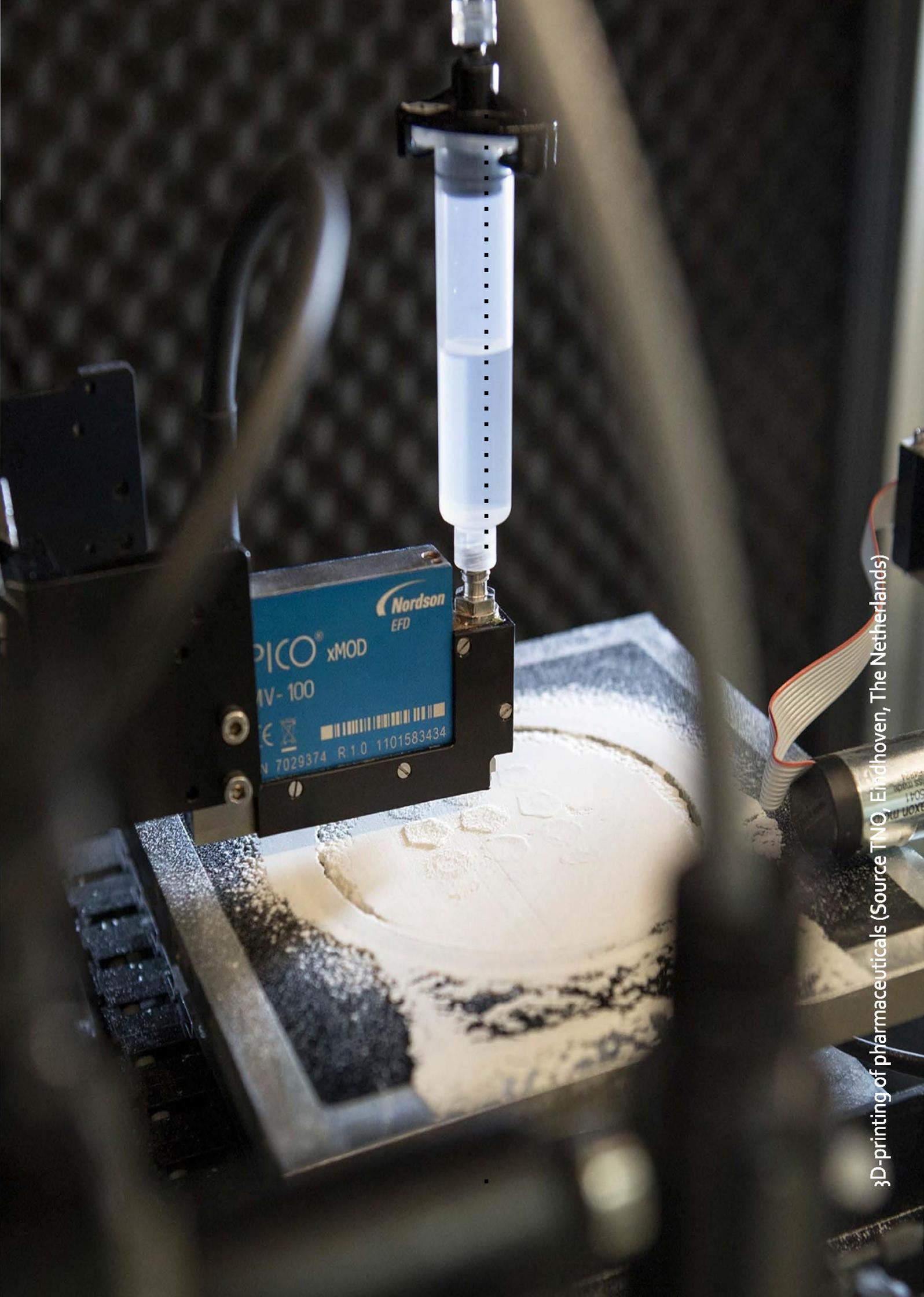


Development of new medicines

Better, faster, cheaper



raad voor **R** Volksgezondheid en
Samenleving



3D-printing of pharmaceuticals (Source TNO, Eindhoven, The Netherlands)

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The Hague, November 2017

Foreword

Numerous new medicines are being put on the market. This means an improvement in the quality of life for many patients, and for others a significant extension in the time left for them when they are severely ill. New medicines are essential for good care, and their development is going to keep progressing further and can be expected to yield ever-improving results.

The question is, however, whether a new medicine must be accepted no matter what the cost. It does sometimes look that way. The price of new medicines is often exorbitantly high; figures of over €100,000 per patient per year are no exception. How is it possible that medicines can be so expensive?

The RVS (Council for Public Health and Society) has shown that the high prices are partially the consequence of an inefficient development process: nine out of ten medications do not end up on the market. The costs of failures are set off against the price of the one medication that does reach the market. Another factor is that the high prices are the result of the market power of the pharmaceutical companies, the limited counterweight provided by government, hospitals, health providers and health insurers and the generally accepted duty of care that we in the Netherlands – rightfully – do not want to give up. In a political administrative sense it is then virtually impossible not to include an expensive medicine in the compulsory standard health insurance.

The RVS wants to break this stranglehold. In these recommendations, the Council sketches out an alternative perspective and states how the development of new medicines can be done better, more quickly and more cheaply. The Netherlands can make a start on this and show that the development and market introduction of new medicines is also perfectly possible for an acceptable price while observing the international norms.

Pauline Meurs

Chair of the Council for Public Health and Society

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(Raad voor Volksgezondheid en Samenleving, RVS)
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The task of the RVS is to advise the government and
the House of Representatives and the Senate of the States General
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Summary

New medicines are becoming increasingly expensive. Amounts of €100,000 a year or more for treating a single patient are no exception. Expenditure on expensive medicines is increasing every year by about 10%. That cannot continue in the long run.

The reason that manufacturers give for the high prices is that developing medicines takes a great deal of time and money. Development timescales averaging twelve to thirteen years are mentioned (ten years for R&D – research and development – plus two to three years for administrative procedures) (EFPIA 2016) and costs of €2.6 billion for a new drug (DiMasi et al. 2016). It is a high-risk venture: nine out of every ten medicines do not reach the finishing line and the costs of those are set off against the pricing for the one medicine that does reach the market. Medicines are developed in the private sector and investors therefore expect an appropriate – high – return on their investments as the reward for the high financial risks. The only companies capable of taking on such financial risks, calculating in the substantial risk of failures and demanding high prices are the major pharmaceutical companies (Big Pharma), thanks to their size. As a sector, the pharmaceuticals industry is consistently in the top three in terms of profitability, with an average return of over 20% (Forbes 2015).

The governmental authorities have to look at both the interests of society and those of the individual patients. This means that the authorities must keep excessively expensive medicines out of the collectively insured package, yet at the same time must not deny any individual patient a life-saving treatment. If a manufacturer is not prepared to ask a socially acceptable price for its products in negotiations, the authorities will have to make use of the opportunities that national and international regulations offer for making the medicine available for patients at an acceptable price, for instance by imposing enforced licences, allowing patients to order medicines from abroad via the Internet to be delivered to their homes, encouraging preparations at the pharmacy and tackling abuse of the position of power.

The classical argument that is used against this kind of government intervention is that it undermines the development of new medicines, because investors will no longer be prepared to make funds available for it. This will certainly be the case if the authorities demand unreasonably low prices for which it is impossible to develop a medicine. However, if the price level is both competitive and realistic, this will encourage businesses – given their aim of at least maintaining their profit levels – to develop medicines more quickly and less expensively.

National and international regulations – in particular requirements to introduce a medicinal product on the European and other markets – are often stated as the root cause of lengthy development at high costs. These requirements apply in particular to time-consuming and expensive clinical studies. While it is certainly desirable that European regulations should be changed in a number of areas, and the Dutch government has been working hard for this, improvements have already been made in the meantime. The current *fast track* procedures are an example. They allow medicinal products to be given access to the market by the European

Medicines Agency (EMA) within just a few years on the basis of what are sometimes very small clinical studies.

The question still remains of whether it is possible to reduce the extremely high probability of failures in the development of new medicines. The answer is yes. But a lot of effort is required from a large number of parties if this is to be achieved. It starts with the scientific research that is often the foundation for developing a new medicine. As stated earlier, an average of nine out of ten drugs drop out during the costly clinical research. These are all drugs that were effective in models and/or test animals such as lab mice, but which were finally shown not to be effective in humans. A more rigid and closely verified look should be taken beforehand at whether the animal and other models used properly represent the specific disease in humans for which they serve as a model. One possible solution is offered by 'natural' models, in animals or otherwise, such as test animals that naturally develop conditions that are very similar to those of humans. This can also reduce the numbers of test animals needed. Other important points are independent clinical research and sharing knowledge, in particular about clinical research data. Although some of the data is public, a lot is still kept secret, causing duplicated work and unnecessary wasted time at research institutions as well as in companies. Assistance from patients in developing new drugs is also important.

The question arises as to what use the advice is from the Council for Health and Society (RVS), because new medicines are developed at the global scale. The Netherlands is just a small player and does not have a large pharmaceutical industry. However, our scientific research is among the best and we also have an innovative biotechnology sector. There are also various initiatives in the Netherlands for developing medicines in a different way. All this creates opportunities. It is important to ensure a good climate for clinical research in the Netherlands. This also requires a proper information infrastructure, among other things. The availability of a personal health record (PHR) adds to the help provided by patients and the efficiency and effectiveness of clinical research.

The recommendations in this advisory document can help encourage the development of new medicines in the Netherlands, so that we can show that things can be done better, faster and less expensively, even given the current international framework. The Netherlands can lead the way in this.

Nevertheless, the efforts already put in by the Dutch government to ensure the desired changes in the regulations at European level have to be continued. This is a task for the long haul. This covers European patent regulations, rules about data exclusivity, orphan drug Regulations and the use of European research funds.

1 Introduction

1.1 Background to the recommendations

The reason these recommendations are being made is the request for advice from the Minister of Health, Welfare and Sport (VWS) in a letter dated 22 March 2016 (Appendix 1). In this letter, the minister asks the RVS to give advice about more efficient development of new medicines and alternative development models. The reason for this request for advice is that more and more often medicines are being developed for small groups of patients. These medicines can mean a great deal to those patients but are often (extremely) expensive at the same time. There is no longer a relationship with the R&D costs, or even with the added value. This is endangering the affordability of care.

The current development process for new medicines takes a long time and is costly. Many medicines fail to cross the finishing line. The minister's main question is:

"How can medicines be developed faster and more efficiently, with the efficiency improvements resulting in lower prices or otherwise benefiting society?"

In addition, the minister points out the problem that it seems impossible in practice for small companies to introduce medicines onto the market independently.

Specific attention was asked to be paid to personalised medicines, i.e. medicines that are tailored to the patient, such as gene therapy. Do these always have to be made available to the patient by a commercial party using market authorisations, or is non-commercial development of medicines one of the possibilities?

1.2 Focus of the advice

New medicines are developed at the global scale and are highly regulated through international legislation and regulations. There is a lot of criticism of these regulations, in particular of the additional protection certificates for medicinal products under patent legislation and market exclusivity for orphan drugs, which is based on the European regulations on orphan drugs.¹ Modifications have to be tackled at the international level. The Netherlands is very active in this field. However, ensuring changes at the international level is a long-term task whereas the problems are urgent right now. That is why this advice is focusing on what is possible in the Netherlands in the shorter term within the context of current international regulations.

By far the majority of new medicines that are introduced on the market in the Netherlands are developed elsewhere, primarily the United States. In the first instance, there were hopeful reports that the new American president wanted to tackle the high prices for medicines in the US. After consultations with large American pharmaceutical companies, he stated, *"The US drug companies have produced extraordinary results for our country, but the pricing has been astronomical for our country."* However, he added that he wants other countries to pay *"their fair share"* for *"US-made"* pharmaceuticals and that *"global freeloading"* must stop (Ramsey 2017).

This does not bode well for the Netherlands and Europe, and an important question is how we can control the costs of new pharmaceuticals to make sure that care remains affordable. As a counterweight, more new pharmaceuticals will have to be developed in Europe, and in different, more affordable ways. The Netherlands does not have any large pharmaceutical companies. This creates opportunities for testing alternative development models. If those are successful, they can be used as examples by other countries.

The current development model has some fundamental problems. For instance, the majority of promising medicines – up to 98% in some areas – drop out during what are often costly clinical studies. The development process must become faster, better and cheaper. The Netherlands can play a pioneering role in the development of alternatives. In this advisory document, we will look into how this could be done.

1.3 Reading guide

In Chapter 2 we give an outline of the current development route for new medicines. Chapter 3 then describes the problems with the current pathway; This also includes the pricing and the possibilities for improvements. In Chapter 4 we explore directions that may yield solutions and in Chapter 5 we give answers to the minister's questions in the form of six recommendations. Appendix 1 contains the request for advice and Appendix 2 describes a number of alternative development models that have been devised or have already taken concrete forms.

Notes

- 1 An orphan drug is a medicinal product for a rare, severe condition. Rare is taken to mean that less than five out of every 10,000 people in the European Union suffer from the condition.

2 The current development route for a new medicine

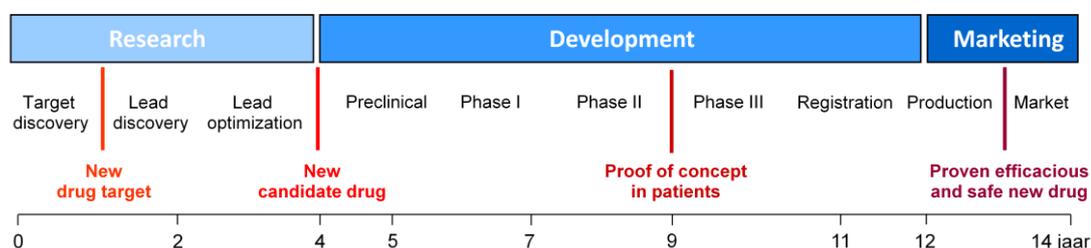
2.1 Stages in the development of a new medicine

There are three phases in the development of a new medicine: the research, development and marketing phases. The research phase is when a new potential medicine is developed. During the development phase, the safety and efficacy of this drug are tested. Once it has been demonstrated that a drug is safe and effective, the European Medicines Agency (EMA) gives permission for the drug to be sold on the European market. We will give a brief description of the three phases.

