left untapped. This needs to be investigated further.

Solution Pathways

Seven solution pathways to stimulate DR are identified in Chapter 7. The criterion was that they can be (fairly easily) made to fit in with the current legal system and implemented in practice. The solutions are not linked one-on-one to the hurdles identified in Chapter 6: the given solution pathways will usually remove or reduce several hurdles. They can also reinforce each other.

The solution pathways sometimes relate to legislation, such as the adjustment of primary legislation, or another application thereof. The main suggestion here is to lay down by law that all exceptions to the obligation to register are strictly limited to cases where there are no adequate registered alternatives. However, the greatest gains can be made from more practical solutions, such as encouraging the exchange of knowledge and improving communication between all parties involved. A few concrete proposals are made for this, of which setting up a Centre for Drug Rediscovery is one of the most important. This centre can become a platform for dialogue between the players, as well as a marketplace for knowledge, dossiers, know-how and research.

Recommendations to ZonMw

In so far as this was possible within the scope of this quickscan, suggestions for possible further action were forwarded to ZonMw. The short-term practical and legal feasibilities were considered. ZonMw can play an important catalysing, facilitating and coordinating role. A follow-up study, e.g. an overview of DR initiatives and solutions in other (EU) countries, is recommended.
It is advisable to take up and carry out the presented solution pathways in conjunction.

The findings and conclusions of this report are based on input from experts at various expert meetings, the experiences of the authors and a scan of the available literature. A complete picture (which was not the intention) proved to be impossible. As became apparent during the study, this is due to ambiguous definitions and major differences in perception of the nature, scope and seriousness of the problem under investigation.

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A great deal of literature was consulted to produce this report. This not only included published books and articles, but also reports and recommendations from various organisations. The literature review below only lists the sources named in the footnotes.

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Consulted Experts and Words of Thanks

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Drs. Y. Bouwman-Boer	Royal Dutch Society for the Advancement of Pharmacy/Laboratory of Dutch Pharmacists
Prof. D.J.A. Crommelin	Top Institute Pharma
Drs. B.M. van Elk	Medicines Evaluation Board
Drs. J.M.M. Hansen	Healthcare Inspectorate
Prof. Y.A. Hekster	Medicines Evaluation Board
Prof. H.G.M. Leufkens	Utrecht University/Medicines Evaluation Board
E.G.W.H. Loof	Teva Pharmachemie
Dr R.W. van Olden	GlaxoSmithKline
Dr P.J. Roos	Erasmus MC Hospital Pharmacy
F.J.T. Sinjorgo	HLW pharma B.V.
Drs. Ing. A. Torqui	Medicines Evaluation Board C.K.W. van
Veldhuizen	ACE Pharmaceuticals B.V.
Dr R. de Vrueh	ZonMw
Dr B.J. van Zwieten-Boot	Medicines Evaluation Board

About the Authors

Joris Langedijk

Joris Langedijk studied pharmacy at Utrecht University, where he is currently doing doctoral research in the Pharmacoepidemiology and Clinical Pharmacology Department, focusing on obstacles in the regulations for registering medicines. He is also studying Dutch law in Utrecht and works in MEB's (Medicines Evaluation Board) Administrative & Legal Affairs Department. His contributions to the report were written in a personal capacity and do not necessarily reflect the views of the MEB.

John Lisman

John Lisman studied pharmacy and Dutch law in Utrecht. Having dealt with pharmaceutical law in government service for fifteen years – seven years as a policy officer at the Ministry of Health, Welfare and Sport and eight years as a policy adviser for the Medicines Evaluation Board – John has practised law since 2007, specialising in pharmaceutical law. In 2010 he established the firm "Lisman Legal Life sciences B.V.".

Pieter Stolk

Pieter Stolk is an independent consultant in the life sciences sector. Much of his work is done where the public sector meets the private sector. He currently works i.a. as project manager for the Escher consortium. In this TI Pharma consortium, four universities and four private parties deal with questions relating to the removal of regulatory hurdles to innovation. Pieter studied pharmacy at Utrecht University, where he also completed his doctoral research.

Aukje Mantel-Teeuwisse

Aukje Mantel-Teeuwisse studied pharmacy at Utrecht University where she also completed her doctoral research. Aukje currently works as a university lecturer in Utrecht University's Pharmacoepidemiology & Clinical Pharmacology Department. She is also the Managing Director of the WHO's Collaborating Centre for Pharmacoepidemiology & Pharmaceutical Policy Analysis. Her research interests include drug regulatory science, pharmacovigilance, pharmaceutical policy research and the use of medicines in clinical practice.

Marie-Hélène Schutjens

Marie-Hélène Schutjens studied Dutch law in Utrecht. She obtained a doctorate on patent law and medicines and specialises in pharmaceutical law. She has
been working part-time in Utrecht University's Pharmacoepidemiology and Clinical Pharmacology Department as Professor in Pharmaceutical Law since 2000. Since 2006, she has been employed at the firm Schutjens De Bruin as legal adviser in the area of health law, in particular pharmaceutical law.