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Minds Open – Sustainability of the European regulatory system for medicinal products

RIVM Report

Colophon

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De houdbaarheid van het Europese regulatoire geneesmiddelensysteem

Het Europese geneesmiddelensysteem is sterk gereguleerd. Voordat een geneesmiddel een handelsvergunning krijgt en op de markt mag worden gebracht, moet eerst worden aangetoond dat de kwaliteit, veiligheid en werkzaamheid voldoende zijn. Dit is geen eenmalige gebeurtenis maar gebeurt continu gedurende de tijd dat het geneesmiddel op de markt is. De maatregelen die hiervoor nodig zijn, zijn erg omvangrijk geworden en hebben effect op innovatie, kosten en de beschikbaarheid van geneesmiddelen. Daardoor leeft zowel binnen de overheid als de maatschappij de vraag of dit systeem toekomstbestendig is.

Het RIVM heeft daarom de knelpunten van het huidige systeem in kaart gebracht. Het blijkt dat de vier belangrijke thema's van het systeem (veiligheid & effectiviteit, kosten, innovatie en beschikbaarheid) nauw met elkaar samenhangen. Een verandering binnen een van de thema's raakt altijd aan de andere, en een optimale balans is lastig te bepalen. Zo zorgen soepelere regels om innovatie te stimuleren ervoor dat geneesmiddelen sneller op de markt beschikbaar zijn. Als keerzijde daarvan is er minder kennis over de veiligheid en effectiviteit op het moment dat een vergunning wordt verleend. Extra veiligheidsmaatregelen leiden daarentegen tot langere studies, en daarmee tot hogere kosten voor (de ontwikkeling van) geneesmiddelen en een beperktere beschikbaarheid.

Bovendien hebben factoren buiten het geneesmiddelensysteem invloed op de vier thema's, zoals commerciële belangen en de besluitvorming over de nationale vergoeding van geneesmiddelen. Ook ontbreekt op meerdere terreinen transparantie, bijvoorbeeld in de opbouw van kosten of de uitwisseling van data.

Aangezien belangen per partij verschillen (van industrie, tot verzekeraars, patiënten en zorgprofessionals), is het lastig om een balans te vinden die alle partijen tevreden stelt. Bij eventuele aanpassingen aan het systeem is het van belang hiermee rekening te houden. Patiënten met een ernstige ziekte waarvoor nog geen behandeling beschikbaar is, zullen bijvoorbeeld meer risico's accepteren op het gebied van veiligheid en effectiviteit dan geneesmiddelenbeoordelaars of het algemene publiek.

Abstract

Minds Open – sustainability of the European regulatory system for medicinal products.

The European system for the production, authorization and marketing of medicinal products is strongly regulated. Medicines have to meet predetermined standards concerning safety, quality and efficacy before they are granted market authorization. Safeguarding these standards does not stop at the moment of market authorization. During the time an authorized medicinal product is available on the market, it is subject to a continuous process of surveillance. The regulation supporting this process of continuous surveillance has expanded increasingly and is affecting the amount of innovation of new medicinal products, the availability and the costs of medicinal products. Against this background, the question whether the current regulatory system for medicinal products is still sustainable in future has come to the fore.

The RIVM analyzed potential vulnerabilities in the current regulatory system with a focus on the themes *safety & efficacy*, *innovation*, *costs* and *availability* of (new) medicinal products.
This report shows that these themes show a strong interdependency and cannot be separated easily. Interventions in one theme will have an effect on another theme or even on multiple themes; e.g. more attention to safety and efficacy will lead to higher costs and a decline in both innovation and availability of medicinal products. The four main themes can be seen as four gear wheels. When one wheel is being turned, the others are also set in motion.

Furthermore, during this study the themes ‘transparency’ and ‘accountability’ were also found to be important. The lack of transparency and accountability of both the pharmaceutical industry and the medicines regulatory authorities leads to public distrust in the system. It also hinders innovation, raises costs and restricts the availability of necessary pharmaceuticals.

Finally, external factors such as national variations in reimbursement decisions or commercial reasons influence these themes. Different interest between stakeholders (industry, patients, health care professionals and regulators) make adjustments to the system complex. This should be kept in mind when discussing possible solutions for improvement of the pharmaceutical regulatory system.

Contents

Summary

This report is a data-driven review of the sustainability of the European Union (EU) regulatory system for pharmaceuticals. It aims at identifying areas of special interest by analysing potential vulnerabilities in the regulatory system with a focus on the themes safety & efficacy, innovation, costs and availability of (new) pharmaceuticals.

The project was split in four main activities: an inventory of the pharmaceutical regulatory history (presented as an outline), a literature review (including 108 documents), semi-structured interviewing of national key experts (n=9) and identification of illustrative cases.

For the analysis of data, we identified four major themes that we defined as follows:

1. Safety & efficacy; the safeguarding of public health by denying market access of ineffective and/or harmful products and/or withdrawing them from the market;
2. Innovation; the possibility to bring pharmaceuticals on the market, either with a new chemical entity (NCE) or a new formulation;
3. Availability; the extent in which (new) pharmaceuticals are available for patients;
4. Costs; the financial expenditure for the development, regulation and monitoring of pharmaceuticals.

Based on a heuristic tool reflecting the four major themes and their interdependence, we analysed the literature data for each research theme separately and for interdependence between the themes. In the semi-structured interviews, we discussed our literature findings with national experts and asked their opinion on emerging issues. Based on both the literature review and the interview outcomes, we identified potential vulnerabilities in the pharmaceutical regulatory system. We completed our report with some cases to illustrate the potential vulnerabilities to the reader.

The European regulatory system has been built on the pillars ‘public health’ and ‘economic interests’: guaranteeing the safety of medicines available on the market, but safeguarding the interest of the European pharmaceutical industry at the same time. This dual nature of the regulatory regime causes tension between economic interests and public health, which is a constant factor in the policy making process around pharmaceuticals.

Our study shows that the existing regulatory system performs well in terms of *safety and efficacy*. Yet, at the same time, ‘the outside world’ does not (always) share this view as has been shown by the increasing public attention to incidents like those with Vioxx® or Diane 35®. The classic response of regulators to public commotion is an increasing emphasis on medicines safety by new rules. Our study shows that this has negative effects on innovation, availability and costs.

Despite some impressive pharmaceutical *innovations* last decennia, fewer new chemical entities reached the market, while there is still a need for new products. Total R&D expenditure rose sharply as did the costs for a new chemical, there is stagnation/decline of output and worsening of attrition rates. The regulatory system responds to this trend by stimulating innovative products

through specific procedures, for example a regulation specifically for orphan medicinal products, fee reduction and administrative assistance for micro, small and medium-sized enterprises, adaptive licensing procedures and guidance to facilitate early dialogue between regulators, health-technology-assessment bodies and medicines developers. Nevertheless, the lack of real innovation can only partly be attached to the regulatory system and remains difficult to resolve.

The growing amount of regulatory guidelines and the additional requirements for reimbursement often gets the blame for the steadily increasing *costs of pharmaceuticals*, but this allegation is difficult to substantiate because most pharmaceutical producers do not disclose how they compile their prices.

The *availability of pharmaceuticals* is a complex issue in which many stakeholders play an important role. In addition, both regulatory system factors and external factors can be linked to variation in availability between products and/or countries. National policy makers have vast range of tools, like pricing policies, to improve medicine availability and affordability for their citizens. Any future changes to the EU regulatory system should be made as robust as possible towards plausible national and international scenarios that may affect availability.

During the study, two additional themes revealed to be important. The lack of *transparency* and *accountability* of both the pharmaceutical industry and the medicines regulatory authorities contributes to the public distrust in the pharmaceutical system. It also hinders innovation, raises costs and restricts the availability of necessary pharmaceuticals.