Research phase

The search for new medicines can be done in several ways. The classical way, phenotype screening, means testing numerous different chemical compounds of low molecular weight on cells or lab animals, looking for a possible therapeutic effect. After that, the biological basis for the effect is investigated. Sometimes this may not be found until many years later. These processes are often trial and error. A therapeutic effect of a substance is often found by accident. There are also various examples of drugs where a side effect became the main effect, such as sildenafil (Viagra) which was originally developed to lower blood pressure.

In addition to these largely trial-and-error methods, target-based pharmacology has also emerged strongly in recent decades (see Figure 1). The basis of the new medicine then comes from fundamental research into processes in the body. This yields knowledge about the specific causes and mechanisms that play a part in certain conditions and which can be a potential drug target. After that an attempt is made to develop a medicine that acts upon this target. This can be done in several ways. For example, large collections of small molecules known as *compound libraries* can be tested for their affinity with a drug target. Computer modeling can also be used to find molecules that can bind to a target. This approach yielded imatinib, for example. This medicine is a small molecule used for chronic lymphatic leukaemia, a type of blood cancer. It inhibits signal transfer within cancerous cells by binding to specific enzymes.



Figuur 1: Moderne, target-based ontwikkeling van nieuwe geneesmiddelen

Bron: Van Gool, 2016

A third biopharmaceutical method is the production of specific proteins: antibodies against the drug target. A receptor can for instance be blocked, which disturbs a signal transfers. The names of this type of biopharmaceuticals end in 'mab' (*monoclonal antibodies*). One example is nivolumab, a drug against cancer.

The first substance that is found to act against the target is called the *lead* compound. This substance is the starting point for further development. The effect must be validated. Changes are made to the chemical compound, attempting to optimise the effectiveness and minimise the side effects. The substance must also be chemically characterised, in detail. Promising products are patented as *new chemical entities* (NCEs). The substance must then be manufactured according to the rules that apply to medicinal products, the Good Manufacturing Practice (GMP) conditions, so that they can be tested on lab animals and humans.

Development phase

Five sub-phases can be distinguished within the development phase: the preclinical phase, the clinical phase (which is further split into phases I, II and III of clinical trials), and the registration phase.

The pharmacology and the acute and chronic toxicity are studied in the *preclinical phase*. These investigations are, among other things, conducted on lab animals. If the results are favourable, the *clinical phase* follows, in which the drug can be tested on humans. It is tested initially on a small number of healthy volunteers to determine the safety and safe dose (*Phase I clinical studies*). If the results are successful, Phase II follows. A distinction is often made between *Phase IIa* and *Phase IIb*. The drug is tested on a small group of patients in Phase IIa and if the results are positive it is often referred to as a *proof of concept*: it has been shown that the drug works or at least appears to work in humans. The drug is tested on a slightly larger group in Phase IIb. The distinction between phases IIa and IIb is mainly of financial importance. A startup often develops a drug and sells it to a larger pharmaceutical company after the proof of concept has been given.

The drug is then tested on an even bigger group of patients (the *Phase III trial*). If this study is also successful, a licence can be requested. As a rule, consultations with the licensing authorities regarding the requirements for those studies will already take place during phases IIa and IIb. When the drug is accepted on the market by the licensing authorities, the manufacturer determines the price; after scaling up production, the product can be released on the market. Moreover, this does not mean that the drug is automatically paid for from the collective healthcare insurance; Acceptance in the insurance package is a separate process: see Section 2.6.

Once the drug is on the market, it is still monitored for any (rare) side effects that were not discovered earlier. This is known as *pharmacovigilance*, *Phase IV research* or *post-marketing surveillance*. This is done by the manufacturer. Additionally, anyone can report side effects to the Lareb Foundation.² This foundation takes care of the national recording and evaluation of side effects and interactions of medicines.

It is important to note that the development of new medicines takes place at an international level. Research into new medicines is done in centres that are spread across the globe. In Phase III, clinical studies of a particular drug are often done in multiple locations around the world at the same time (*multicentre studies*). The financing and patenting discussed below are also done on a global scale. Current legislation for patenting and market approval is regulated almost in its entirety at the European level. The decision taken at the national level is whether or not to reimburse a medicine through the health insurance that is mandatory in the Netherlands.

2.2 Costs of developing medicines

Developing a new medicine costs a lot of money. The actual costs will vary from one medicine to the next. Sometimes the development proceeds quickly, and sometimes there are major, expensive setbacks. Estimates of the average costs of developing a new medicine vary widely, from hundreds of millions of euros to several billion. The Flemish Biotechnology Institute works on the basis of total costs of €900 million. Other calculations give a figure of €2.6 billion for a new medicine. The costs of the research phase are estimated in the first case at €100 million, plus €190 million for the preclinical phase, €475 million for the clinical phase and €135 million for the licensing and so forth. De European Federation of Pharmaceutical Industries and Associations (EFPIA) gave the following percentages of the overall development costs in 2016 for the various phases: preclinical studies 21.2%, phase I clinical trials 8.9%, phase II 10.7% and phase III 28.7%, licensing 5.1%, phase IV 13.7% and other costs 8.9%.

2.3 Patenting new chemical entities

As stated above, it costs a lot of money to develop a new medicine. Investors are only willing to invest large sums if they can earn them back in the longer term (with a profit). This is possible if the medicine is protected by a patent. A patent is a social contract between the patent holder and society at large: in exchange for full publication of the details of the invention, the patent holder is granted a number of rights for a limited timeframe, the patent period. A patent gives the holder the exclusive right (subject to a number of exceptions) to produce, apply, use or trade "*the patented product or method*".³ Rights can be claimed for a period of twenty years after the patent is granted, with (for drugs) a maximum extension of five additional years as a Supplementary Protection Certificate to compensate for the time it takes to get market authorisation. If the drug is tested for paediatric use, another six months may be added.

Anyone may replicate the drug after the patent expires. The investors are expected to have recovered their investments by then. For example, if the development of a drug takes ten years, within a remaining patent period of ten years plus additional protection certificates the investments can be earned back in 15.5 years at most.

2.4 Who does what?

As stated in Section 2.1, new medicines can be developed in various ways. Research and development based on classical development methods (such as phenotype screening as mentioned above) is done almost entirely within the pharmaceutical industry. A number of large pharmaceutical companies have large collections of different low molecular-weight compounds (*compound libraries*) for this.

Target-based pharmacology, based on fundamental research into biological processes, is generally carried out in academic centres and the results are published in scientific journals. This knowledge can lead to potential drug targets being identified. Various parties can proceed from there. A university may make a suitable molecule itself and patent it. The university can then set up a company, a spin-off that develops the drug further. The university can also sell the patent directly to a company that develops the medicine further.

Pharmaceutical companies can also make a new molecule entirely by themselves or in collaboration with universities, and then patent it and develop it further themselves. What often happens in practice is that when a promising new drug target is published in the literature, companies descend upon it and attempt to use it as the basis for developing new medicines. If this is successful, it means that multiple new medicines targeting the same drug target will appear on the market after ten to fifteen years. The compounds often look very similar to each other and work in the same way. A good example of this is ACE inhibitors, a group of medicinal products that lower blood pressure, all looking chemically similar to each other and acting upon the same enzyme, angiotensin I converting enzyme (ACE). In a number of cases, this is because small modifications have been made: a variation of an agent patented by a competitor may also be patentable because it is seen as a new chemical entity. These are then referred to as *me-too* drugs, from the point of view of them being (modified) copies. The medicines are, however, often developed in parallel.

As stated earlier, the biggest cost item for this is clinical trials. As a rule, pharmaceutical companies have these studies performed for them by contract research organisations (CROs). These are commercial companies that specialise in setting up and evaluating clinical trials. Many of these studies are *multicentre trials*, running concurrently in a large number of different countries, not only in the United States and Europe but also for example in India and African countries. Coordination between the various centres is a significant cost item. In addition, hospitals and care providers often ask for money for carrying out clinical trials. This accounts for a quarter of the costs. The costs of recruiting the patients are one third of the overall costs (McGuire 2011). The overall costs are in the region of €100,000 per patient per trial. This means that the Phase III study with 2000 patients costs around €200 million (Schellekens 2016). The paradoxical aspect of this is that the smaller the anticipated effect of a medicine is, the greater the number of patients who have to be included in the study to demonstrate this effect – and the more expensive it becomes.

2.5 Who funds what?

The fundamental research that is carried out by academic centres is partially paid from collective resources (direct governmental funding and other public cash flows) and partly from private resources, for example from companies or health funds (the external cash flow).

As stated earlier, the development of a drug costs many hundreds of millions of euros. This money is provided by investors. Intermediaries select highly promising initiatives and raise funds from investors, such as institutional investors and wealthy private individuals. Given that these are high-risk investments, the investors generally require returns of at least 20%. The money is used for setting up startups for carrying out preclinical and clinical research. If the drug appears to be successful, this is generally sold in Phase II to a large pharmaceuticals company – Big Pharma – because they have the expertise that is needed for licensing and marketing, and because they have a strong enough capital position to fund and organise Phase III studies and the licensing procedure and the marketing, but above all because they are capable of handling the high risk of failure. Where the medicines are for a small market, for instance orphan drugs for which the clinical trials are necessarily smaller (and therefore cheaper), a medium-sized pharmaceuticals company can also take this risk.

2.6 Marketing authorisations, pricing and remunerations

In order to be able to earn back the investments, it is of course important that a medicine must be approved for use on the market worldwide. Decisions about this in the United States are taken by the Food and Drug Administration (FDA). They are taken centrally in Europe for the majority of drugs, with the EMA making the decision (see box). As can be seen from the boxed text, cancer drugs for instance are covered by the European regulations, but medicines against cardiovascular disease are not. These may be licensed selectively in one or more European countries. In the Netherlands, this assessment is made by the Medicines Evaluation Board (MEB).

Medicines that have to be authorised at the European level

European regulation 726/2004 states which medicines are obliged to be licensed at the European level (by the EMA). These have to meet one of the following criteria:

- Products that are developed using one of the following processes: recombinant DNA technology, controlled expression of genes, methods for hybridomas and monoclonal antibodies, and biosimilars that are also developed using one of the above-mentioned processes.
- Products that are in the 'Advanced Therapy Medicinal Product' category (ATMPs); gene therapy, somatic cell therapy, tissue manipulation therapy or a combination thereof.
- Products that focus on one of the following diseases: acquired immune diseases, autoimmune diseases, viral conditions, cancer, neurodegenerative conditions, diabetes.
- Products that have acquired the status of an orphan drug.

The EMA checks whether a medicine is safe and effective. If, in the EMA's opinion, the research data provided means that this is the case, the medicine will be approved for the European market. It should be noted here that the term 'effective' is taken to mean that the medicine in question is not inferior in efficacy to the treatment standard or, in the absence thereof, that it is not less effective than a placebo.

The EMA makes no evaluation of the price of the medicine. A medicine is developed on the free market and the manufacturer is therefore free to set the price level for a medicine. In the Netherlands, the maximum price is legally regulated and set to the average of the prices of the same medicine in the United Kingdom, Germany, Belgium and France.

An authorisation to market the medicine does not mean that it is automatically recompensed in the Netherlands through the mandatory health insurance (the *basic health insurance* package). A distinction has to be made here between *extramural* and *intramural* medicines. Extramural medicines are generally handed over to the patient by an external – public – pharmacy. Intramural medicines are in general used in a hospital in the context of specialist medical treatment. An extramural medicine is recompensed if it has been entered in the GVS (Medicines Reimbursement System). This is a closed system. If the medicine has not been included in the GVS, it will not be reimbursed. Manufacturers can ask the Ministry of Health, Welfare and Sport (VWS) for a medicine to be included in the GVS. The minister decides whether or not to do this on advice from the National Health Care Institute (ZIN).

The system for intramural medicines is open: they are reimbursed if they meet the criteria listed in law, such as being in line with the current state of scientific knowledge and practice, and the requirement that those insured can reasonably expect it. This is subject to the assessment of the parties themselves: professional groups, patients and insurers. There is an exception for extremely expensive medicines. The minister may decide to put these in what is referred to as the lock (in Dutch: *sluis*). This is a legal option for excluding an intramural medicine from the compensated package until the ZIN has assessed it and the VWS ministry has had an opportunity to negotiate about the price. If the negotiations are successful, the medicine will be reimbursed (possibly also with conditions imposed). If not, the product is not included in the package of insured items.

Notes

- 2 <https://www.lareb.nl/>.
- 3 Dutch Patents Act 1995, Article 53, paragraph 1.

3 Problems with the current development pathway and possibilities for improvement

3.1 The current development process is lengthy and costly

The previous section outlined the current development path for a new medicine. One reason given by manufacturers for the high prices of new medicines is that the current development pathway is very lengthy and costly. Development timescales averaging twelve to thirteen years are mentioned (ten years for R&D plus two to three years for administrative procedures) (EFPIA 2016) and costs of €2.6 billion for a new drug (DiMasi et al., 2016). It is a high-risk venture. Many medicines fail to cross the finishing line. Investors therefore expect an appropriate (i.e. high) return on their investments as the reward for the high financial risks.

As stated earlier, at least half the costs and the development time are taken up by clinical studies. The licensing authority requires these studies so that the safety and efficacy of a medicine can be assessed. The strict rules have been set up as a consequence of disasters in the past, such as the thalidomide affair in the nineteen sixties (sold in the Netherlands under the brand name Softenon). This was popular for helping people sleep and as a medicine for morning sickness during pregnancy. Although it was thought to be safe for pregnant women to use, it caused severe birth defects.

3.2 Strict rules do not guarantee good outcomes

As well as allowing side effects to be uncovered, the clinical studies also determine the effectiveness of a medicine. It is important to note that the clinical studies are carried out by the manufacturers themselves or on their behalf. Various studies have shown that trials paid for by the pharmaceuticals industry yield more positive results more often for their products than independently financed ones (Lexchin 2012). A significant proportion – 65% – of clinical research that is carried out in Dutch hospitals is initiated by the pharmaceutical industry (CCMO 2015).

In the past, the licensing authority generally required studies to be carried out as double-blind, randomised controlled trials (RCTs). To ensure that the internal validity was as high as possible, the patients are selected rigorously. Patients who have already been treated with other medicines are generally excluded, as are elderly patients, those who are or could be pregnant, children and patients with multiple morbidity. This means that generalising the outcomes is often dubious, as only a select group have participated in the study. In the advice by the Council for Public Health and Society (RVS) issued as *Zonder context geen bewijs* [No evidence without context] there is a more detailed discussion of inter alia RCTs (RVS 2017a).