The potential vulnerabilities of the pharmaceutical regulatory system, as described in this report, are strongly interrelated. Interventions in one theme will have an effect on another theme or even on multiple themes; e.g. more attention to safety and efficacy will affect costs, innovation and availability of pharmaceuticals. The four major themes can be seen as a four gear wheel. When one wheel is being turned, the others are also set in motion. In addition, all four themes are influenced by transparency and accountability. This interrelatedness makes adjustments to the system complex and should always be kept in mind when discussing possible solutions for improvement of the pharmaceutical regulatory system.

The results show that a mixture of factors, internal and external to the system, combined with a slow-moving organizational structure, give reasons to believe that the current regulatory system for pharmaceuticals is not sustainable in the future. There is a growing need to rethink the balance between ensuring medicines safety on the one hand and the need to promote innovation, ensure availability and limit costs on the other. This rethinking should take into consideration risks perceived by society and patients, benefit-risk communication needs, medical needs and expected risks related to use in daily practice. Second, all experts and decision makers in the marketing approval process should be aware of the balance between the gain in safety versus the feasibility and costs of requesting additional information or data. Third, a continuous dialogue between regulators, the public at large, patients, healthcare professionals and pharmaceutical industry is needed to address both balances and to aim for development of products with greater efficacy benefits for patients. Regulation should keep pace with (fast) changes in society and adopt

societal dynamics. Finally, establishing a robust baseline of transparency and accountability is a prerequisite for success.

1 Introduction

1.1 Background

In recent years, the efficiency of the pharmaceutical regulatory system is under debate by governments as well as society. These concerns relate to the possibilities for innovation, lack of flexibility in the system, the timely availability on the market, pharmacovigilance and resources necessary to comply with and to check all requirements (1). An important issue for the pharmaceutical industry sector is that it is confronted with increasing research and development (R&D) costs, while at the same time the success rate of innovation seems to decline.(2) In addition, recent developments, like the new European legislation for Pharmacovigilance, the development of the European Union (EU) Clinical Trial Regulation to replace Directive 2001/20/EC and the increased focus on the development of personalized medicine, provoke a re-assessment of the current system. The European Medicines Agency (EMA) itself emphasizes that "medicines regulation today is characterized by the increasing complexity of applications for new medicines, such as nanomedicines or personalized medicines, and the drug-development environment as a whole."(3) Finally, reduced public finances, the need for less (restrictive) rules and the call from society for greater transparency, require a review of the current regulatory system.

1.2 Aim of this study

This report is a data-driven review of the sustainability of the EU regulatory system for pharmaceuticals. It aims at identifying areas of special interest by analysing potential vulnerabilities (that demand closer attention) in the regulatory system; with a special focus on innovation, availability of (new) pharmaceuticals, safety & efficacy and costs.

1.3 Definitions and scope

In this study, the research area includes the marketing authorization procedure and other stages relevant to the marketing authorization; the preregistration stage and the post marketing stage. For both stages we only took legislation specifically related to the marketing authorization process of pharmaceuticals into account (see figure 1.1). Legislation is taken in a 'broad sense': laws (e.g. European regulations, directives and decisions; legally binding) as well as 'soft laws' (e.g. guidelines, communications; not legally binding) and companies'/person's interpretation of legislation.

Figure 1.1 The drug development pathway from discovery to product launch and post market monitoring. All areas in green are within the scope of this research.

2 Historical background European regulation of pharmaceuticals

Today pharmaceuticals are one of the most regulated products on the market. Their safety, efficacy and quality are under permanent surveillance. Before new medicinal products can be put on the market, they have to undergo an authorization procedure. After they have gained market access, new medicinal products are supervised for unknown adverse effects. Furthermore, most European countries have extensive legislation concerning the prices, labels and promotion of medicinal products, while the European Pharmacopoeia guards the compilation of pharmaceutical products, their formulas and methods of preparation (4).

This has not always been the case. The European Union and its predecessors – the European Economic Community (EEC) and the European Community (EC) – have played a central role in the development of pharmaceutical legislation in Europe, which eventually lead to a centralized and comprehensive regulatory system for medicinal products. This development was driven by two conflicting forces: the endeavour of 'Europe' to be something more than a free trade area or customs union and the constant political resistance of individual member states against the limitation of their sovereign power (5). Knowledge of the historical dynamics that have shaped the European regulatory regime is crucial for a careful assessment of its strengths and weaknesses.

In the following chapter, we give a short overview of some of the main developments in the history of the pharmaceutical risk governance in Europe. Risk governance incorporates all regulations, institutions and stakeholders (embedded in their own legal, institutional, social and economic context) that deal with various aspects of a risk process. Within a risk process several phases can be discerned, such as risk assessment (identifying and exploring risks), risk management (prevent, reduce or alter the consequences identified by the risk) and risk communication (bridging the tension between expert judgment and public perceptions of risks) (6, 7). In other words, the regulatory framework ascribes responsibilities to different actors, both horizontally (government, industry, science) and vertically (regional, national or supranational levels), who are often interlinked to one another.

During the course of the 20th and 21st century the focus of the European regulatory system for pharmaceuticals has shifted between various aspects of risk governance, depending on and driven by the constant interaction between various actors and institutions in the arena of pharmaceuticals.

2.1 The era of therapeutic catastrophes, 1900-1964

The development of pharmaceutical legislation in Europe (and the United States of America) is intrinsically interwoven with the ascent of industrially produced medicinal products during the first decades of the 20th century. Around 1900, the production of vast majority of available pharmaceuticals, which was still largely in the hands of individual pharmacists, was regulated by national pharmacopoeia. The education and professional status of pharmacists was governed by law as well. On the contrary, there was no or very little legislation specifically aimed at industrially produced medicinal products - at this time still a very small segment of market for pharmaceuticals.

There was no clear 'European' legislative tradition. In Germany, the United Kingdom and the United States (US), the pharmaceutical industry was largely left unregulated. In France and the Netherlands, on the other hand, monitoring agencies were established, though their authority was limited. The Dutch Rijks Instituut voor Pharmaco-Therapeutisch Onderzoek (National Institute for Pharmacotherapeutic Research) was founded in 1920. This institute, however, could only inform the public and physicians about hazardous products, but was not able to prevent medicinal products from entering the market. The French Visa Ministériel-system, under which firms had to apply for a 'visa' before being able to sell pharmaceuticals in France, did contain regulations concerning the safety of medicinal products, but it was primarily aimed at protecting the French pharmaceutical industry from foreign competition (4).

Partially due to the focus on production by individual pharmacists, nobody seemed to be prepared for the large-scale consequences that the large-scale (industrial) production and distribution of hazardous medicinal products could have. The implicit reliance on the self-control (or self-regulation) of the pharmaceutical industry that underlined the government's restraint, turned out to be misplaced. Selling lethal drugs might be bad for business, but this did not mean it did not happen. In 1937, the 'sulfanilamide incident' shocked the United States. In order to cater the demand for a liquid form of sulfanilamide, a product that was widely used for the treatment of streptococcal infections, the firm S.E. Massengill launched an *Elixir Sulfanilamide*. More than a 100 people died. The company had erroneously mixed sulfanilamide with diethylene glycol, more commonly used as antifreeze. Under the then existing regime, the US government could not charge Massengill with selling lethal medicines. It could only fine the company for using an incorrect (and misleading) label: according to the pharmacopoeia, elixirs were solutions based on alcohol, which was evidently not the case with *Elixir Sulfanilamide*. The American federal Food and Drug Authority (FDA) was established as a direct result of this incident (8, 9).

In Europe, two similar events lie at the basis of the introduction of pharmaceutical legislation. Of these incidents, the thalidomide disaster is indisputably the most well-known. The German company Grünenthal started to market Contergan® (NL: Softenon®, UK: Distaval®) in the late 1950s as a safe and non-addictive sleeping pill. It contained high levels of thalidomide. Shortly after the market introduction of the product, reports of previously unknown neural damage surfaced which could be traced back to the intake of Contergan. The most devastating effect, however, was the deformities thalidomide caused in unborn children whose mothers took Contergan® during pregnancy. During the 1958 and 1960, Contergan was introduced in 46 different countries worldwide resulting in an estimated 10.000 babies being born with phocomelia and other deformities. (4, 9).

In France, thalidomide did not gain market access, but the stalinon drama had the same devastating effect. Stalinon®, a mix of diiododiethyl tin and isolinoleic acid esters, was a popular product used to treat staphylococcal infections. A dispensing error lead to a product being sold in which the levels of diiododiethyl tin were three times higher than in the sample that was used in the clinical trial. Around a 100 people died and a similar number was left permanently affected (9, 10).

2.2 The birth of a European framework, 1965

The response to these incidents varied from country to country. Some years prior to the Thalidomide incident, in 1958, the Netherlands had introduced a pharmaceutical law and a regulatory agency – *het College ter beoordeling van verpakte geneesmiddelen*. Still, even after the effects of thalidomide became

fully clear, it took some years – until 1963 – before the law actually came into force (11). In France, the United Kingdom and Germany pre-market controls for pharmaceuticals were introduced in 1967, 1968 and 1976 (4).

On the European level, actions were taken at a faster pace. In 1964, a Convention was signed for the elaboration of a *European Pharmacopoeia* between eight member states of the Council of Europe[1]: Belgium, France, Germany, Italy, Luxemburg, The Netherlands, Switzerland and the United Kingdom. Both the European Economic Community and the World Health Organization (WHO) became observers in the *European Pharmacopoeia*-committee. The convention was based on a dual commitment: 1. to create a common pharmacopoeia by contributing both financially and in manpower; 2. to make it the official pharmacopoeia, if necessary replacing the existing national requirements (12).

The European Economic Community played an important role by canalizing and reinforcing the regulatory reactions of national governments to the thalidomide incident. Directive 65/65/EEC, issued in 1965, stated that 'no proprietary medicinal product may be placed on the market in a Member State unless an authorization has been issued by the competent authority of that Member State'.[2] This meant that all member states were obliged to establish pre-market controls for medicinal products. Furthermore, the Directive established that all authorizations, as well as withdrawals or suspensions of authorization, could only be based on the evaluation of the safety, therapeutic efficacy and the quality of the pharmaceutical product. Economic or political reasons to deny authorization were no longer regarded as valid justifications (4).

According to its preamble, the primary purpose of the directive was 'to safeguard public health'. For the first time the EEC formulated goals that were not directly connected to its original aim: a market-oriented union based on the idea of economic cooperation. However, the EEC founding treaty – the Treaty of Rome (1957) – did not contain any provisions on health care, because nobody at the time thought the EEC should have any competence in this area. On the other hand, it did contain certain provisions that could be used as a 'back door' for the creation of a system of harmonized pharmaceutical law in Europe. In this case, the paragraphs concerning the freedom of movement of goods (trade in medicinal products) and the freedom to provide services (distribution of medicinal products and provision of health care services) were of particular importance. Legislation concerning market integration became the 'available institution' through which the EEC could address public health concerns. After all, medicinal products were commodities, and commodities had to be safe before they could be put on the market (5).

The fact that the EEC used economic law to regulate a public health issue, would become a source of constant tension in European health policy (13). The promotion and protection of public health and economic integration did not necessarily rule each other out, but they did automatically support each other either. It was a difficult line to tread, as became clear in Directive 65/65/EC. The Directive clearly stated that the introduction of a pharmaceutical regulatory regime should be 'attained by means which will not hinder the development of the pharmaceutical industry or trade in medicinal products within the Community'. Public health should not hinder economic development, an opinion that was reflected by the fact that it was the Directorate-general of Industry (in its various incarnations) that set out the lines for European pharmaceutical policymaking.

[1] Not to be mistaken with the European Council/Council of the European Union. See: Glossary.
[2] Directive 65/65/EEC.

The EEC took as active a stance as it possibly could in the debate on the safety of medicinal products. Yet, it took a considerable time before member states had implemented the new European rules. Pharmaceutical legislation was an integral part of health legislation and it needed to fit with the already existing national health systems. The scope of Directive 65/65/EEC was limited to proprietary medicinal products. What we now call generic medicines were excluded from mandatory authorization. Exemptions were also made for products which traditionally were not considered to be 'medicinal product', such as homeopathic medicines, radiopharmaceuticals, blood products and immunological medicinal products, like sera and vaccines (14).

2.3 Between fragmentation and centralization, 1975-1985

With the safety of pharmaceuticals protected by mandatory pre-market authorization procedures, the EEC shifted its focus to two other aspects of pharmaceutical risk assessment: the quality and efficacy of medicinal products. The annex of Directive 75/318/EEC, issued in 1975, described the trials that had to be conducted to prove the safety and efficacy of a medicinal product. The Directive made compliance with the European Pharmacopoeia Monographs mandatory when requesting marketing authorization for medicines for human use, thus firmly integrating market authorization and quality control (9, 12). At the same time, the Second Directive on medicinal products (75/319/EC) introduced a compulsory authorization procedure for manufacturers of pharmaceuticals, in order to safeguard the quality of the production process (14).

The underlying aim of market-integration was not forgotten. In 1975, the EEC also introduced a 'community procedure'. If a medicinal product had received a positive authorization in one member state, the pharmaceutical company was allowed to apply for recognition of this authorization by at least five (and later two) other Member States. These Member States had to decide whether or not they accepted the positive verdict of the so called 'reference member state'. In order to facilitate this 'mutual recognition'-process an expert committee was set up, consisting of representatives of the regulatory agencies of all member states: the Committee for Proprietary Medicinal Product (CPMP). This committee only had an advisory role and could no issue binding resolutions. For advice regarding legislation and policy issues concerning medicinal products the European Commission established another advisory body: the Pharmaceutical Committee (4, 14).

The main goal of the Community Procedure (later renamed to 'Multi-State Procedure') was market integration. The procedure aimed to ease access for pharmaceutical products to the entire ECC-market. This did not work as planned. Most member states cherished the authority they had. The CPMP, lacking a clear regulatory mandate, could only voice its opinion, but could not force decisions. The vast majority of Multi-State applications were blocked by objections from one or more concerned member states, proving that cultural differences and economic considerations still played an important role in the assessment and evaluation of medicinal products, despite uniform EEC-law. The implicit call for interagency communication and cooperation on which the Multi-State Procedure relied heavily, eventually led to little convergence concerning the final (national) authorization decisions (15, 16).

The CPMP, however, did provide a platform for experts to meet on a regular basis. The influence of working groups, established by the CPMP for the development of uniform guidelines regarding the dossier-requirements, cannot be underestimated. From 1980 onwards, with the publication of the first 'Notice to Applicants', European guidelines concerning application dossiers and

principles of Good Manufacturing, started to replace existing national procedures (17).

Despite this success, the creation of a single European market for medicinal products seemed to have ground to halt during the first years of the 1980s; not unlike the entire process of European integration. By the end of the 1970s, the initial enthusiasm that had accompanied the founding of the EEC in 1957, had turned into a form of 'eurosclerosis'. Continuous economic stagnation and the (perceived) democratic deficit of EEC-institutions had led to an increasingly apathetic attitude towards a 'united Europe'. The Single European Act of 1986 tried to revive European integration. The treaty, amongst other things, aimed to have established a single 'common' market in Europe by the end of 1992 (18).