It is estimated that only 5% of the patients that care providers see every day in their consulting rooms meet the inclusion criteria of the RCTs that are the basis for marketing authorisation for a new medicine for a frequently occurring condition. This percentage is higher for rare conditions: there are often so few patients, sometimes only a few dozen, that it is not possible to be too choosy.

There are even occasions where virtually all possible patients are in one trial and there are insufficient patients available for a new trial.

The safety of medicines is important, but it is also relative. It is logical that a new medicine against a cancer that is going to cause the death of the patient in the short term, with or without the existing treatment, is subject to lower safety requirements than those imposed on medicines against non-life threatening conditions such as e.g. a sleeping pill for (healthy) pregnant women or a medication for ADHD in children. However, safety in the longer term cannot be determined using the current, relatively short-duration studies. The current licensing procedure only provides superficial certainty for this category of medicines. For instance, children are currently treated for ADHD with amphetamine-like substances, although nobody knows what the consequences in the longer term are. The newspapers recently had banner headlines after a PhD thesis (Schwern 2016) stated that ADHD medication is not harmful in the longer term. This was, however, research carried out among children, adolescents and young adults. The actual effect at older ages will only become known in 30 to 50 years' time. The same applies to prescribing contraceptive pills to adolescents. Although these medicines have been on the market for decades, little or no research has been done into the effects on this specific group of patients. The manufacturer will – justifiably – counter with the argument that these medicines are not intended for these indications or patient groups. The patient information leaflet for contraceptive pills based on desogestrel states for example: "*There is not yet enough information about the use of desogestrel in children and adolescents aged under 18*".⁴

Guidelines are applied flexibly

The licensing authorities are aware of the issues sketched out above and always weigh up the risks and benefits for the patient. In contrast to what manufacturers often claim, the guidelines are applied flexibly in practice. For instance, Hatswell et al. found in a study examining the period 1999-2014 that a considerable proportion of new medicines were allowed onto the market on the basis of single-arm (i.e. non-randomised) studies (Hatswell et al., 2016). These are studies in which all the patients in the trial are treated with the new medicine and the efficacy is determined based on comparisons with historical information, i.e. on the basis of known treatment outcomes. The patient groups are often small, sometimes consisting of just a few dozen people. Examples of products that have been approved by this route are Sovaldi®, a medicine from the company Gilead for treating hepatitis C, and Strimvelis®, a gene therapy medicine from the company GSK for the condition ADA-SCID, a rare and severe congenital immune system disorder.

There is therefore most certainly flexibility in the shape of *adaptive pathways* that examine whether certain categories of medicines can be allowed onto the market via a modified route. This can range from fast-track assessment to limiting or skipping one or more phases from the development pathway. Another development is provisional authorisation for medicines before the licensing authorisation is complete. The EMA then imposes the requirement that the medicine will be followed up via registries in which data about the treatment of patients is included. Manufacturers now set up separate registries for that purpose for their products.

3.3 The current development process is extremely inefficient

By far the largest cost burden in the development of new medicines is the very large number of failures. Only one out of twenty-four *new molecular entities* (NMEs) reaches the finishing line

(Bunnage 2007). According to a recent study that looked at the period 2006-2015, 9.6% of the new medicines that go into Phase I clinical trials ultimately end up being introduced on the market (Thomas et al., 2016). A study in 2004 gave this figure as 11% (Kola and Landis, 2004). It seems therefore as if the success percentage is decreasing. Broken down by the various phases, the success percentages are:

- Phase I to phase II: 63,2%;
- Phase II to phase III: 30,7%;
- Phase III through to submitting an application for marketing authorisation : 58,1%;
- and from submission of an application through to marketing authorisation: 85,3% (Thomas et al. 2016).

This means that more than half of all medicines fall by the wayside during the very costly clinical trials in Phase III, and all the investments that have been made are lost.

These are only averages. The success percentage is higher in some areas. The overall chance of success is 20% for drugs for cardiovascular conditions, whereas the figure for neurodegenerative conditions is just 8%. The success percentage in the period 2002-2012 for medicines against Alzheimer's disease was 0.4%. In addition, the few medicines that did reach the market were not very effective. They only slowed the course of the disease down to a small extent. This also applies for many of the new and costly medicines against cancer, which often only prolong life by a few months.

The costs of all the misfires are ultimately set off in the price of new medicines that do get licensed and authorised for the market. This happens largely indirectly because investors demand high returns on their investments because of the high likelihood of failure.

This raises the question of why so many medicines fail. Various causes for this can be discerned. A key factor is the fact that there is a distinct lack of knowledge about the causes of diseases and knowledge about the exact working mechanisms and the potential side effects of new medicines. Risk factors are often known, but the underlying mechanisms of disease are unknown (Gregori-Pujané et al. 2012; Bowes et al. 2012). Attempts are made to unravel these issues using animal models, usually mice. However, these animal models often turn out not to be very good models of the disease process in humans. Drug targets found in mice often turn out not to be valid in humans. Many medicines that work in mice turn out not to work in humans or to be too toxic.

Why is the laboratory mouse such a poor predictor? Is it because mice are too far removed from humans, from an evolutionary point of view, or are mice under laboratory conditions too far removed from humans? Various researchers believe that the latter is the case. Lab mice – and laboratory animals in general are kept in highly artificial circumstances that are very different from the natural surroundings. Specially bred lab mice that for example develop tumours spontaneously are also very different from the way diseases and conditions develop 'naturally'.

The question that then rises is why the academic world is working with the 'wrong' animal models. A key reason for this is the reductionist approach. In order to unravel a biological mechanism, that mechanism is interfered with while keeping all other conditions as constant as possible. This is often done nowadays using 'knock-out' mice. If it is suspected that a particular protein plays a part in a given biological mechanism – a *biological pathway* – then the gene that codes for that protein can be

disabled ('knocked out'). The effects that then occur in the mouse can help clarify the working mechanism. In order to keep the other conditions as consistent as possible, the experiments are carried out using mice that are genetically as similar as possible, that are kept in identical laboratory conditions, with the same food and so forth. Mice are bred that exhibit symptoms that appear similar to conditions in humans. For instance, genetic studies in humans showed a link between Gilles de la Tourette syndrome and the *SLITRK1* gene. These results were published in a respected journal (Abelson et al., 2005). A knock-out mouse was then created in which this gene was disabled. The mouse then exhibited behaviour that looked as if it was obsessive-compulsive (Schmelkov et al., 2010). In addition to this *Tourette-like* mouse, there are also *Parkinson-like* and *Alzheimer-like* mice and others. Potential medicines against these conditions are tested using these mouse models, with people often forgetting that only disease-'like' mouse models are involved, without it being clear whether this mouse is a good model.

There are numerous other examples of animal models with major question marks hanging over them. One example is the EAE mouse. Mice do not spontaneously develop multiple sclerosis (MS), but it is possible to create a condition with a similar clinical picture in mice, namely Experimental Autoimmune Encephalomyelitis (EAE). It is a highly artificial model that – amazingly – ultimately has yielded successful treatments for patients with relapse-remitting MS. It has however also yielded numerous drugs that appeared promising in the EAE mouse but did not work in patients, or even exacerbated the condition ('t Hart 2015).

Another important factor is the market mechanism. Both academic research institutions – particularly if held to account for the value they add – and companies carry out research behind closed doors. After all, once findings are published they can no longer be patented. Multiple parties will often descend upon a particular drug target as soon as it becomes 'hot'. A great deal of research into suitable molecules is then replicated. Given that the majority fail, a lot of money is wasted.

But even when a drug is patented and the invention is published, a large proportion still fall by the wayside during the clinical phases. Pharmaceuticals companies are of course perfectly aware of this. Given the extremely high costs of clinical research, it might be expected that these companies would do everything possible to improve the situation. After all, if a company was able to improve the probability of success, it would generate a considerable competitive advantage – as well as profits. Nevertheless, this does not happen in practice.

One possible explanation for this is that the high failure rates are in fact the very source of the position of power enjoyed by large pharmaceutical companies. Thanks to their size, they are the only companies capable of taking on such financial risks, calculating in the substantial risk of failures and demanding high prices. Within the current system, with a monopoly that is based on patents, they can charge the costs of the large number of failures through to the customers (the patient or insured party or society, as the case may be), thereby still achieving generous profit margins. The pharmaceuticals industry, compared with other sectors, is consistently in the top three in terms of profitability (Forbes 2015), with an average return of over 20%.

The ethical aspect

The problem outlined above also has a significant ethical aspect. A lot of work is duplicated. This means that a lot of clinical studies, largely in the form of RCTs, are done that are not actually

necessary. Patients who submit to this voluntarily are thus being exposed to unnecessary risks. They are also not able – taking the group as a whole – to benefit from any positive results. After all, these are kept confidential. The only ones who benefit from the RCT are those in the group that are given the new drug, and only then if it is successful. All the others do not benefit. In addition, the people who were benefiting from a new drug do not receive it any longer once an RCT is completed, as they only get the drug during the clinical trial and then have to wait until it gets licensed. And once the drug does come onto the market, there is still the question of whether it will be reimbursed through the basic health insurance.

The market mechanism is not the only source of waste. Things go wrong in the academic world as well at times. In 2005, Ioannidis published an article entitled *Why most research findings are false*. In that article, which caused a great deal of fuss, he demonstrated that the majority of published research results were incorrect (Ioannidis 2005). Macleod et al. stated in an article in the *Lancet* in 2014 that they estimated that 85% of the billions of dollars and euros expended annually on biomedical research, including clinical research, is wasted (McLeod et al., 2014).

3.4 Pricing in a monopolistic market

The high development costs for new medicines – which cover the costs of drugs that fail, plus a monopoly based on patents, high marketing expenditure and generous margins – lead to what are sometimes very high prices. This does not yet automatically mean that lower development costs will lead to lower prices.

In a competitive market, the price of a product is related to the development and production costs. However, the market for new drugs is monopolistic in nature because the medicines are protected by patents. In a monopolistic market, the price of a medicine is determined by what the customer is prepared to pay for it – their *willingness to pay*, or *value-based pricing*. The insurance principle used in healthcare means that the *willingness to pay* is the result of a complex process of regulation plus political and administrative decision-making.

For rare conditions, this monopoly on medicines is strongly exacerbated by the European regulations that came into force in 2000 for orphan drugs. These are medications for conditions that occur in the European Union in less than five out of every 10,000 inhabitants. In addition to protection by patents, a company has additional protection such as ten years' market exclusivity after licensing. This means that no medicines based on the same mechanism of operation for the disease in question may be put on the market during that period.⁵ The regulation has strongly encouraged the development of new orphan drugs. It has however also had the perverse effect of medicines being investigated and licensed for narrow and restricted indications in order to obtain the status of an orphan drug, while the study results indicate that its efficacy is broader. A reduction in price would then be the consequence of this broadening of the indication, but that does not happen. In order to encourage this, price versus volume agreements have been made in a number of countries, such as France. The EMA no longer gives a medicine the status of an orphan drug so quickly.

An important effect in the pricing in a monopoly-based market are the guide-line price levels known as *anchor prices*. These are prices that are seen as a 'normal' price at a given moment and are

accepted without much discussion by customers, i.e. political circles and society. There is a discussion in the first instance, such as the discussions in the past about Taxol and Herceptin, but once the political world agrees, the new price level is accepted without many difficulties.

The phenomenon of anchor prices is clearly visible in medicines that are based on the same mechanism of operation. When the first *me-too* products appear, the price level of the original medicine is retained. If the new medicine is or appears to be more effective, it will even be offered at a higher price. This is despite the fact that a manufacturer generally has lower development costs for a *me-too* medicine. It is a law of economics that in an oligopoly market – one in which there are only a small number of providers of the product – the providers will adjust their prices to match each other even if (prohibited) agreements to that effect are not being made. The pharmaceutical markets and sub-markets for new medicines are oligopolies, particularly after the major mergers and takeovers in the past. This does not mean that competition is entirely absent, but that it is principally driven by marketing instruments – getting the medicine familiar to the doctor's pen – rather than by the price. A lot of money is therefore spent on marketing in this sector.

For innovative companies who put an entirely new medicine according to a new mechanism of operation onto the market, it is frustrating to see that competitors can then jump on the gravy train of their success and make much more profit from it. Extra strict requirements are imposed on any entirely new type of medicine. A great deal of expensive research has to be done. These are also the companies that have to put in a great deal of effort and expense to achieve new, higher *anchor prices*. They have to sort out all the teething problems for manufacturers who later market a similar product.

We should note that the issue raised is generally not about ill will or malice on the part of individual companies. In a capitalist system, pharmaceuticals companies – like any other – are ultimately forced by their shareholders to maximise returns. A company that does not charge high prices will be taken over, voluntarily or otherwise, and the new investor will maximise the returns. This phenomenon is occurring more and more often. One example is the takeover in 2011 of Pharmasset by Gilead for \$11.2 billion. The drug Harvoni that was developed by Pharmasset generated sales worldwide of \$15.3 billion in the year that it was introduced.

The phenomenon of guideline prices also works backwards down the 'pharmaceutical tree'. Promising products made by startups are acquired by Big Pharma on the basis of turnover expectations, which are in turn derived from the achievable market prices or anchor prices. Original patent holders such as universities attempt in turn to sell patents to startups for the highest possible price. The final result is that there is no longer any relationship between the price of a new medicine and the development costs. A good example is the drug acalabrutinib for treating certain forms of leukaemia and lymphomas. It was developed by a small Dutch startup called Acerta Pharma, whose participating interests included the Brabantse Ontwikkelingsmaatschappij [Brabant Development Company]. The pharmaceuticals concern AstraZeneca acquired a majority interest in the company in 2015 for the sum of €4 billion, with an option on the remaining shares for €3 billion when the drug receives marketing authorisation, which is expected to be in 2018.⁶ The readiness to pay a total of €7 billion is based on the turnover that they expect to achieve at a specific price. A drug that resembles acalabrutinib, ibrutinib for treating chronic lymphatic leukaemia, costs €70,000 per year. In 2016, the minister put this drug into the 'safe' and the National Healthcare Institute advised the Minister

on 8 June 2017 at the medicine should only be included in the package for a specific group of patients.⁷ Given that acalabrutinib seems to be more effective than ibrutinib and has fewer side effects, it may be expected that it will command a higher price.

3.5 Possibilities for improvement

The issues that we outlined in the previous section suggest approaches for efficiency improvements in the development process. We will list a number of these here.

Natural animal and other models and reverse translation

Various aspects of the use of animal models could be improved. First of all, there is the question of whether an animal model is in fact always needed. We are seeing a development in practice in which human cell lines and artificial organ systems such as organoids are being used increasingly often. Effort is being put into *next-generation* technologies such as *genomics*, *transcriptomics*, *metabolomics*, *epigenomics* and *microbiomics* in order to understand the biological processes better. This is certainly a step forwards in the search for drug targets and leads. However, they remain reductionist approaches that are indeed needed initially, but which are still a long way removed from humans as complex organisms interacting with their surroundings. Potential medicines will therefore always still have to be tested on a complete organism.

One possible solution is offered by 'natural' models, in animals or otherwise, such as test animals that naturally develop conditions that are very similar to those of humans, instead of selectively bred laboratory mice. One example that could be mentioned is the Ossabaw hog. This breed of pig, named after the island of Ossabaw in Georgia in the United States, is highly susceptible to obesity and then exhibits a metabolic syndrome with insulin resistance, glucose intolerance and so forth: it develops type 2 diabetes. Another way of improving the validity of animal models is to study why medicines that turn out not to work during the clinical phases did work in the animal models. If the reason for this can be determined, that knowledge can be used to improve the animal model. Research such as this, which is also known as *reverse translation*, is not very popular. Researchers like to investigate things that can yield positive results, such as new breakthrough medicines.

Biomarkers for validating animal and other models

The term biomarker is used generally for any clinical feature, often biochemical in nature, that is correlated with a condition. Elevated glyHb or HbA1c concentrations in the blood are for example a biomarker for diabetes. Biomarkers are increasingly being adopted in the treatment of specific groups of patients (*personalised medicine*). Biomarkers allow precision medication to be administered, for example Herceptin in HER2-positive breast cancer.

The purpose of these biomarkers is to make better predictions about the outcomes of treatments in specific patients or groups of patients. In order to improve the probability of success for a new medicine, it is also extremely important to investigate biomarkers for validating the animal model that was used. Checks must be made to see if the biomarkers for a condition in humans match those in the animal model. The reverse also needs to be checked: if biomarkers are found in the animal model, they also need to be demonstrated in human patients. If not, the way the disease progresses is clearly different and the model may not be suitable; further research is required.

Drug rediscovery

Humans are of course the best experimental model for conditions that affect humans. Existing medicines that have proved safe sometimes transpire in practice to have unexpected useful side-effects that are discovered by chance, such as the healing effect of the antihypertensive propranolol in haemangiomas. The major benefit of these examples of *drug rediscovery* is that they involve existing medicines for which a great deal is already known about the safety, posology and side-effects. It only has to be tried out with a new group of patients. This sounds easier than it is, because it turns out to be difficult to find funding for such research in practice. Companies are generally not interested because it concerns existing medicines for which the patent has often already expired. There are occasions when a company is interested. An existing medicine can be licensed for a new indication. That costs money, but the company can impose a higher price, because unlicensed prescribing of the drug is no longer allowed once it is authorised for the indication. The patent for the antifungal ketoconazole expired thirty years ago. However, it turns out also to work in Cushing's disease. The company Laboratoire HRA Pharma registered it for this indication and raised the price by a factor of ten with respect to the original price.

Do-it-yourself medicine

An important development in this regard is that patients are increasingly taking matters into their own hands and starting experimenting with existing medicines that may possibly be effective for other indications, cancer in particular. The Internet is an important source of information for this. A well-known example from the pre-Internet age is Ben Williams, an American emeritus professor of psychology who was diagnosed with a glioblastoma multiforme brain tumour. The average length of survival after diagnosis is fifteen months. After studying the results of scientific research, he put together his own cocktail of medicines. He is still alive over twenty years later. Other patients have copied his strategy (Akst 2013; Williams 2017).

Tales abound on the Internet about similar 'wonder cures'. It is understandable that these may be taken with a pinch of salt, but it remains a fact that patients are able to use the Internet for instance to see (possible) *drug rediscovery* results and they are experimenting increasingly often. Care providers do not generally want to work along with this, which means that patients are forced to use the illegal circuit. This is an undesirable situation. The solution is to bring such experiments into the regular care fold, in the form of clinical trials and by offering supervision and assistance. It might then progress to become a valuable alternative development model. The costs of these trials can be kept very low. These are after all existing and often very cheap medicines. The Netherlands could take a pioneering role in this.

Public availability of clinical research data

The belief that the results of clinical research should be made publicly available enjoys broad support (not traceable back to individual patients, naturally). The methods used, the data and the analyses can then be checked by anyone afterwards. The EMA agrees with these opinions and, since 20 October 2016, has been publishing all clinical research data within 60 days of a new medicine being authorised for the market or rejected.

Publication after the clinical research is completed does not solve the problem of duplicated work mentioned above, though. All research with medicines in Europe does have to be registered in the EudraCT database⁸, but this register is confidential and only accessible to the competent authorities

of the various member states. The core data of clinical research within the EU is publicly available via the EU Clinical Trials Register, though. During the clinical phases, which can last a number of years, a lot of information therefore remains confidential. To prevent double work, it is desirable that information about clinical research should be available for everyone from the very beginning. This allows an open discussion about e.g. the trial design and aspects may come to the fore that the evaluating and supervisory agencies may have overlooked. Particularly for reducing the change of failure during clinical research projects, a discussion about the validity of the results of the preclinical studies of the animal and other models used is essential. Interim reports during clinical research are also important, as they can for example be the first indication of possible problems in the process later on. The researchers who are involved may miss these signals, but publication of the data increases the likelihood of them being picked up and measures being taken in good time. In the extreme case, this can mean that a project will be terminated early, saving a great deal of time and money. The above means that the entire research process has to be transparent.

No financial links between researchers and financiers/the pharmaceutical industry

Disclosure alone is not enough. The results can still contain biases that are very difficult to detect. Patients have the right to independent research. The researchers must not have any interest in a particular study outcome. It must be separate from the researchers who developed the medicine. It also means that there should not be any direct financial relationship between the people conducting the research and those who finance it, the pharmaceutical industry. A similar type of disconnection is incidentally also desirable in the case of e.g. patenting agencies. These organisations currently finance 'themselves' from fees paid by patent holders and so have a vested interest in granting as many patents as possible.

In addition, patients who have taken part in a clinical trial and benefit from a new drug ought to be able to keep receiving that drug after the study is terminated.

3.6 Alternative development models

The problems within the current system of medicine development have led to ideas and initiatives for alternative development models. Initiatives within the Netherlands are for example Cinderella Therapeutics, Fair Medicine and my Tomorrows and the Netherlands Antibiotic Development Platform (NADP). These initiatives and a number of ideas are described further in Appendix 2. Many of these initiatives demand an international approach that can be difficult to realise, particularly in the short or medium term. However, a number of them present opportunities, particularly the Dutch ones mentioned earlier.

3.7 Summary conclusion

This chapter has described a number of problems as well as debunking a number of myths. The regulations turn out to be more flexible than is often claimed, for instance. The statement that medicines are pricey – sometimes extremely so – because the development costs are so high does not hold water. The price that the manufacturer demands is related less to the development costs and more to what the customer is prepared to pay. The high likelihood of failure during the development is often seen as a *fait accompli*, but there are in fact various possibilities for reducing that risk.

Notes

- 4 PIL for desogestrel 0.075 mg, Teva film-coated tablets, 7 Dec 2015, db.cbg-med.nl/Bijsluiters/h111004.pdf.
- 5 http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000393.jsp&mid=WC0b01ac058061f017.
- 6 <https://en.wikipedia.org/wiki/Acalabrutinib>.
- 7 Care package advice for ibrutinib (Imbravica®) 8 June 2017, reference 2017023606.
- 8 EudraCT database (2017) eudract.ema.europa.eu/eudract-web/index.faces.

4 Solution directions

4.1 Introduction

In the previous chapter we discussed the problems with the current way of developing new medicines that are expressed as or are the underlying causes of the questions that the minister asked the Council and for which solutions are badly needed. For the governmental authorities, the most urgent problem is the high prices – often very high – of new medicines, which are endangering the affordability of care.

The key problem is that there is no relationship (or there is no longer one) between the development costs and the high – sometimes very high – price. This means that a decrease in development costs, for example by reducing the risk of failure or accelerating the development and authorisation for marketing will not necessarily result in lower costs. That does have to be tackled, but more than that is needed. The minister's observation that it is practically impossible for small companies to bring a medicine onto the market independently shows that the barrier for new entrants on the market is too high, which obstructs competition. In addition, she has specifically asked the Council for Public Health and Society which areas non-commercial drug development would be desirable in.

This means that answers have to be found for the following questions:

- How can the high (and very high) prices be reined in?
- How can the chance of a development project failing be reduced?
- How can the development process be made quicker?
- How can we create room for smaller companies (Dutch in particular) to get medicine onto the market independently?
- In what areas is non-commercial drug development desirable?

We will outline some directions that the solutions could take in this chapter. These require efforts from a variety of parties: not only from the authorities but also from e.g. research institutions, care providers, care insurers and patients.

4.2 Reining in the high and very high prices

European regulations must be updated

The authorities grant a company a monopoly on an invention, in the form of patent rights. Many experts believe, particularly in the case of medicines, that the method used for encouraging innovation (the patents system) creates more trouble than it resolves. They make the case, based on the interests of public health, for excluding medicines from patenting. This was incidentally the case until recently in various countries, such as Brazil and India. This only came to an end when the international TRIPS Agreement (Agreement on Trade-Related Aspects of Intellectual Property Rights) came into effect on 1 January 1995. That treaty originated in initiatives in the early 1980s by Edmund Pratt, CEO of the American pharmaceuticals company Pfizer, and John Opel, CEO of the computer company IBM. The TRIPS Agreement and national patent legislation give countries options for tackling misuse of patents, for instance through compulsory licences. Countries are

however extremely reluctant to use such measures because of the fear of trade repercussions (Boulet et al. 2003).

If medicines are excluded from patenting, alternative public sources of funding will be needed. Appendix 2 of these recommendations describes a number of development models that present such alternatives. However, the Council for Public Health and Society believes that it is not feasible given the current international power relationships – certainly not in the short or medium term – to exclude medicines from patenting worldwide and to develop new medicines using only public resources and get them on the market. It is important though that the problems with the current patents systems should be put on the international agenda, for instance as the Netherlands did when it had the presidency of the EU in 2016. The additional protection certificates can be given as an example. The regulations for orphan drugs and authorisation for the European and other markets need amending. Specifically, the problems associated with data exclusivity are one such issue. During its EU presidency, the Netherlands already took the initiative in this area. It is important that these efforts are maintained; they are something for the long run.

The authorities must represent the interests of society and of individuals by using legal instruments

The tasks of the authorities include keeping healthcare affordable. According to Article 22 of the Constitution, the government must promote public health. This means that it must exclude excessively expensive medicines – drugs for which the price demanded is unacceptable for society – from the insurance packages. At the same time, it must not deny any individual patient a life-saving treatment. The authorities must use every available legal possibility to that end. In the case of medicinal products, these are primarily instruments of international regulation. These tools are:

- compulsory licences;
- encouragement of pharmacy preparations;
- allowing patients, on a doctor's prescription, to purchase medicinal products abroad for their own use (for example via the Internet) and have them delivered in the Netherlands;
- tackling abuse of positions of power.

1 Compulsory licences

Article 8 of the TRIP Agreement expressly allows measures that protect public health and Article 31 creates the possibility of issuing compulsory licences. The Dutch Patents Act also offers such an opportunity. Granting compulsory licences means that other companies are allowed to make the patented medicines and put it on the market in the Netherlands. This creates competition, which will make prices drop.

When compulsory licences are issued, there is a requirement though that the authorities must observe the boundaries set by the Paris Convention and the TRIPS Agreement in particular, which give fairly detailed limits for issuing compulsory licences.

The requirements include among others:

- that the law must allow for the possibility of compulsory licences;
- that permission to use the patented invention must be examined on a case-by-case basis;
- that the scope and duration of that use must be limited to the purposes for which the licence is issued;
- that such use may not be exclusive;

- that such use is non-transferable, except together with that part of the business or goodwill that has the right of use;
- that the holder of the original right is paid sufficient remuneration, given the circumstances of the case.

It is interesting in this context to note that Belgian law has not based the possibility of compulsory licences for medicinal products on articles 8 and 31 of the TRIPS Agreement but on articles 8 and 30. Article 30 states: “Members may provide limited exceptions to the exclusive rights conferred by a patent, provided that such exceptions do not unreasonably conflict with a normal exploitation of the patent and do not unreasonably prejudice the legitimate interests of the patent owner, taking account of the legitimate interests of third parties”. The reason for circumventing Article 31 is to avoid having to comply with all the requirements in that article. To date, Belgium has not issued any compulsory licences for medicinal products.

The Patents Act (ROW) already allows for the possibility of a ministerial order granting a licence “if it is in the general interest [...], for precisely described content [...] that is subject to a patent” (Article 57 paragraph 1). It may be assumed that the interpretation of ‘general interest’ is wide-ranging and can extend to public health interests.

As yet, it is the Minister of Economic Affairs who would issue the compulsory licence. The Council would like to emphasise the point that the authorisation to issue a compulsory licence based on public health interests should reside with the minister who is responsible for public health.

Countries are often reluctant to issue compulsory licences, partly out of fear of economic reprisals and partly out of ignorance. As regards the economic reprisals: when Thailand granted compulsory licences for the period 2006-2007 for two HIV inhibitors and the anticoagulant clopidogrel (Plavix®), the United States Trade Representative (USTR) – a governmental body that advises the president of the United States about trade relations – threatened to cancel a trade agreement with the country (Food & Drug Letter 2007). There is often conflict within a country between the ministers or ministries of trade and health, given that the trade ministry has to issue the compulsory licences and may have to face reprisals, whereas the benefits in the form of lower prices for medicines are reaped by the health ministry (Agarwal and Agarwal 2016).

As regards the ignorance within countries: the World Trade Organization (WTO) has drawn up a Q&A specifically for medicinal products (WTO 2017a). This states the countries are free to determine the ground for issuing compulsory licences, based on the Doha Declaration on TRIPS and Public Health of 2001 (WTO 2017b). The WTO says:

“The separate Doha Declaration explained

First, it emphasizes that the TRIPS Agreement does not and should not prevent WTO members governments from taking measures to protect public health. It reaffirms the members’ rights to use fully the provisions of the TRIPS Agreement, which provide flexibility for this purpose.

These important statements are a signal from all WTO members: they will not try to prevent each other from using these provisions.

Second, the declaration makes it clear that the TRIPS Agreement should be interpreted and implemented in a manner that supports WTO members' right to protect public health and, in particular, to promote access to medicines for all".