2.4 Breaking the stalemate, 1985-1999

The Single European Act also revived the idea of a single European market for medicinal products. In order to break the stalemate, the EEC established a new (more binding) procedure, the so-called Concertation Procedure in 1987.[3] The directive stated that all applications concerning biotechnologically produced medicinal products in Europe had to go through the same centralized procedure, supervised by the CPMP. Even though the CPMP-decision was not legally binding, it was difficult for national agencies to deny authorization once the CPMP had approved it (14).

It was not surprising that the EEC embraced 'biotechs' to break the impasse in the European debate on the regulation of medicinal products. The biotechnologically produced pharmaceuticals worked differently than conventional medicines and the production and development of these products were not comparable with the development and production of conventional pharmaceuticals. The growing market for biotechnologically produced pharmaceuticals forced all stakeholders to change their outlook on the topic of a uniformed European authorization procedure, especially the industry. Biotechnologically produced medicinal products were almost impossible to patent under the then existing patent-law, which varied widely between member states. Placing these products under specific EU-law would indirectly protect the producers of biotech pharmaceuticals from competition with cheaper generic equivalents (19).

The Association of the British Pharmaceutical Industry (ABPI) seized the initiative by publishing its 'Blueprint for Europe' in 1988. The blueprint stressed the importance of a single authorization procedure in Europe and suggested to making 'biotech'-medicines subject to a mandatory centralized procedure supervised by a single European agency, whereas other 'innovative products' should be able to be voluntarily subjected to the same procedure (20, 21). According to ABPI all generic products – and other 'less innovative' pharmaceuticals – should remain subjected to the procedure of mutual recognition. Still, if mutual recognition failed, the new European agency should be able to issue a binding decision.

The European Commission realized that the creation of a single market also meant that the regulation of proprietary medicines alone was no longer sufficient. The scope of European legislation was extended to new categories of medicinal products that were unregulated before, such as generic medicines; immunological medicinal products (sera, vaccines, allergens)[4];

[3] Directive 87/22/EEC.
[4] Directive 89/342/EEC.

radiopharmaceuticals[5]; blood products[6] and homeopathic products.[7] Gradually, the European regulatory framework became a comprehensive system, which not only focused on risk assessment, but on risk management as well. With the introduction of the 'Rational Use'-package[8], aspects like the distribution of medicinal products, their classification, labeling and patient information leaflets (PILs), and advertising were brought under European jurisdiction. However, market integration was never out of sight. In 1989, the EEC took measures relating to the transparency of regulating the prices of medicinal products and their inclusion in the scope of national health insurance systems.[9] It forced Member States to be more open when it came to question whether certain pharmaceutical products would be reimbursed or not, hoping this would prevent indirect market protection.

During the 1990s, the creation of a truly 'European' market for pharmaceutical products gained more and more momentum. The EEC adopted the suggestions that the ABPI had made a few years earlier and planned to install a new regulatory agency in London, the European Agency for the Evaluation of Medicinal Products (EMEA). Furthermore, the existing European authorization procedures were to be replaced by a new mutual recognition procedure and a centralized procedure for biotechnologically produced (and other 'innovative) medicinal products (4). The EMEA and the Centralized Procedure (CP) would come into force in 1995.[10]

Though the Centralized Procedure was certainly more centralized than its predecessors were, individual member states did have influence. The producers of medicinal products filed their application with the EMEA, but the CPMP – now fully integrated within the EMEA framework – delivered its opinion based on scientific evaluation by national regulatory agencies. This decision was then forwarded to the European Commission, which would draft a European Marketing Authorization. This authorization could only come into force if the Standing Committee on Human Medicinal Products – also a member state committee – accepted it with a qualified majority. If this procedure failed, the European Council would make the final decision (17). The Mutual Recognition Procedure was similar to the old Multi-State procedure, but in case of a dispute, arbitration was compulsory and the decision of the CPMP was no longer noncommittal (4, 22).

Though far-reaching in its consequences, the 1993 reform of the European regulatory system for medicinal products was primarily aimed at the procedural rules of the regime. Both the Centralized and Mutual Recognition Procedure still used the criteria for authorization that were laid down in 1965 and 1975. Still, it was clear that the European Community wanted a more centralized 'European' approach when it came to certain public health issues. Contrary to the Treaty of Rome, the treaty of Maastricht (1992) explicitly mentioned health care as a field of European interest. The role of the EC would be complementary, encouraging cooperation between Member States and lend support when necessary (5).

The more active stance of the EU in matters of public health also resulted in the decision of the European Commission to make the EU a full member of the European Pharmacopoeia. The EC signed a contract with the

[5] Directive 89/343/EEC.
[6] Directive 89/381/EEC.
[7] Directive 92/73/EEC.
[8] The 'Rational-Use'-package consists of the following directives: Directive 92/25/EEC; Directive 92/26/EEC; Directive 92/27/EEC and Directive 92/28/EEC.
[9] Directive 89/105/EEC.
[10] Regulation 2309/93.

Council of Europe's European Pharmacopoeia Secretariat to set up a European network of Official Medicines Control Laboratories (OMCLs). This network of 'national laboratories' would function as a framework of quality control of marketed medicinal products for human and veterinary use. To set up and coordinate this new network, the European Directorate for the Quality of Medicines (EDQM) was created by the Council of Europe in 1995 (and partly financed by the EU). In 1997 the EDQM and the EMEA agreed to allow sampling and testing of centrally authorized products (CAP) by the OMCL's, forging a more comprehensive system of the still separate institutions of quality control and market approval.

2.5 A more centralized regulatory system, 2000-2013

As was stipulated in Regulation 2309/93, the European Commission conducted an evaluation of both the Centralized Procedure and the Mutual Recognition Procedure within six years of their operation. After an extensive survey among all concerned stakeholders, an evaluation-report was published in October 2000 (15). Though the report demonstrated general contentment, especially with the Centralized Procedure, the industry regarded the 'political phase' after the initial verdict of the EMEA, as superfluous. It only delayed market access, since the Commission and Member States had not altered any authorization up to 2000.

The dissatisfaction with the Mutual Recognition Procedure remained relatively high. The procedure did not achieve its main goal, the creation of a single European market for 'less innovative' pharmaceuticals. Arbitration procedures rarely started after the failure of a mutual recognition application, mainly because the applying companies withdrew their submissions from Member States that raised serious objections against the authorization of their products (23). Most patients' and physicians' organizations clearly favored the Centralized Procedure, since it rushed the availability of innovative medicinal products and removed regional differences between countries.

The subsequent 2001 Review[11] addressed these issues. The scope of both the compulsory and voluntary application to the Centralized Procedure was extended and the influence of individual Member States on the political phase of the authorization procedure was reduced. The cumbersome name of the European Agency for the Evaluation of Medicinal Products was changed to European Medicines Agency. The recruitment of the CPMP expert committee (renamed the Committee for Human Medicinal Products, CHMP) and the management board of the EMA was opened to independent experts and stakeholder representatives. The Mutual Recognition Procedure was strengthened by the introduction of compulsory arbitration, even if the company had decided to withdraw its application. Furthermore, national agencies were allowed to inform their international counterparts of their findings before they would issue authorization, hoping this would lead to more discussion (and less quarrelling) among national agencies (4, 14).

In response to concerns – mostly voiced by the industry and scientists – that the introduction of truly effective and innovative pharmaceuticals was slowed down by European 'red tape', two new 'accelerated' procedures were introduced: Conditional Approval (CA) and approval under Exceptional Circumstances (ECs). The authorization of Orphan Drugs was brought under the Centralized Procedure via separate legislation: Regulation 141/2000. With these new procedures, improved access to effective medication (mainly for unmet medical needs) seemed to overrule the pursuit of 100% safety (14). Risk

[11] More specifically Directive 2001/83/EC and Regulation 2001/20/EC.

management became more and more important. In order to control post-registration safety issues that might arise from earlier market access, the post-market safety control needed to be bolstered. The somewhat noncommittal system of EU pharmacovigilance, installed in 1993, was strengthened. The European Commission gained the authority to take immediate Union-wide emergency measures – without the need for support of either the Council or the Member States – if medicinal products were deemed to be unsafe (24).