The above states clearly that countries are entitled for protect their public health interests and that they may make medicinal products widely accessible. The WTO is clear about intimidation: countries may not obstruct other WTO members in exercising this right. This means that if they do, it can be notified to the WTO and sanctions can be imposed on the country in question.

Other international organisations also champion compulsory licences

United Nations

The United Nations Secretary-General's High-Level Panel on Access to Medicine also champions the use of compulsory licences in the interests of public health in its 2016 report *Promoting innovation and access to health technologies*: "Governments should adopt and implement legislation that facilitates the issuance of compulsory licenses. Such legislation must be designed to effectuate quick, fair, predictable and implementable compulsory licenses for legitimate public health needs, and particularly with regards to essential medicines. The use of compulsory licensing must be based on the provisions based in the Doha Declaration and the grounds for the issuance of compulsory licenses left to the discretion of governments" (United Nations Secretary-General's High-Level Panel on Access to Medicine (2017)).

Compulsory licences actually issued

The majority of compulsory licences for medicines were issued in the period 2001-2006 by developing countries and countries with a low per capita income, such as Brazil, South Africa, Malaysia, Zimbabwe, Mozambique and Zambia for medicines against HIV/aids (Beall and Kuhn 2012).

Threatening with compulsory licences is often enough to get a company to concede to an acceptable negotiating result. It is not known how often this happens, because negotiations with pharmaceutical companies are usually secret. Nevertheless, a number of cases have become known. For instance, the USA threatened the German company Bayer in 2001 with a compulsory licence for the drug ciprofloxacin (Cipro®). Because of attacks involving anthrax bacteria, the USA wanted to create a stockpile of this drug. In the end, Bayer lowered the price of the drug drastically. Indonesia, India, Vietnam and South Korea threatened Roche with compulsory licences for the drug oseltamivir (Tamiflu®) in the period 2003-2006. The result was that Roche agreed that it would help partners in those countries produce sufficient stocks of the drug to tackle the Asian flu virus (Reichman 2009). For the same drug, the USA reached an agreement with Roche in 2005 that the company would build factories in the USA to produce it, so that the country would have access to the drug in the event of a flu epidemic (Love 2007).

European countries have also resorted to compulsory licences. For instance, Italy granted compulsory licences in 2005 on the grounds that Merck had been misusing its position of strength in the market for a number of antibiotics containing the active compounds imipenem and cilastin, and in 2006 against Glaxo for its refusal to provide a licence for sumatriptan for treating migraines. In 2007 Italy demanded that Merck should issue licences free of charge for finasteride, a drug against (inter alia) prostate cancer. France imposed compulsory licences in 2004 for diagnostic tests for breast cancer based on French law, which allows compulsory licences when medicinal products are insufficiently available for the populace or only available at unacceptably high prices (Love 2007).

Calls have recently been made in various European countries for compulsory licences to be used as a tool. For instance, the Irish doctors' organisation asked its government earlier this year to issue a compulsory licence for sofosbuvir, a drug against hepatitis C.⁹ In the Netherlands, 't Hoen et al. pleaded the case in 2016 in the journal NRC for the use of compulsory licences ('t Hoen et al. 2016).

OECD

The Organisation for Economic Co-operation and Development (OECD) stated in its recent report *Key Findings of the 2017 analytical report on sustainable access to innovative therapies* (OECD 2017)²² that it is unethical to withhold effective medicinal products from patients. If price negotiations fail, the report gives pricing measures and compulsory licences as possible options. These instruments must not be deployed randomly. Clear criteria must be drawn up in advance, for instance in the form of limits for cost-efficiency and budgetary impact. This requirement has been met in the Netherlands; the National Health Care Institute has drawn up clear criteria for the purpose.¹⁰

It should be noted for the sake of clarity that a single compulsory licence is not sufficient in the majority of cases. A new medicine is generally protected by several patents, often in the dozens. This is also referred to as the 'patent wall'. Companies try to make it as difficult as possible for potential competitors in all sorts of ways. The European Commission is investigating this.¹¹ Other instruments are sometimes also used for this, such as signing contracts with suppliers of active pharmaceutical ingredients, requiring that the company is the only buyer and that it cannot be supplied to other parties.

A medicine that is produced under a compulsory licence must – like any other generic medicine – be authorised in the EU and it is also possible in this case that data exclusivity can be an obstacle, as could any status that the original medicine has as an orphan drug. Other companies are therefore not likely to ask for market authorisation and production exclusively for the Netherlands. However, if a generic version is already available elsewhere in the world, the barrier is lower.

2 Encouraging pharmacy preparation

If a pharmacist prepares a medicine on prescription for immediate use by an individual patient (known as extemporaneous or pharmacy preparation), any patent on the medicine does not apply. This situation also does not require a licence and marketing authorisation under the Medicines Act (Article 40 paragraph 3 sub a).¹² The exemption also applies for keeping stocks of a medicine and importing it (exemption to the stipulation in Article 40 paragraph 2). The deciding factor is always the small scale, which is a consequence of the provisions in European directive 2001/83/EC: the medicinal products must be destined for being directly provided – to the pharmacy's customers. Supply to non-customers or forwarding to other pharmacies is not allowed.

The knowledge required for preparing medicines in the pharmacy is available in abundance in the Netherlands. In 2015, preparations were made according to the directives and instructions of the professional organisation KNMP (Royal Dutch Society for the Advancement of Pharmacy) in hundreds of pharmacies (Foundation for Pharmaceutical Statistics 2016). New technology can be utilised here in the future too, such as 3D printing, allowing medicines to be produced that are tailored to the patient (Mearian 2016). This is small-scale preparation in its optimum form.

Pharmacy preparation is suitable for medicines that a pharmacist can reasonably prepare themselves, for example because the raw materials are commercially available or because a raw material only requires simple chemical treatment. Facilities are already available in the Netherlands to allow the quality of the end product to be determined, for example the Laboratorium Nederlandse Apothekers (Dutch Pharmacists' Laboratory).

There was recently a furore about the high price of the drug Orkambi® for treating cystic fibrosis. The drug, a combination of the substances ivacaftor and lumacaftor for treating cystic fibrosis, was not authorised for the mandatory health insurance package because the manufacturer was demanding an excessive price and the pricing negotiations had failed (Parliamentary records, 2016/2017). The two active ingredients, ivacaftor and lumacaftor, are both easy to order via the Internet from China. On the alibaba.com website, more than twenty companies offer ivacaftor¹³ and five or so companies offer lumacaftor¹⁵. In 2016, the Indian patent office rejected a patent request for lumacaftor¹⁴ (PMLive 2016). It is not inconceivable that a generic variant of the drug will be available within the foreseeable future on the Indian market. A Dutch pharmacy would be allowed to import the drug for its own patients. Although pharmacists have this right in law, they do not dare to exercise it out of fear of legal reprisals by manufacturers. This did actually happen in the past to a pharmacist from The Hague (Van den Brink and Van der Parre 2012).¹⁵ It is not inconceivable that an individual pharmacist who actually does make a pharmacy preparation of a patented drug could be kept tied up in legal procedures by the patent owner company until bankrupt, in order to scare off others. If the authorities genuinely want to be able to use this tool in practice, they will have to protect pharmacists against such tactics.

A key point here is that the so-called pharmacist's exemption has not been (or not yet) included explicitly in the Patents Act, as a result of which pharmacists are particularly cautious about making pharmacy preparations of patented drugs. Many other European countries do have this exception in their patent legislation. In 2012, the Netherlands signed the *European Agreement on a Unified Patent Court*. It follows from that agreement that the Patents Act of 1995 needs to be amended, inter alia so that the pharmacists' exemption is stated explicitly. A bill amending the Patents Act has in the meantime been drawn up that includes the pharmacists' exemption (Article 54d paragraph e).¹⁶ The Council believes that this bill should be dealt with quickly. At the same time, this could be an opportunity to give the authorisation for imposing compulsory licences as a result of public health interests to the minister responsible for public health.

3 Allowing patients, on a doctor's prescription, to purchase medicinal products abroad for their own use (for example via the Internet) and have them delivered in the Netherlands

Patients may source medicines for their own use abroad, but they have to bring them in across the border in person (Article 18 paragraph 6 sub a).¹⁷ They may not order medicines abroad, for example via the Internet, and then have them delivered in the Netherlands

In March 2017, the Italian minister of public health allowed patients and their doctors to source medicines from other countries for personal use if patients have no access in Italy to those drugs because of restrictive prescribing criteria or because they are too expensive for the patient (Bocci 2017). Patients are also allowed to do this in Switzerland, where a number of health insurers even reimburse such purchases.

As stated in the previous section, pharmacists in the Netherlands are already allowed to do this, but the patient depends on the goodwill of the pharmacist. This issue can be resolved by giving the patients the right to use a prescription from their doctor to purchase medicinal products themselves abroad, for example via the Internet, and then have them delivered in the Netherlands. Under Article 18 paragraph 4 of the Medicines Act, this can be implemented by ministerial order.

4 *Tackling abuse of positions of power*

Misusing positions of economic power is forbidden. Article 102 of the European Union's own *Treaty on the Functioning of the European Union* forbids misuse of a dominant position. Based on the Dutch Competitive Trading Act, the Netherlands Authority for Consumers and Markets (ACM) can take action against abuses of positions of economic power. If a company is guilty of this, the ACM can impose fines that can be as high as 10% of the company's net annual turnover.

Patients themselves becomes buyers and/or preparers of medicines

A very different direction in which solutions can be sought, which is entirely separate from the authorities, is that a patient or group of patients takes action themselves. Some new medicines are available much more cheaply elsewhere in the world. This applies for instance for Truvada®, a drug that reduces the risk of HIV infection. In the United Kingdom, the drug costs 400 pounds per month, whereas a generic version in India costs 40 pounds. The drug is bought a lot via the Internet from India and Swaziland. The number of new HIV infections in London went down 40% in 2016 compared with the previous year. It is suspected that this is because of the mass purchasing of the cheap generic drug via the Internet (Wilson 2017).

Based on Article 18 of the Medicines Act, it is currently forbidden to import medicinal products without an authorisation, and based on Article 67a it is forbidden to offer medicinal products remotely, but both these prohibitions are difficult to enforce. For a number of medicines, it is possible that illegal production in the Netherlands could occur, along the lines seen for party drugs. In some situations, the patients could even prepare their own medicines. The quality of these kinds of illegal medicines is not known and it could endanger the health of patients.

Allowing patients to purchase medicines for their own personal use via the Internet when backed up by a doctor's prescription, as proposed earlier, will drastically reduce the probability of patients resorting to the illegal circuit. In situations where patients do take that step, facilities should be made available at which the patients can have the quality of their medicines tested anonymously, just as is currently done with hard drugs at e.g. the Jellinek clinic.¹⁸

Negotiate when medicines have a major budgetary impact

Notwithstanding the above, the authorities must always negotiate with companies to achieve lower prices if the drugs concerned have a major impact on the budget. In many cases, several similar drugs may be available or in the pipeline. As stated earlier, the marketing is one of the tools that companies deploy competitively. Pharmaceutical companies expend over 22% of their turnover on marketing. This is of course reflected in the pricing. For medicines that have a major budgetary impact, the authorities can select a single drug from the various alternatives through a tendering process. Companies can then tender at a lower price because the marketing costs are eliminated: the pre-scribers no longer have to be convinced. For society at large, this means that the drug

becomes substantially cheaper. One consequence is that the freedom of choice of the prescriber is limited, though. For drugs that are therapeutically equivalent, this is acceptable.

Another possibility is that the authorities can enter negotiations with the manufacturer to buy off the development costs of a new medicine for the Netherlands, based on the scale of the Dutch market (1% to 2% of the global market). The manufacturer then provides the drug at production and transportation costs. If a number of similar medicines are on the market, this can be attractive for both a manufacturer and Dutch society. The manufacturer then gets a proportion of its development costs back straight away and no longer has to obtain a market share in the Netherlands, which saves on marketing costs. For society, the benefit is that the drug is cheaper per dose and can therefore be used widely, for instance in combination treatments or for new indications. For the manufacturer, this again provides valuable information and they will be prepared to make financial concessions for that. It can be an attractive alternative to volume pricing agreements.

Items such as appropriate use and prevention of waste can also help significantly in limiting the costs. A good formulary¹⁹ is a tool that helps the prescriber be cost-effective when prescribing medicines for a particular indication. Other aspects of a medicine, such as the package size and packaging method, also affect the overall costs of using a new medicine. It is therefore important that all aspects that are important for cost-effective prescribing and administration of medicines are included in the negotiations with manufacturers.

4.3 Reducing the risk of failure along the development pathway

Setting limits on the prices of new medicines is immediately a strong stimulus for more efficient development projects

The greater the extent to which countries set limits on the prices they are prepared to pay for new medicines, the more companies that want to keep their profit margins up will have to take a more critical look at the development pathways and the amounts that they are prepared to pay startups for a particular drug. Startups will in turn have to look critically – even more so – at the drugs they are going to develop. Whether the animal and other models used are valid and whether there are good biomarkers will have to be examined more closely. It is a powerful driving force to reduce the likelihood of failures. It will also have a knock-on effect on research institutions, which will have to be able to demonstrate more clearly that their invention genuinely works.

Give universities more negotiating power as the inventors

It was noted earlier that a lot of new medicines originate in research at universities that is funded with public money. They are then often the patent holder, meaning in principle that they have the power to determine what happens to their invention. However, that power is in the first instance very limited, because it is uncertain whether the invention does really have any potential. This can only be estimated once the proof of concept is delivered, once it has been shown that the drug is effective in a small group of patients (Phase IIa). Universities often do not have the financial resources to carry out this research and they are therefore forced to sell their inventions at an early stage in which they do not have much negotiating power. If there is already a proof of concept, the universities are in a much stronger negotiating position.

The Council for Public Health and Society therefore deems it desirable that the authorities should finance the development of highly promising, potential new medicines for longer, up to and including the *proof of concept*. They can do this together with other sources of funding such as e.g. collection box funds. Startups can also be involved in this. Strict conditions will have to be imposed on this financing, though. This could include socially responsible licensing conditions, as proposed by eight cooperating Political Youth Organisations in their manifesto *Licence to Heal, Accessible Medicines* (Samenwerkende Politieke Jongeren Organisaties & Partners, 2016). One example that can be mentioned is *Maastricht University Socially Responsible Research and Licensing Policy in the field of Health, Medicine and Life Sciences* (Universiteit van Maastricht/UAEM 2015), which is based on the *Global Access Licensing Framework* by the Universities Allied for Essential Medicines (UAEM 2013).

The intention is not that the government should become a provider of risk capital, but that it ensures medicines are developed effectively and efficiently at an acceptable price. The authorities must therefore also be highly selective as to which developments it supports.

Involve the patients

An important condition that should be imposed is that all the necessary disciplines work closely together. Input from the patients is also exceptionally important. The successful development of medicines against HIV at the end of the 1980s was thanks to close cooperation between an active patients' movement, researchers and companies. The War on Cancer at the beginning of the nineties in the USA was initially a success. This was directed from the US Department of Defense towards specific targets, focusing not on the scientific interests and relationships of power, but on the needs of the patients: the patients' hands were on the steering wheel. The later failure of the project shows that it is very difficult to maintain that targeted focus and keep resisting e.g. the interests of the researchers. It is therefore important that the governmental authorities impose strict conditions on the funding of research in terms of the objectives to be achieved, stopping if it then goes in the wrong directions. One example of exactly how it should not be done, is the Innovative Medicines Initiative (IMI), the largest European public-private initiative aimed at developing new medicines.²⁰ It is a cooperative venture between the EU and the European Federation of Pharmaceutical Industries and Associations (EFPIA). Although €1.6 billion of public funding is involved, the agenda is determined entirely by the industry and the general public or patients have virtually no say.

Be prepared to pull the plug

Stopping in good time is in fact the most important thing of all: the authorities must have both the time and the courage to stop initiatives or research that has become aimless. One example that can be given is the research into Alzheimer's disease and Parkinson's disease that are based on mouse models. It has become clear in the meantime that these lab animals are not a good model for the disease process. In addition, the lab animals suffer unnecessarily. Even so, this type of research is still being carried out in the Netherlands because scientists can publish the results of their research and their remuneration is based on the number of publications. The study by Macleod et al. has already been mentioned in section 3.4. They state that 85% of the money spent on biomedical research is wasted. Financing 'useless' biomedical research, useless from the patients' point of view, should be stopped.

4.4 Bundling expertise

To make the above possible, it is important that inventions made by public research institutions are appropriately patented. At the moment, the requisite knowledge is fragmented, scattered among a number of Technology Transfer Offices (TTOs). The Council therefore recommends bundling the expertise into a national TTO for new medicinal products; this case was previously also made by the Royal Netherlands Academy of Arts and Sciences (KNAW 2014). This institute assesses the potential of discoveries and ensures that intellectual property rights are acquired for inventions developed wholly or partly with public money. It also makes sure that licensing conditions are socially responsible. One hazard of centralisation of expertise is that it is then further removed from the work floor. Short lines of communication to the researchers in the various research institutions are crucial. This must be monitored

4.5 Shortening development processes

The problem of the lengthy development processes can partly be resolved by the recommendations made above. If inventions are patented quickly and properly and highly promising potential drugs are developed further under strict, targeted conditions and timelines, wholly or partly with public money, then the development timelines can be shortened considerably. As indicated in Section 3.3, the widely heard argument that the licensing authorities are a major cause of the lengthy development projects is unfounded.

For rapid, thorough and effective implementation of clinical research, a good information infrastructure is needed. The Council pleads the case in its advisory letter *Implementatie van e-health vraagt om durven ruimte* (Implementation of e-health requires courage and space) (RVS 2017b), that the authorities should implement an e-health highway by obliging healthcare providers and suppliers of information systems to provide open interfaces, make their data available to patients free of charge, and comply with defined standards and identification requirements. This is in line with the earlier advice *Patiënteninformatie* (Patient information) from the Council for Public Health and Care (RVZ 2014), which makes the case for a personal health record (Dutch: PGD). The e-health highway and the PGD will give the patient an important, more significant role in the development of new medicines. Work has in the meantime been started on the PGD in the shape of the MedMij initiative.²¹ It is important that the PGD offers patients the possibility of making data available for clinical research.

Section 3.4 described a number of ethical issues associated with current clinical research, such as financial links between researchers and the industry or patients who benefit from a new drug when taking part in a trial and who are then left without it when the trial ends. If patients have the power to do with their data as they wish, they can impose requirements beforehand on the design of clinical trials and the use of that data.

4.6 Making space for smaller (Dutch) companies to access the market independently

If the recommendations listed above are implemented so that (Dutch) universities have patents on new and valuable medicines for which the effectiveness has been demonstrated and reliable and efficient clinical research can be carried out in the Netherlands, then the preconditions have been met for letting smaller companies bring new medicines onto the market. As indicated earlier, the

supervisory agencies have already licensed a number of new medicines without large Phase III studies, on the basis of relatively small studies. Studies such as those are within reach for smaller companies. One problem is still the expertise that is required for the licensing procedure. The Council's opinion is that there is a task here for the authorities, principally for the Ministry of Economic Affairs, in assisting Dutch companies.

The Netherlands has all the ingredients for acquiring a leading position in the world, particularly in biopharmaceuticals. Biomedical scientific research and the quality of the healthcare system are high. There are active patient groups, collection box funds, and so forth. Cooperation between numerous different disciplines across organisational boundaries can allow breakthroughs in medicine research to be made.

The pharmaceutical industry spent €642 million on research and development in the Netherlands in 2011 (EFPIA 2017). It finances numerous clinical studies, which are a source of income for UMCs in particular. Of all assessment dossiers for clinical research submitted to the Central Committee on Research Involving Human Subjects (CCMO), 65% come from the industry (CCMO 2017). The biopharmaceutical industry in the Netherlands has potential and there is therefore a task for the Ministry of Economic Affairs in encouraging this branch of the business.

4.7 Finding out when non-commercial development of medicines is desirable

The Minister of Health, Welfare and Sport has also asked the Council for Public Health and Society whether personalised medicines (such as gene therapy agents) always have to be brought onto the market by a commercial party via an marketing authorisation and to explore whether greater social returns can be expected from non-commercial medicines developments.

The Council's opinion is that experiments into how other non-commercial, socially responsible methods of medicines development should focus, at least initially, on niche markets. Aspects that can in particular be considered are drug rediscovery, development of new antibiotics and certainly also personalised treatments with e.g. advanced therapy medicinal products (ATMPs) such as somatic cell therapy, tissue therapy and gene therapy.

There are various highly promising initiatives in the Netherlands such as Stichting Oncode Institute (looking at inter alia drug rediscovery in oncology), the Netherlands Antibiotic Development Platform (NADP) for the development of new antimicrobial agents, the Fair Medicine Initiative and Cinderella Therapeutics. In addition there are initiatives such as myTomorrows that are attempting to get changes to happen within the 'classical' system, and there is an initiative to make pharmacy preparations of biopharmaceuticals possible (Schellekens et al., 2017).

4.8 Summary conclusion

This chapter has stated that it is important that excessively high prices should be reined in. Various instruments have been listed that the authorities can use. Pressure on prices encourages manufacturers to look more closely at the development process. In addition, it is important that the government encourages reliable and efficient clinical research. This creates possibilities for smaller companies to market medicines independently. In addition, there is scope for non-commercial

medicines development in areas such as drug rediscovery, development of new antibiotics and personalised treatments.

Notes

- 9 Irish Medical Association (2017) www.imo.ie/news-media/agm/agm-2017/motions/general-motions-2017/ onder GENERAL MOTIONS SESSION 2 FRIDAY 21st APRIL 2.30pm – 3.45pm , motie 33: *"The IMO calls upon the Government to issue a compulsory licence for Sofosbuvir for public non-commercial use consistent with article 70 of the Patents Act to facilitate the importation, distribution and use of lower priced generic Sofosbuvir of assured quality"*.
- 10 <https://www.zorginstituutnederland.nl/over-ons/werkwijzen-en-procedures/adviseren-over-en-verduidelijken-van-het-basispakket-aan-zorg/beoordeling-van-geneesmiddelen>.
- 11 *Executive Summary of the Pharmaceutical Sector Inquiry Report* http://ec.europa.eu/competition/sectors/pharmaceuticals/inquiry/communication_en.pdf.
- 12 Medicines Act, Article 40: *"1 It is forbidden to bring a medicinal product onto the market without marketing authorisation from the European Community (as granted by virtue of regulation 726/2004 or by virtue of that regulation combined with regulation 1394/2007) or from the College (as granted pursuant to this chapter). 2 It is forbidden to keep stocks of a medicinal product for which there is no marketing authorisation, or to sell it, deliver it, provide it to individuals, to import it or otherwise bring it into or take it out of Dutch national territory. 3 A prohibition as defined in the first or second paragraph does not apply a) to medicinal products that are prepared and handed over by or on instructions from a pharmacist or general practitioner as defined in Article 61 paragraph 1 under b on a small scale in their own pharmacy;"*.
- 13 http://www.alibaba.com/trade/search?fsb=y&IndexArea=product_en&CatId=&SearchText=ivacaftor.
- 14 http://www.alibaba.com/trade/search?IndexArea=product_en&CatId=&fsb=y&SearchText=lumacaftor.
- 15 See also the ruling by the 's-Gravenhage District Court, 20-09-2007 ECLI:NL:RBSGR:2007:BB3975.
<https://uitspraken.rechtspraak.nl/inziendocument?id=ECLI:NL:RBSGR:2007:BB3975&showbutton=true&keyword=ECLI%3aNL%3aRBSGR%3a2007%3aBB3975>.
- 16 Bill for Amendment of the 1995 Patents Act regarding the Agreement on a Unified Patent Court and EU Regulation 1257/2012.
- 17 Article 18 paragraph 6 sub a: *"the importing, exporting or otherwise bringing medicinal products into Dutch national territory or taking them from Dutch national territory where such products are evidently intended for personal use by the individual transporting the medicinal products"*;
- 18 <http://www.jellinek.nl/informatie-over-alcohol-drugs/drugs-test-service/>.
- 19 A formulary is a detailed summary of medication advice for a condition or indication upon which care providers have reached agreement. www.formularium.nl.
- 20 <http://www.imi.europa.eu/>.
- 21 <http://www.medmij.nl/>.
- 22 This document provides a preliminary overview. It does not represent the official views of the OECD or its member countries. The final analytical report on the project is to be published by the end of 2017.

5 Recommendations

This chapter outlines briefly the vision that the Council for Public Health and Society has of the Netherlands' position in the development of new medicines. The solutions that have been discussed in the previous chapter are also summarised concisely in the form of six recommendations.

The Netherlands as a pioneering country

The title of these recommendations is *Development of new medicines. Better, faster, cheaper*. As indicated in the earlier chapters, new medicines are developed at the global scale. The current method of development for new medicines is threatening to become bogged down: it is grossly inefficient and the medicines are threatening to become unaffordable. The Netherlands does not have a large pharmaceuticals industry, but it does have a high-quality, innovative biotech sector. This offers opportunities. The recommendations below in this advisory document can help encourage the development of new medicines in the Netherlands, so that the sector can show that things can be done better, faster and less expensively, even given the current international frameworks.

Nevertheless, the efforts already made by the Dutch government to ensure the desired changes in the regulations at European level have to be continued. This is a task for the long haul. This could cover European patent regulations, data exclusivity rules, orphan drug regulations and the use of European research funds.

Recommendations

When a company is not prepared (after negotiations) to charge a socially acceptable price for a medicine, the Council advises the minister to use other instruments such as compulsory licences, import permits, encouragement of pharmacy preparation, allowing patients to order medicinal products abroad subject to certain conditions, and tackling misuses of position of power, in order to ensure that the medicines is made available to the patient at an acceptable price.

1 *Make use of legal instruments to improve the negotiating strength.*

When a company is not prepared (after negotiations) to charge a socially acceptable price for a medicine, the Council advises the minister to use other instruments such as compulsory licences, import permits, encouragement of pharmacy preparation and tackling misuses of position of power, in order to ensure that the medicines is made available to the patient at an acceptable price.

2 *Use innovative negotiation strategies.*

The Council advises the minister to use innovative negotiation strategies in all cases of new medicines with a substantial budgetary impact, such as tendering and buying off the development costs, and to include all relevant aspects in the negotiations, such as prescription by doctors in terms of appropriate use, reduction of waste and a formulary that must be used.

3 Give research institutions more negotiating power for their patents

The Council recommends that the first phases of clinical research into highly promising, potential new medicines should be funded if they have been developed and patented by universities and other research institutions that are funded from public resources. This will give these institutions more negotiating power with respect to private investors. Impose strict conditions on this financing, particularly with regard to cooperation, the objectives being set, the timelines, the licensing conditions to be adopted, and (last but not least) input from the patients. Be tough when halting the funding of initiatives and biomedical research that is 'wandering aimlessly', i.e. not helping to find effective treatments, and impose higher requirements on the use of animal models in the lab.

4 Bundle expertise into a national TTO for new medicines.

Securing intellectual property rights demands thorough expertise. The bundling of expertise into a national TTO can ensure that inventions developed entirely or partly using public funding are properly patented and licensed in a socially acceptable way. Make sure that this national TTO does remain close to the actual work floor.

5 Use the e-health highway and personal health dossiers for efficient medicine development too.

Make sure that the e-health highway and personal health dossiers can also be used for developing new medicines and for clinical studies.

6 Encourage alternative development models for drug development.

Highly promising new initiatives must be encouraged under similarly strict conditions as those stated in the third recommendation about the universities: requirements for cooperation, the objectives to be set, the timelines, and input from the patients. And above all: discontinue funding of initiatives that have lost their innovative strength.

Appendix 1

Request for an opinion

4910/ Drie geneesmiddelen
 Advies aanvraag 49.10-951533



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*Correspondentie uitsluitend
 richten aan het retouradres
 met vermelding van de
 datum en het kenmerk van
 deze brief.*

Datum **22 MAART 2016**
 Betreft adviesaanvraag ontwikkeling van geneesmiddelen

Geachte mevrouw Meurs,

Bij mij bestaat behoefte aan advies over de efficiëntie van de ontwikkeling van nieuwe geneesmiddelen en over alternatieve ontwikkelmodellen.