The centralization process that was started in 2001 continued with the implementation of Regulation 726/2004 in 2004. The obligation to apply for authorization under the Centralized Procedure was extended to include all medicinal products meant for the treatment of Acquired immunodeficiency syndrome (AIDS), cancer, neurodegenerative disorders and diabetes. Simultaneously, a new multi-state authorization procedure was introduced: the Decentralized Procedure (DP). This procedure more or less worked like the Mutual Recognition Procedure, but it made it possible for a company to file an application for the marketing authorization in several Member States at the same time. It was no longer required to have authorization in one of the Member States prior to the submission of an application, which would speed up the authorization process. At the same time the legal position of the EDQM within the EU-framework was strengthened by allowing the EDQM to ask national inspection services to collaborate on inspections of manufacturing and distribution sites for raw materials for pharmaceutical use and by legally recognizing the role played by OMCLs in independent testing.[12]

By the end of 2007, the year in which Regulation 1394/2007 brought all advanced therapy medicinal products (ATMP's) under European supervision[13], the institutional contours of the regulatory framework that is in place today was more or less finished. Furthermore, the economic emphasis that had always accompanied Europe's pharmaceutical policymaking seemed to make place for a more public health oriented approach. In 2009, the EU transferred all control over pharmaceutical legislation, policymaking and regulation – with the EMA as its most visible figurehead – from the Directorate-general for Enterprise and Industry to the Directorate-general for Health and Consumers (25). The scope of pharmacovigilance (post-market safety controls) gradually expanded. After a high profile controversy between the Nordic Cochrane Centre and the EMA (13), complaints of a chronic lack of transparency – a recurrent reproach in virtually all European institutions – was addressed as well.[14]

2.6 Conclusions

Looking back on a century of European pharmaceutical legislation, we can identify four major groups of actors that have shaped the regulatory framework: supranational organizations like the European Union (and it predecessors) and the Council of Europe, national governments, the pharmaceutical industry and experts. As we have seen, each group tried to steer the system according to their own specific needs.

As the pharmaceutical industry gained in importance during the twentieth century, it became clear that the existing regulatory framework was not prepared to cope with this new actor. Pharmaceutical law was still primarily aimed at individual pharmacists and manual or small-scale production of medicinal products, and remained so for a long time. Various incidents – with the Thalidomide-scandal as its tragic climax – proved that the implicit reliance of

[12] Directives 2004/27/EC and 2004/28/EC.
[13] Regulation 1394/2007.
[14] Directive 2010/84/EU; Directive 2012/26/EU; Regulation 1027/2012.

national governments, both in Europe and the US, on self-regulation of the industry was misplaced.

These incidents formed the basis of regulatory interventions on both the national and the European level in the late 1950s and early 1960s. The Council of Europe focused its attention to quality control and launched the *European Pharmacopoeia* which would eventually evolve into the European Directorate for the Quality of Medicines. The European Economic Community tried to reinforce and canalize national regulatory interventions, yet the difference in perspective and available policy instruments between the EEC and national governments lead to two distinct fields of tensions: a. the tension between public health protection and market integration; b. the tension between supranational legislation and national sovereignty.

While national governments established regulatory systems based on the principle of public health protection, the legal basis of European pharmaceutical law – Directive 65/65/EEC – was firmly grounded on principles of market freedom and market integration (and was therefore inherently more 'industry-friendly'). Despite their common goal – the distribution of safe medicinal products – both the national and the European regulatory frameworks had secondary goals, which did not necessarily agree with each other. The EEC for example had quite explicitly formulated its secondary goal: stimulate the European pharmaceutical industry. For national governments the main concern was to remain in control of their own national health system. These tensions still exist today.

Up until the mid-1980s, the tension between supranational unification and national sovereignty more or less paralyzed the entire process of European integration. This also had its effects on the European regulatory system for medicinal products. Despite much effort, the authorization procedure for medicinal products largely remained in the hands of individual Member States. The true motor behind centralization were the individual expert-committees, since they could work in relative anonymity and focused their work on issues that were 'politically safe', such as guidelines for application-dossiers and manufacturing.

Only after the decision was made that Europe should indeed become 'an ever closer union' – with the Single European Act of 1986, it was possible to fast-track the creation of a single European market for medicinal products and subsequently a single regulatory system. The industry welcomed the new drive towards market integration, since it could solve the problem of patenting biotechnologically produced pharmaceuticals. Driven by the EEC and the industry, Europe gradually extended its influence to almost every aspect of the market for pharmaceutical, except reimbursement. With regard to quality control the relations between the EU and the EDQM and its network of Official Medicines Control Laboratories was intensified.

Though the Thalidomide-disaster lies at the basis of the European Regulatory system, the regulations and directives that followed were – as we have seen – were not always a direct reaction to other safety-incidents. As of yet, the European pharmaceutical sector has not suffered from any crisis of consumer confidence as fundamental as the Thalidomide affair (26). It was the strive towards European integration that proved to be one of the strongest motors behind the expansion of regulation. This does not mean that the focus of the system did not change over time. While it began as a system that was primarily concentrated on the safety and quality of medicinal products, by the end of the 1970s the efficacy of pharmaceuticals had come to the fore. The focus gradually shifted from risk assessment towards risk management during the 1980s. With the recent complaints about the lack of transparency and

accountability, one might ask if the regulatory system has yet to make another shift, towards risk communication.

3 Methods

3.1 Overview

We have split this project, starting in May 2013, in three main activities:

- Step 1, literature review;
- Step 2, semi-structured interviewing of national key experts;
- Step 3, identification of illustrative cases.

The details of these steps are outlined below. For step 1, we identified potential vulnerabilities related to the EU pharmaceutical regulatory system. We used these potential vulnerabilities as input for step 2 and step 3.

3.2 Step 1, literature review

The literature review consisted of two parts:

- snowball search
- scientific literature search (based on the search terms as identified in the snowball search)

3.2.1 Snowball search

The aim of the snowball search was twofold; a) to define a list of search terms, to be used in the literature search and b) to collect all relevant information not available in literature databases.

The snowball search started with a free internet search in engines, such as Google and Bing. We looked for any information related to the (dis)functioning of the current regulatory system for pharmaceuticals. Furthermore, websites of relevant national and international organizations were screened (see table 3.1) and information was included when it related directly to EU regulatory system for pharmaceuticals.

Organisations	**Website**
European Medicines Agency	http://www.ema.europa.eu
World Health Organization	http://www.who.int
European Commission	http://ec.europa.eu
RAND Corporation	http://www.rand.org
European network of Health Technology Assessment	http://www.eunethta.eu
European Federation of Pharmaceutical Industries and Associates	http://www.efpia.eu
London School of Economics and Political Science	www.lse.ac.uk
Top Institute Pharma	www.tipharma.com
Innovative Medicines Initiative	www.imi.europe.eu
Heads of Medicines Agencies	www.hma.eu

Table 3.1 Websites screened

In addition, national experts (n=14) were asked for information on additional relevant documents, such as dissertations and governmental reports, relevant websites, possible keywords or search terms and other experts in this area. This first snowball search resulted in 57 documents, ranging from reports, figures, conference papers, dissertations and opinions.

3.2.2 Scientific literature search

We conducted a structured, rather than fully systematic literature search, designed efficiently to meet the functional requirements of this project. Relevant publications in the scientific literature were drawn from the electronic database Ovid-Medline up to August 2013. This database includes practically all references included in the databases Pubmed and Scopus. Based on the snowball search we defined search terms (see table 3.2) and inclusion- and exclusion criteria (see table 3.3). We used a combination of key words and synonyms to find as much relevant scientific publications as possible.