In de Kamerbrief met mijn visie op geneesmiddelen¹ constateer ik dat medicijnen steeds vaker voor kleine groepen patiënten worden ontwikkeld (personalised medicine of precision medicine). Veel van de nu en in de toekomst op de markt komende medicijnen betekenen veel voor de patiënt. Een aanzienlijke verbetering van de kwaliteit van leven en/of een aanzienlijke verlenging van de levensduur betekenen dat de vaak wanhopige, uitbehandelde patiënten weer nieuw perspectief krijgen. Dat is een geweldige ontwikkeling! De prijs van deze medicijnen is echter vaak (extreem) hoog en zet de betaalbaarheid van de zorg onder druk. De relatie met de onderzoeks- en ontwikkelkosten en zelfs met de toegevoegde waarde is daarbij zoek. Nieuwe ontwikkelingen in de diagnostiek waardoor alleen patiënten die baat hebben bij de geneesmiddelen deze krijgen voorgeschreven, en andere patiënten veel leed van de vaak forse bijwerkingen en valse hoop worden bespaard, bieden een belangrijk perspectief.

Los daarvan schrijf ik in mijn geneesmiddelenvisie dat ik zeer geïnteresseerd ben in nieuwe modellen voor de ontwikkeling van geneesmiddelen. Bij deze zoektocht vraag ik tevens aandacht voor de gemiddelde tijd die een geneesmiddel erover doet om bij de patiënt te komen. Die is erg lang. Onderweg is het uitvalspercentage hoog. Ook lijkt het voor kleine bedrijven praktisch onmogelijk om zelfstandig een geneesmiddel naar de markt te brengen.

Ik vraag de Raad voor Volksgezondheid en Samenleving daarom met vernieuwende inzichten te komen en strategische oplossingen aan te dragen voor de geschetste problemen. Ik verwacht van de Raad dat hij het gehele traject van de ontwikkeling van een nieuw middel - van het fundamentele onderzoek tot en met de toepassing ervan in de dagelijkse praktijk - onder de loep legt. Hoe kan de ontwikkeling van nieuwe geneesmiddelen doelmatiger, waarbij bereikte

¹ Visie op geneesmiddelen: Nieuwe geneesmiddelen snel bij de patiënt tegen aanvaardbare kosten. Brief van minister Schippers aan de Tweede Kamer, 29 januari 2016.

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efficiencyverbeteringen resulteren in lagere prijzen of anderszins ten goede komen aan de samenleving? Daarbij vraag ik de Raad te kijken naar het hele ecosysteem van overheid, publieke kennisinstellingen, kleine en grote bedrijven, patiënten en hun behandelaars, gezondheidsfondsen en investeerders dat een rol speelt bij geneesmiddelontwikkeling en prijsvorming. Ik verzoek de Raad echter zich niet te richten op terrein dat al bestreken is door de recente adviezen van KWF, NZa en Actal over geneesmiddelen en ga er vanuit dat de Raad daar waar nodig in overleg treedt met de Gezondheidsraad.

Directie Geneesmiddelen
en Medische Technologie

Kenmerk
925603-147593-GMT

Een punt van aandacht daarbij is de verhouding tussen publieke en private rekenen, gegeven dat vaak een deel van het ontwikkeltraject met publieke middelen wordt gefinancierd. Alhoewel de ontwikkeling van nieuwe geneesmiddelen voor het grootste deel internationaal plaats vindt, is dit aspect zeker van belang voor Nederland. Biowetenschap en biotechnologie staan hier op hoog niveau en zijn een bron van nieuwe geneesmiddelen. De overheid ondersteunt dit financieel, onder andere via ZonMW.

Een ander punt van aandacht is dat waar de ontwikkeling van geneesmiddelen zich richt op steeds kleinere patiëntenpopulaties de vraag rijst of gepersonaliseerde geneesmiddelen (zoals gentherapeutica) altijd via marktregistratie door een commerciële partij naar de patiënt moeten worden gebracht. Ik vraag de Raad dan ook te verkennen of er een terrein is waar meer maatschappelijk rendement te verwachten is van een niet-commerciële geneesmiddelenontwikkeling.

Ik verwacht dat het advies van de Raad ertoe bijdraagt dat publieke en private partijen (inclusief patiënten) op een nieuwe manier met elkaar gaan samenwerken bij de ontwikkeling van geneesmiddelen, leidend tot maatschappelijk aanvaardbare prijzen van geneesmiddelen met duidelijke meerwaarde. Gezien de geformuleerde acties in de ontwikkelagenda bij de brief met mijn visie op geneesmiddelen, verzoek ik de Raad om zo mogelijk binnen een jaar te adviseren.

Ik stuur een afschrift van deze brief ter informatie aan de Voorzitter van de Tweede Kamer der Staten-Generaal.

Hoogachtend,

de minister van Volksgezondheid,
Welzijn en Sport,

mw. drs. E.I. Schippers

Appendix 2

Alternative development models

The previous chapter described a number of issues in the current system. These problems are recognised by those in the field and there are various initiatives and ideas for alternative development models for new medicines ('game changers'). In this chapter, we will be taking a brief look at these and examining the pros and cons of each of the options. The principle when doing so will be the focal point of these recommendations: What can the *Dutch* governmental authorities do in order to encourage and accelerate the development of alternative development routes for new medicines in *the Netherlands*, so that medicines come onto the *Dutch* market more cheaply and more quickly?

ZIN/KCE future scenarios

In June 2016, the Belgian Federal Healthcare Knowledge Centre (KCE) and the Dutch National Health Care Institute (ZIN) jointly issued a report called *Toekomstscenario's voor de ontwikkeling en prijszetting van geneesmiddelen* (Future Scenarios for the Development and Pricing of Medicinal Products). The report outlines four alternative development models for new medicines in the form of scenarios. The scenarios were drawn up on the basis of interviews and meetings with experts and stakeholders from Europe and North America, including patients' representatives, sector leaders, academics, supervisory bodies, health insurers and governmental agencies. The purpose of this discussion process was to "*search for possible solutions for the high prices of medicines*".

We will discuss the four scenarios briefly, placing a number of marginal notes by each of them, given the focal points of these recommendations.

Scenario 1: public-private partnerships for specific needs

Description

This scenario is derived from the existing practices for governmental orders in research-intensive domains such as public transport, defence and space exploration. Public parties define a number of performance criteria for this and guarantee the procurement at a specific price if a developer complies with those criteria. There are already examples at the international level in the public health field, in which partnerships have been set up to develop drugs for the third world, for instance against malaria and river blindness (onchocerciasis).

In the case of new medicines, a public body - which could for instance be the European Union or the government of a (large) country - draws up the criteria for the performance levels of medicines that are to be developed to meet those needs, and states what it is prepared to pay for that medicine. The performance criteria could include the profile, the safety, the efficacy and the clinical effectiveness.

The public agency then enters a partnership with the drug developers via tenders with enforceable contractual agreements. These will generally be commercial companies, but independent or

publicly funded research institutions or combinations are also possible. The drug developer gets access to the market and a remuneration if it succeeds in developing a medicine that meets the criteria.

The development process is monitored closely right from the start of development by a platform in which experts and representatives of both the developers and the public partner take part. Patients' representatives, funding parties (health insurers) and independent experts can also be involved in this platform. All the data is available within the cooperative venture. The platform takes decisions about aspects such as the design of the clinical studies and the outcomes used. The outcomes are assessed after each development phase and communicated to the outside world. An independent evaluation committee validates the results. Supervisory bodies such as the EMA are brought on board at an early stage.

The role of patents and the exclusivity of data will be discussed and negotiated right at the very start of the partnership. It may be agreed that no patents will be requested and that the data will be made entirely public.

The performance level requirements of the public agency must be in line with current scientific knowledge when the partnership commences. The development process must also be flexible. It must be possible to include new scientific insights and make adjustments in the light of them.

According to those who drafted this scenario, the model is attractive for governmental authorities because it yields affordable medicines that are the ones patients most need and which best serve public health interests. It is attractive for pharmaceuticals companies because they do not have to take such large financial risks; this is in exchange for not being able to set prices freely. After all, the supervisory bodies and the funding parties are involved in the development from an early stage. They eliminate the uncertainties regarding licensing approval and insurance reimbursement.

Remarks

Although the title of scenario 1 refers to 'public-private partnership', the system actually most closely resembles public tendering. As stated in the description, this approach is suitable for large-scale public bodies such as the European Union or large countries. In practice it means that this scenario is only achievable for a small country such as the Netherlands in a European or WHO-based context. It demands a great deal of coordination and integration between the parties. The international projects for combating tropical diseases that have already been based on this scenario seem to have been a success. This scenario also seems highly suitable for the development of new antibiotics, which are badly needed given the increasing levels of resistance to existing drugs. These new medicines should however be used as little as possible (as a *last resort*). That makes it unattractive for companies to develop these drugs within the current system.

Scenario 2: parallel track for drug development

Description

In this scenario, governmental agencies of EU member states set up a parallel track for non-profit medicines development, in addition to (but independent of) the pharmaceutical and biotech industries.

The authorities first make an inventory of the gaps in healthcare and the priorities. They then ask leading research centres such as academic hospitals and universities about the discoveries, resources, instruments and capacity they have for developing solutions that provide answers to some or all of the needs listed in the inventory. If it turns out that there are possible solutions, then consortiums are set up between the research institutions (not for profit), payers such as health insurers, government bodies and patients' organisations. These partners undertake to participate openly and transparently in clinical research projects. Creative funding plans cover the costs of the R&D efforts. These could for instance involve advance payments or remuneration bands instead of payments for the use of medicines. Sources such as crowdfunding and social bonds could also be used.

Intellectual property rights can be obtained early in the development process and shared between the partners, or the project may simply do without them. The latter approach encourages open science, cooperation and innovation, because other players are then able to pick up the results at an early stage and start using them.

As a precondition for this scenario to succeed, the authors note that the system used for resolving disputes about intellectual property and permits will have to be organised differently.

Remarks

This scenario also assumes cooperation between government agencies, e.g. at the European level. In addition - as the authors note - it requires changes to dispute resolution related to intellectual property and permits. Patent law does not provide active protection. Infringements of patents and contesting such claims can easily be deployed strategically with the aim of hurting the other party - in this case the government agency. Not taking out patents also has its own risks. The English discovered this when penicillin was discovered. They did not ask for a patent (after modifying the molecule somewhat as needed first, of course). English companies were then not prepared to produce the drug. American companies were, but they then patented the entire production process. The net result was that the British had to pay high prices for penicillin. Pharmaceutical companies nowadays protect not only the product itself but also the production process, through many dozens of patents.

Scenario 3: paying for patents

In this scenario, a number of European countries join forces and set up a 'public fund for affordable medicines'. Each participating country deposits a fixed percentage into the fund annually of what it currently expends on medicines. The fund keeps a close watch on the research market looking for interesting medicines that are in phases II or III of their development and that are aimed at indications that are clearly among the priorities. The fund buys patents from developers and carries out the final research phases itself, or gives instructions to public bodies to do so. The fund supervises the procedure for requesting market authorisation. Manufacturers and distributors can then compete amongst themselves for the rights to produce, distribute and sell the drug, on the condition that they must offer the highest quality, safety and accessibility at the lowest cost price.

Remarks

This scenario also envisages a number of countries joining forces. Another point is that the parties, as described earlier, work 'backwards' when setting the price for new medicines: what might a

suitable anchor price for this drug be? Particularly for patents on drugs in Phase III, where there is more certainty that a drug works, the prices asked will be very substantial. The public fund will have to compete with Big Pharma on this point.

Scenario 4: the public good from start to finish

Description

In this scenario, the patients and society determine what the research must be investigating. Government agencies regularly publish lists of research priorities that are based on medical needs that are objectively determined in consultation with patients. The authorities fund all the research that is required and all the results of that research are public, as is the raw patient data (in anonymous form). Medicines can no longer be patented in this scenario and pharmaceuticals companies produce the medicines as generic drugs.

Supervisory agencies are entirely financed from public resources in this scenario and medicines are approved on the basis of quality, efficacy, safety and added therapeutic value. Studies must be organised on a sufficiently large scale and last long enough for the clinical risks and benefits in the longer term to be determined. Medicines are no longer approved on the basis of surrogate outcomes, but are only approved and reimbursed once their clinical benefits have been demonstrated in independently performed studies among relevant patient populations.

The authors propose a transitional period in which international trade agreements about limited property rights, secrecy and commercial confidentiality can be broken open and renegotiated. The patents system will also be modified step by step and finally (in the case of medicines) abolished.

Remarks

This scenario demands rigorous reworking of European legislation in particular. It also requires Europe to have the strength and willpower to want to break trade treaties open.

Modellen voorgesteld door de Vereniging Innovatieve Geneesmiddelen

The Dutch sector organisation, the Vereniging Innovatieve Geneesmiddelen (Association Innovative Medicines) has proposed three models for discovering new medicines.²²

Model 1: the public model

Description

This model is virtually the same as KCE/ZIN scenario 4: the governmental authorities pay and do all the research into new medicines. The model is not worked out in further detail.

Model 2: the patient model

Description

This model is intended for getting new medicines to the patients more quickly. Medicines are provided to the patient in this model before they are in fact authorised for the market - i.e. not indicated (or not yet) for a specific condition such as a certain type of cancer. If it then transpires that the drug is also effective for this condition, the indication can be broadened. If it does not work, the indication can be restricted again.

Model 3: the umbrella model

Description

In this model, all patients who could benefit from a particular new medicine are brought together under a single financial 'umbrella'. This can be done for example by paying a manufacturer a fixed amount per year, or a fixed amount per patient or group of patients. This model builds upon the *pay-for-benefit* agreements or decentralised tailored agreements that can already sometimes be found. If a drug does not work, society does not have to pay for it.

Remarks

As stated earlier, the public model requires international cooperation between governments. The second model, the patient model, is essentially about *adaptive licensing*. The third model is not so much an alternative development model as an alternative funding model.

Fair Medicine

Description

Fair Medicine is a foundation that aims to get better medicines to the patients more quickly and more cheaply by deploying a new model. The classical, linear model starts with an inventor discovering something. A manufacturer then uses money from an investor to develop a medicine and get it onto the market, after which treating physicians can prescribe it for their patients. In the new model, the patient, treating physician, clinic, inventor, producer and investor cooperate (see Figure 2).