Research topics	**Key words or synonyms**
European regulatory system for medicinal products	Regulation, legislation, jurisprudence, guidelines, market authorization, registration, pre marketing stage, post marketing stage, pharmacovigilance, reimbursement, drug approval, organization, administration, market access, drug discovery
	European, Europe, EU, European Union
	Medicines, drugs, medicinal products, pharmaceuticals, pharmaceutical preparations
Sustainability system	Effectiveness, strengths, weaknesses, bottlenecks, cost effectiveness, health technology assessment (HTA), HTA, risk benefit analysis, risk assessment, evaluation, assessment, evidence based medicine, review, sustainability, quality assurance
	Safety, health protection, innovation, availability, access, costs, expenditures

Table 3.2 Keywords used for literature search

Inclusion criteria: Publications included met all of the following criteria:
1. Describing the (dys)functioning of the EU regulatory system for pharmaceuticals or certain aspects of this system
2. Belonging to one of the following publication categories: research articles (quantitative or qualitative research), editorial, opinions, commentary, perspectives, books, technical reports, working papers, scientific papers on the World Wide Web and dissertations
Exclusion criteria Publications excluded were:
1. Publications reporting on issues other than those related to the EU regulatory system for pharmaceuticals
2. Publications in a language other than English or Dutch
3. Publications with an inaccessible full text document
4. Publications older than 2003

Table 3.3 Inclusion and exclusion criteria

3.2.3 Study Selection

The literature search resulted in a list of 162 publications. A single researcher selected 120 publications for analysis based on the information in the summary and the predefined inclusion criteria. Two researchers independently assessed these publications by using a one to five points rating system. A publication was given five points if it was judged as very important and one point if it was judged as not relevant. Publications were selected if they were assigned four of five points by both researchers and were removed if they were assigned only

one or two points by both researchers. The relevance of all other publications were discussed between the two researchers. This resulted in the final selection of 54 articles.

3.2.4 *Snowball search – collection of relevant information not available in scientific literature databases*

Throughout the course of the whole project, we added additional information (publications, reports, opinions etc.). We obtained these publications through meetings, conferences, information from experts (via interviews) and journals. This 'search' resulted in 64 additional publications.

3.2.5 *Analysis*

We identified four major themes of the regulatory system for pharmaceuticals. In order to operationalize these themes for research, we defined them as follows:

1. Safety & efficacy; safeguarding public health by denying market access of ineffective and/or harmful products and/or withdrawing them from the market;
2. Innovation; the possibility to bring pharmaceuticals on the market, either with a new chemical entity (NCE) or a new formulation;
3. Availability; the extent in which (new) pharmaceuticals are available for patients;
4. Costs; Financial expenditure for the development, regulation and monitoring of pharmaceuticals.

Two researchers independently analysed all selected literature. In order to assist this analysis and to structure the findings, we used a heuristic tool consisting of the four major themes. The collected information was first analysed for each research theme separately. However, because of overlap, we also studied the interdependence between the themes (see figure 3.1 below).

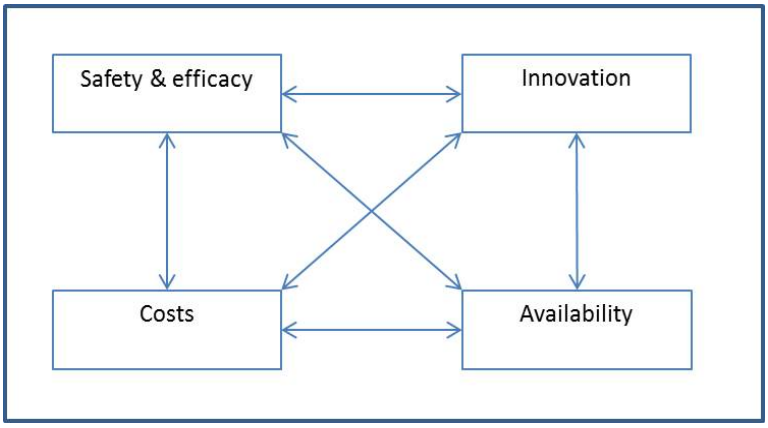

Figure 3.1 Heuristic tool, interdependence between themes

The results of this literature review are shown in chapter 4.

3.3 Step 2, semi-structured interviewing of national experts

As a second step, we interviewed nine national key persons who are active in the field of biomedical science and have expertise in/with the pharmaceutical regulatory system.

Expert	Professional Background
1	Hospital pharmacy, clinical pharmacology
2	Pharmacovigilance
3	Medical Ethics
4	Law and pharmaceutical science
5	Fast track treatments on a commercial basis
6	Health Economics and reimbursement
7	Oncology, clinical pharmacology
8	Biotechnology
9	Patient representation

Table 3.4 Professional background interviewees

In the interviews we discussed the findings of the literature review and asked for in their opinion, possibly other potential vulnerabilities within the (EU) pharmaceutical regulatory system. We applied a semi-structured interview approach with a topic list. This list was divided into two parts; a general part with questions ordered around the four major themes, and a part in which the questions were geared towards the interviewees' expertise. All interviews were audio recorded. The audio recordings were transcribed. The transcription was crosschecked with the field notes of the second interviewer. We discussed any inconsistency and if necessary, went back to the original audio recording. The researchers invited respondents to react on the transcripts of the interviews

The data analysis phase involved an inductive content analysis of the interviews, starting with a close line-by-line reading of the transcripts and developing a conceptual coding scheme based on the four major themes identified earlier (safety, innovation, costs, availability). We based the code list initially on the conceptual framework and completed it with inductive codes. While coding, researchers paid special attention to similarities and differences in opinion and perception between experts. The results were then clustered in descriptive themes (27). Actual quotes were translated into English and crosschecked with the respondents. The results of the interviews are described in chapter 5.

Based on both the literature review (Step 1) and the interview outcomes (Step 2) we identified possible vulnerabilities in the pharmaceutical regulatory system.

3.4 Step 3, identification of illustrative cases

In the third and last step of the project we identified cases to illustrate (some of the) identified potential vulnerabilities within the EU regulatory system in our literature review. The cases are taken up in chapter 4.
We first searched for examples within the EMA website by analyzing medicinal products that were withdrawn post-approval, suspended or refused. We used EMA documentation, such as European public assessment reports (EPAR), but also public information on the internet on the specific product to get an impression of the encountered problems. We selected those products that envisaged problems in the pre-, post-, and/or registration phase related to the regulatory process (although not necessarily caused by the regulatory system). Finally, we completed our literature review with some cases to illustrate the potential vulnerabilities to the reader.

4 Literature review results

4.1 Introduction

In this chapter we present the findings of the literature review, illustrated with case examples. The findings are grouped according to their major theme: Safety & efficacy, Innovation, Costs, Availability and Transparency & Accountability. The methodology behind the structured review and the selection process of the cases is explained in chapter 3: Methods.

The following paragraphs are structured similarly. Each paragraph starts with a subparagraph 'current issues' in which we introduce the main problem(s) that were mentioned in the international literature in relation to the overarching theme. Subsequently we try to determine if these incidents are caused by potential vulnerabilities in the current regulatory regime or by factors not directly related to the system? This will be done in the subparagraph: 'potential causes'. The question how regulators (and governments) address these problems is discussed in the subparagraph 'government reactions'. The illustrative cases can be found throughout the whole chapter.

4.2 Safety & Efficacy

4.2.1 Current issues

One of the most important aims of the European regulatory system for pharmaceuticals is to protect public health by guarding the safety and efficacy of pharmaceuticals (5, 28, 29). Initially motivated by the tragic events of the Thalidomide-catastrophe of the 1960s [see: historical background], the process for developing, manufacturing and marketing pharmaceuticals has become one of the most regulated – and safest – processes in the world (5, 28-31). However, during the last ten years the regulatory system suffers from a seeming decrease in public trust in its ability to guarantee the safety of pharmaceuticals. The press, the public and politicians seem to pay an increasing amount of attention to recalls and concerns regarding pharmaceuticals which have been granted market authorization (and were thus deemed to be 'safe'), such as Baycol®, Vioxx®, Avandia® and, more recently, Diane-35® (19, 32).

Adverse drug events, whether or not due to (in)correct use of pharmaceuticals, are estimated to be a leading cause of unplanned hospital admission (33, 34). Between 1 January 1999 to 31 December 2011, the amount of withdrawals of new active substances approved under the European Centralized Procedure was relatively low: 9 out of a total of 279. At the same time, the number of serious safety issues - defined as issues requiring a Direct Healthcare Professional Communication (DHPC) to alert individual healthcare professionals or a safety related drug withdrawals – amounted to 55 (53 first DHPCs and two safety-related withdrawals without a prior DHPC (the epoetins)) (35).

4.2.2 Potential causes

Randomized Controlled Trials (RCT) & limited data

At the time of approval of a new medicine, there are limited long-term data on the medicine's benefit–risk balance (19). Clinical trials are designed to demonstrate efficacy, but have major limitations with regard to safety in terms

of patient exposure and length of follow-up. A study by Duijnhoven *et al.* determined the number of patients who had been administered medicines at the time of medicine approval by the European Medicines Agency (see figure 4.1) and the number of patients studied long term for chronic medication use, and compared these numbers with the International Conference on Harmonisation's (ICH) E1 guideline recommendations (36). They conclude that for medicines intended for chronic use, the number of patients studied before marketing, is insufficient to evaluate safety (and long-term efficacy). Although increasing the number of patients exposed to a medicine before approval can be justified, especially for medicines intended for long-term use, the requirement can delay new products entering the market (see: Innovation) (32).

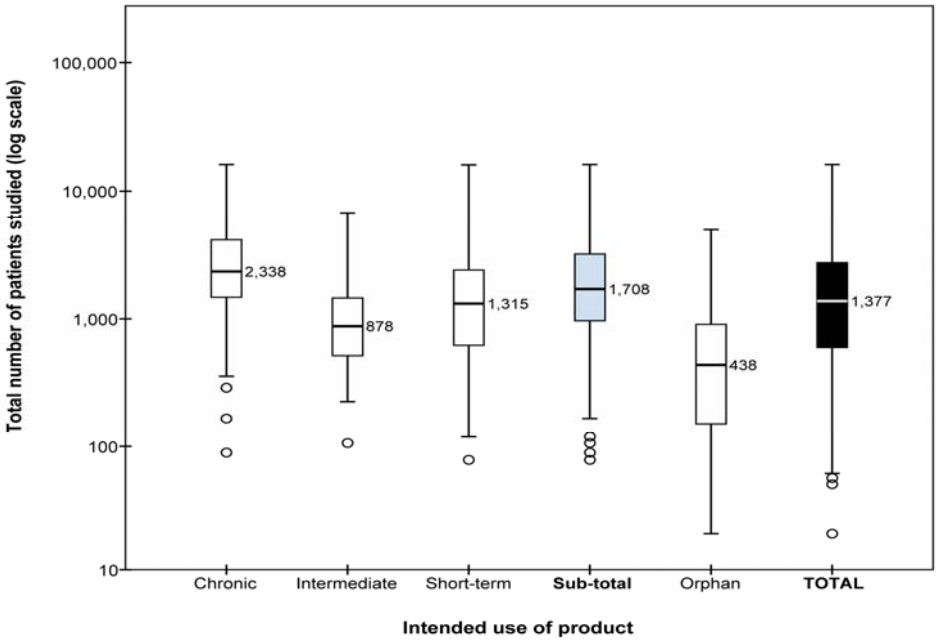

Figure 4.1 Boxplots with medians of the number of patients studied before approval. This figure includes all medicines containing new molecular entities approved between 2000 and 2010, including orphan medicines as a separate category. Results for standard (non-orphan) medicines are presented by intended length of use of the products (chronic, intermediate, or short-term) and as one group (sub-total). Boxplots present the 50th percentile, i.e., the median value is given, with the interquartile range (25th and 75th percentiles) indicated by the box, the 2nd and 98th percentiles indicated by the horizontal bars of the whiskers, and outliers indicated by individual circles. The total number of patients studied (y-axis) is plotted on a logarithmic scale. Source: (36).

Another major problem is that data from clinical trials provide an incomplete and/or a too optimistic indication of the efficacy of pharmaceuticals in real life (31, 37). Randomized controlled trials are typically performed in carefully selected patient populations not fully representing 'real world' patients. The effectiveness may be lower in the population with specific comorbidities. After all, many factors influence the benefit-risk profile at an individual level. Therefore, it is difficult to predict how a product, proved to be safe and effective in a 'standardized' population, will respond in a given patient. This problem is called the 'efficacy-effectiveness gap'. Efficacy is shown under controlled circumstances and effectiveness in clinical practice in daily care (32). The

current regulatory framework does not reflect this unpredictability of the confounded real world populations.

Stakeholders may therefore arrive at divergent conclusions when balancing the expected benefits of a pharmaceutical against the harms it might cause, once allowed on the market (38). For this reason, Lumpkin *et al*. mentioned that benefit-risk profile assessments should also involve an assessment of the tolerance for risk within the intended population. However, data gathered in randomized controlled trials do not provide information on this (31).

Box 1; Tolcapone (Tasmar®)

Tolcapone is used for the treatment of Parkinsons's disease and marketed under the proprietary name Tasmar®. This medicinal product received an initial EU marketing authorization in 1997. However, due to three cases of fatal hepatotoxicity that emerged out of post-marketing surveillance studies, CHMP advised to suspend Tasmar's EU marketing authorization in 1998. Due to the rare and unexpected adverse events, the patients who benefitted from Tasmar® had to deal with the sudden unavailability of the product. According to Eichler et al, patients and physicians pled for the right of patients to gain access to Tasmar® at their own risk. Some patients tried to obtain the medicinal product from sources outside the European Union. In 2004, based on new clinical data and ongoing monitoring of the use of Tasmar® in other countries, CHMP lifted the suspension of Tasmar® and the product became available again in the EU (38, 39).

Off-label use

As explained above, clinical trials are performed in specific 'standardized' populations. Often these populations are not fully representative of the patients who may need the drug in daily practice, e.g. children, pregnant women and the elderly. This may lead to off-label use (19, 40). The term 'off-label use' refers to the prescription of a licensed pharmaceutical outside the terms agreed in its Summary of Product Characteristics (SPC), e.g. for an indication, patient group or dose for which the product is not officially licensed (41).

Off-label use is a common phenomenon (19, 41). For some subpopulations, like children, pregnant women and elderly, there is usually no information available on the effectiveness and safety of pharmaceuticals, because they were not included in the standard population used in clinical trials (in the case of children mainly due to ethical concerns). From a governance perspective, off label use is a reason for concern: it could point out that the current regulatory system might not be functioning adequately with regard to the adding and/or alteration of indications of already licensed products (19).