Classical Model

Sequential involvement of parties



Fair Medicine model

All parties around the table at once

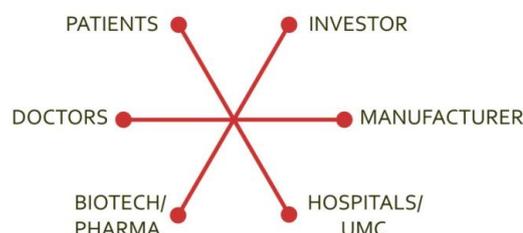


Figure 2: The classical model versus the Fair Medicine model

Source: ZonMw, 2016. 'Pearl' award for Fair Medicine, p.2

The various parties form a coalition to which they commit contractually for the entire process; this will ultimately take the form of an independent company. This is based on four core principles:

- 1 the Fair Medicine Chain, the coalition of all those involved, based on mutual trust and balanced interests.
- 2 Fair Medicine Distribution: the ownership is based on the contributions and added value actually provided, and on sharing the responsibilities, risk and revenues.
- 3 Fair Medicine Value: the treatment is continually improved thanks to records that the patients themselves complete (in consultation with those treating them).
- 4 Fair Medicine Price: these are transparent development costs and long-lasting margins. The participants are open about the costs that they incur and the contributions they actually make. Investors earn their investments back, plus a socially acceptable margin based on the sales of the drug (after it has been licensed) on the free market. The pricing is determined by the actual development and production costs plus a clearly described margin. This price will thus be lower -

a lot lower - than the prices of new drugs that are developed using the classical model, which are based on maximum anchor prices.

Remarks

Fair Medicine is an interesting initiative. It resembles the earlier scenario of a parallel track for pharmaceutical development. It does not require amendments to international regulations and the development costs and the final pricing of the drug can come out significantly lower than in the current model. However, there is again a danger here of patent law being used to strangle an opponent in the courts until bankrupt.

In particular the idea of getting the patients themselves (in consultation with those treating them) to provide data can yield cost savings on the clinical studies. It is however open to question whether separately recorded datasets are a suitable method for this. We will examine this in more detail in the next chapter.

Involving patients and those treating them from the very start guarantees that medicines are developed for which there is a genuine need.

It will have to be seen in practice whether there are enough investors who are prepared to make capital available at modest margins and whether the various parties can build up enough of a relationship of mutual trust.

Cinderella Therapeutics

Description

Cinderella Therapeutics is a foundation. It is the sole shareholder of Cinderella Therapeutics BV, a company that focuses on medicines that the industry does not want to develop further because the potential for profits is too limited. These are in other words drugs that will just be left 'on the shelf'. If such a drug is noticed and thought to have potential, a working group or consortium is set up in which interested clinical researchers cooperate without vested interests. If a valuable effect is found and large numbers of patients could be treated with it, the drug is made available at cost price.

Remarks

Cinderella Therapeutics focuses on drugs that the industry is not interested in. As the organisation itself says, it is not a competitor to the pharmaceuticals industry. This also means, though, that it does not offer a solution to the issue of new medicines that are developed by that industry being very expensive.

myTomorrows

Description

myTomorrows is a company that operates in seventeen countries, including the Netherlands, Belgium, France, Turkey and the United Kingdom. It helps doctors and their patients obtain access to medicines that are not yet licensed. The medicines offered have passed Phase I successfully along with one or more Phase II studies that have also demonstrated their safety and initial efficacy. It is all done on a *named patient basis*. This is one of the two possibilities, in addition to the

compassionate use programme that the European regulations offer for making drugs available to patients outside the context of clinical studies that are not yet authorised and therefore not yet on the market. When working on a *named patient basis*, the treating physician asks the Dutch Health Care Inspectorate (IGZ) for permission to treat a specific, named patient with an appropriate medicine under their own personal responsibility. If the IGZ gives permission and the company is prepared to supply the medicine, the patient may be treated.

myTomorrows offers an Internet-based platform on which these drugs are offered and where treating physicians and medicine manufacturers are brought together. To that end, myTomorrows employs a number of doctors and other specialists who determine what medicines and treatment methods the platform offers. In the Netherlands, unlike for example France or Turkey, insurers reimburse the drugs to a limited extent. The company generates its income from the fact that the manufacturer pays it a percentage of the sales price of the product when it actually does come onto the market. In addition, myTomorrows receives a *transaction fee* from the manufacturer each time the medicine is handed over to a treating physician.

myTomorrows is starting pilots up in the Netherlands in which patients are treated with non-licensed medicines that are nevertheless reimbursed. Agreements are signed for this with governmental bodies, insurers and manufacturers. These agreements cover aspects such as publication of treatment outcomes and the determination of the pricing after market authorisation.

Remarks

The pilots that myTomorrows is carrying out are a new development model in parallel with the existing one. The model of open access to the treatment outcomes and agreements about the pricing before and after licensing has the potential to lower the prices for certain medicines in the longer term. Pilots in the Netherlands are interesting for manufacturers, because they only represent 1% to 2% of the global market for medicines.

Netherlands Antibiotic Development Platform (NADP)

The Netherlands Antibiotic Development Platform (NADP) assists cooperation between public and private organisations in order to promote the development of new antibiotics and alternative treatments for infectious diseases in people and animals. In a later stage, the platform also wants to offer management support for the development of new drugs and to act as a TTO. Participants in the NADP are the Centre for Antimicrobial Research (CARES), the Centre for Sustainable Antimicrobials (CeSAM), the network organisation Immuno Valley and the Netherlands Centre for One Health (NCOH).

Remarks

Resistance to numerous existing antibiotics among bacteria is a large-scale problem and new drugs are badly needed. In order to avoid resistance to these new drugs developing (as far as possible), these new medicines should be used as little as possible - only as a last resort. From a purely commercial point of view, this makes development of new antimicrobial drugs awkward. After all, the 'conventional' system means that a company has to earn back its development costs through the sales of the new antibiotic and it therefore wants to sell as much of it as possible, whereas public health considerations mean that it needs to be available but should be used as little as possible.

Current business models are inappropriate and alternatives, for example in forms such as the NADP, are therefore needed.

Summary

The majority of the proposed angles to be used in the search for solutions require changes to international cooperation or amendments to international regulations. These solutions are a less good fit for the context of these recommendations, in which the international regulations are seen as a *fait accompli*. A number of possible solutions do offer perspectives in that context, such as Fair Medicine, Cinderella Therapeutics and myTomorrows. These three initiatives cover different aspect of the development pathways. This is shown in more detail in Figure 3. In addition there is the NADP, which focuses on R&D specifically for antimicrobial agents.

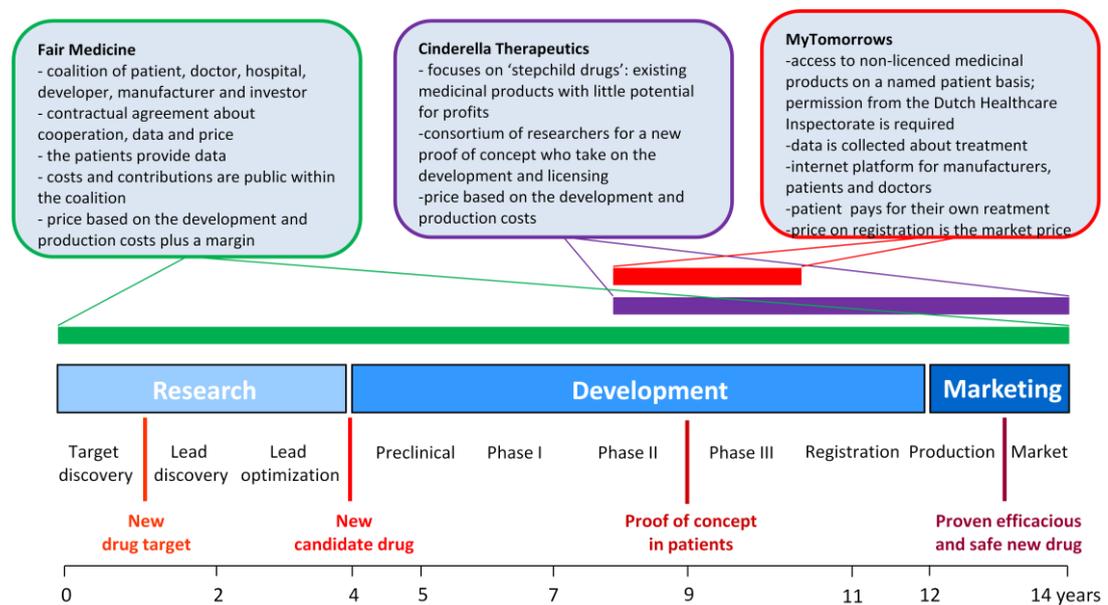


Figure 3: Positioning of Fair Medicine, Cinderella Therapeutics and myTomorrows in the development process

Notes

- 22 Presented at a symposium of the cancer charity KWF Kankerbestrijding on 23 June. In: KWF Kankerbestrijding (Dutch Cancer Society, 2016). *Eighteen innovative ideas for making expensive medicines accessible*.

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Abbreviations

ACE	angiotensin-converting enzyme
ACM	Authority for Consumers and Markets
ADA	adenosine deaminase
ADHD	attention deficit hyperactivity disorder
ATMP	advanced therapy medicinal products
CARES	Centre for Antimicrobial Research
CBG, MEB	Medicines Evaluation Board
CCMO	Central Committee on Research Involving Human Subjects
CEO	chief executive officer
CeSAM	Centre for Sustainable Antimicrobials
CRO	contract research organisation
EAE	experimental autoimmune ecephalomyelitis
EFPIA	European Federation of Pharmaceutical Industries and Associations
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
glyHb	glycohaemoglobin
GMP	Good Manufacturing Practice
GSK	Glaxo SmithKline
GVS	reimbursement system for medicines
HbA _{1c}	haemoglobin A _{1c}
HER ₂	human epidermal receptor 2
HIV	human immunodeficiency virus
IGZ	Dutch Healthcare Inspectorate
IMI	Innovative Medicines Initiative
KCE	Belgian Federal Healthcare Knowledge Centre
KNAW	Royal Dutch Academy of Sciences
KNMP	Royal Dutch Pharmacists Association
Lareb	Netherlands Pharmacovigilance Centre
MS	multiple sclerosis
NADP	Netherlands Antibiotic Development Initiative
NCE	new chemical entity
NCOH	Netherlands Centre for One Health
NME	new molecular entities
OECD	Organisation for Economic Cooperation and Development
PGD	personal health file
R&D	research and development
RCT	randomized controlled trial
ROW	Patents Act
RVS	Council for Public Health and Society
RVZ	Council for Public Health and Care
SCID	severe combined immune deficiency

TRIPS	Trade-Related Aspects of Intellectual Property Rights
TTO	Technology Transfer Office
UN	United Nations
USTR	United States Trade Representative
VWS	Health, Welfare & Sport (Ministry)
WTO	World Trade Organization
ZIN	National Health Care Institute:
ZonMw	Netherlands Organisation for Health Research and Development

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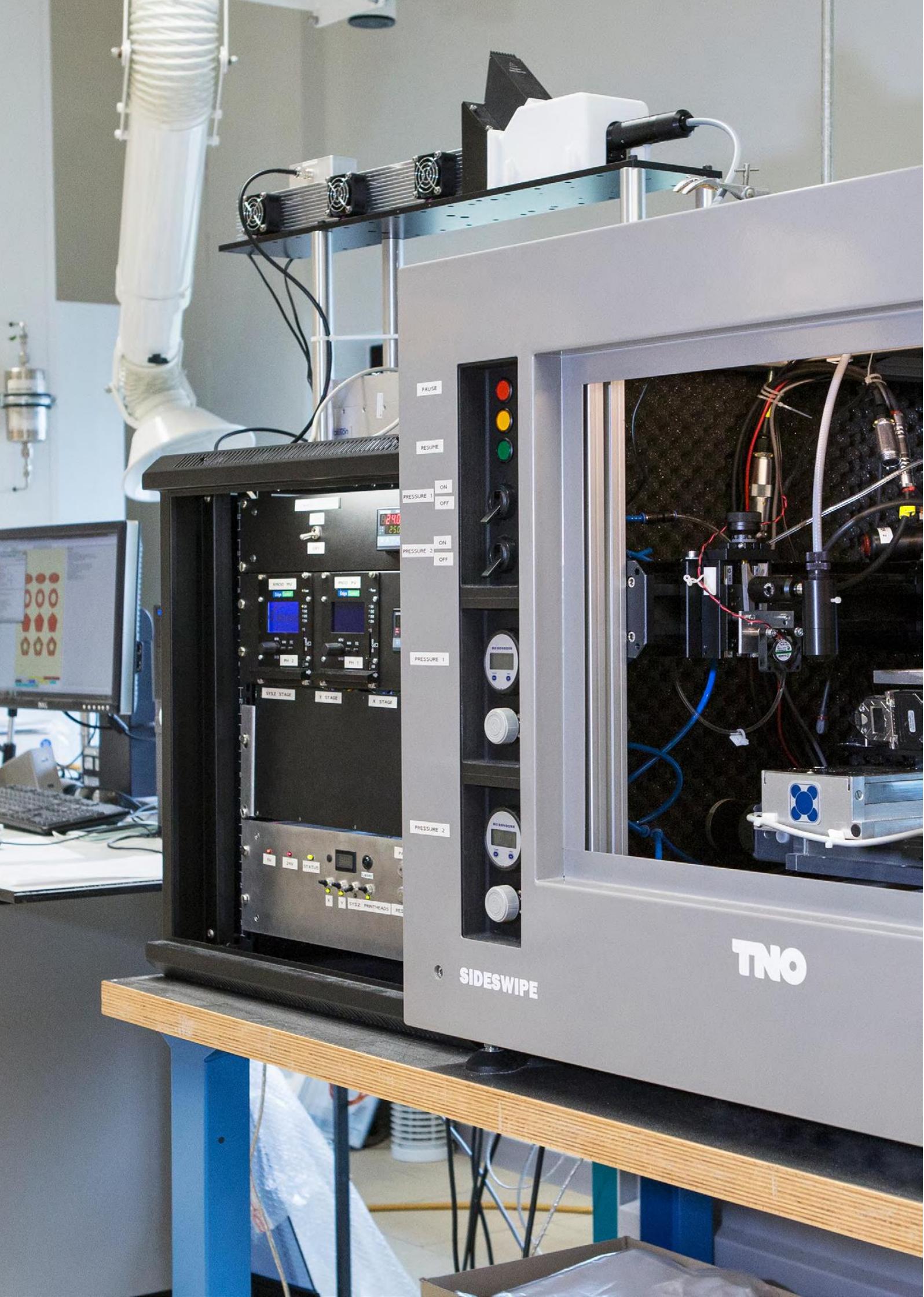
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SIDESWIPE

TNO

PAUSE

RESUME

PRESSURE 1
ON
OFF

PRESSURE 2
ON
OFF

PRESSURE 1

PRESSURE 2

STOP
PH 1
PH 2
SYS2 STAGE
1 STAGE
X STAGE

STOP
24V
STATUS
SYS2 PANTHEAD
RED

raad voor **R** Volksgezondheid en
Samenleving