Although, the term off-label in itself indicates nothing about safety of use, it is often perceived that way. Stefansdottir *et al.* show that the off-label population does not differ much from the licensed domain regarding major characteristics hence, higher risk is not expected. When patients are more vulnerable to Type A[15] adverse drug reactions (ADRs), higher risk can be expected. Type B ADRs will occur randomly, also in the off-label population. Hence, different steps out of the domain do not necessarily entail higher risk. However, they conclude that an exception can be pharmaceutical constituents which can introduce risk in neonates, and administration through an alternative

[15] Type A, in which the ADRs are generally dose dependent, predictable, and considered to be related to augmented pharmacologic effects, and Type B, which are atypical or idiosyncratic effects that are independent of dose and generally unpredictable. Source: Rawlins, M. & Thompson, W. Mechanisms of adverse drug reactions. In: Davies D, ed. Textbook of Adverse Drug Reactions (Oxford University Press, New York, 1991).

route (42). Furthermore, they conclude that lack of efficacy is the main concern, since the lack of evidence for other indications than registered will not be included in the PIL/SPC, whereas safety concerns are listed.

Box 2; Phentermine/topiramate (Qsiva®)
In 2013, CHMP confirmed its initial recommendation to refuse a marketing authorisation for Qsiva® after re-examination of its negative opinion on request of the applicant Vivus BV. Qsiva® contained appetite suppressants and was indicated for the treatment of obesity. Although treatment with Qsiva® induced clinically relevant weight loss in the pivotal studies, CHMP was very concerned about its possible side effects, such as long-term coronary and psychiatric side effects. Furthermore, one component of Qsiva® was harmful to the unborn baby if taken during pregnancy. Since it can be expected that Qsiva® will be used off-label outside the intended patient group, the CHMP concluded that the Qsiva's® benefits did not outweigh its risks (43).

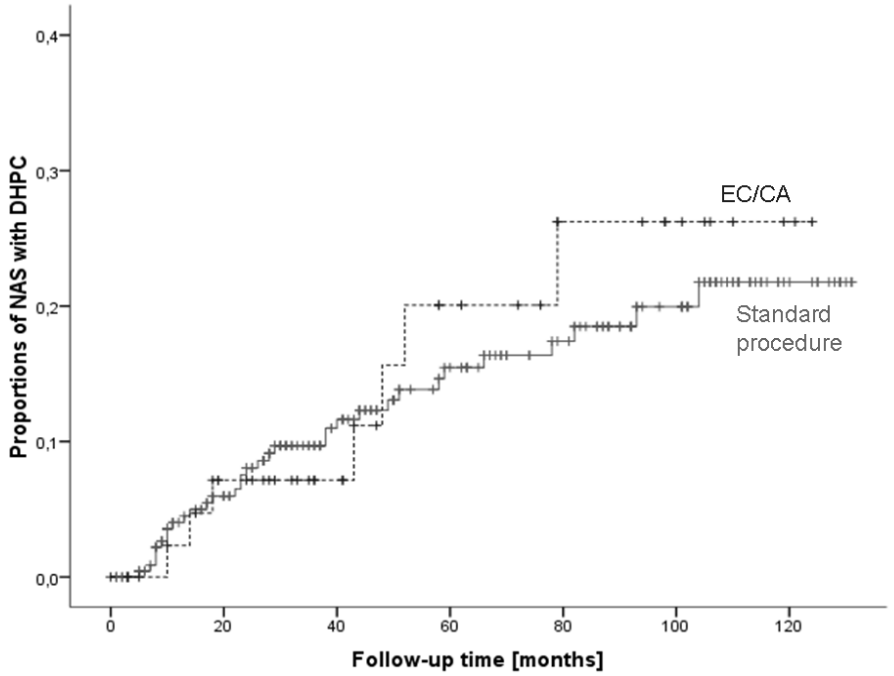

Figure 4.2 Proportion of new active substances authorized under Exceptional Circumstances/Conditional Approval (EC/CA) or standard conditions with a subsequent Direct Healthcare Provider Communication (44). NAS New active substances, DHPC Direct Healthcare Professional Communication, EC/CA Exceptional circumstances and Conditional Approval marketing authorizations.

4.2.3 Government reactions

The 'cautious regulator'-problem
Acknowledging the limitations of clinical trials with regard to safety, regulatory authorities have increased their pre-approval requirements over time. For example, thorough QT studies have become part of many new drug applications since QT prolongation and associated life-threatening arrhythmias have led to several drugs being withdrawn from the market (45). More recently, the debate on Rosiglitazone (Avandia®) has triggered the FDA to step up its pre-approval

requirements for new drugs for diabetes, to demonstrate absence of an excess risk of cardiovascular events (46). The negative consequences are that drug development times and costs (estimated upward of 800 million USD) may increase, limiting development of all but the most lucrative drugs (47).

To some the regulation of medicines is seen as setting minimum safety standards, whereas others see them as 'burdensome' (28). Scannel *et al.* point out that *each real or perceived sin by the industry, or genuine drug misfortune, leads to a tightening of the regulatory ratchet, and the ratchet is rarely loosened, even if it seems as though this could be achieved without causing significant risk to drug safety* (48). The concern of regulators, politicians and the public, that drug companies can (and will) find legislative loopholes, has led to an audit-based approach to regulatory documentation. This approach is based on the philosophy that the more demanding the reporting requirements are, the harder it is to outfox the system without leaving some kind of error or inconsistency (48).

This phenomenon – that once added, requirements are rarely removed from the regulatory framework – is called the 'cautious regulator'-problem. Brian D. Smith suggests that risk-aversion by regulators may be a symptom of a broader, societal intolerance of risk that has emerged alongside increasing affluence combined with a culture that increasingly holds companies and regulators accountable when things go wrong (49). However, risk aversion itself is risky and does not serve public health well. Increasing demands and requirements by regulatory agencies may reduce the risk of false-positive decisions – i.e. to license a drug that causes more harm than good. They also may increase the risk of false-negative decision: i.e. to deny a drug a license that would have caused more good than harm. This risk-averse approach increases R&D-costs (see: innovation), reduce availability (see: availability) without necessarily resulting into better public health (38, 50).

Box 3; Ramelteon (Rozerem®)

In 2005, the FDA approved Rozerem®, a medicinal product containing ramelteon for the treatment of insomnia. Two years later, in 2007, the Japanese company Takeda applied for the EU marketing authorization of Rozerem®, at EMA. After an initial negative CHMP opinion, Takeda withdrew its application in 2008. The CHMP had the opinion that Rozerem's®, effectiveness was insufficiently demonstrated and that the benefit risk balance was negative. In their withdrawal letter to EMA, the company mentioned their intention to seek scientific advice (SA) with respect to extending their clinical trial program for Rozerem® to address CHMP's concerns. In a press release in 2011, Takeda announced that they decided to discontinue the development of Rozerem® in Europe and not to re-submit a new marketing authorization application that had to include new clinical data. Considerations for this decision were on one hand the European requirements for approval of medicinal products for the treatment of insomnia and on the other hand Takeda's strategy to optimize their resources for research and development activities. The product Rozerem® is currently available in the USA and Japan(51, 52).

Emphasizing the benefit-risk balance of pharmaceuticals

Partly as a reaction to the 'cautious-regulator'-problem there is a shift in the way that regulators communicate about pharmaceuticals. The assessment of the benefit-risk balance has always been the basis for marketing authorization. However, in the communication towards the public regulators mainly used to emphasize the lack of risks of the pharmaceutical. (28, 37, 53), since exorbitant attention to the downside of medicines might reduce trust in medicinal products, and in the regulatory system as a whole (54).

Recently the focus is shifting towards a more even approach of risk. The EMA, for example, ceased to use to the expression ‘ensuring safety of medicinal products’ and instead adopted the phrase: ‘ensuring a positive benefit-risk profile’, which implies a higher tolerability of risk. Pharmaceutical companies traditionally promote the benefits of pharmaceuticals, while regulators focused on the risks and safety. Regulators should communicate about both the risks and benefits of pharmaceuticals in order to provide balanced information. This might reduce the spiral of increasing risk aversion and prevent further erosion of public trust (54).

The life-cycle approach

Emphasizing that pharmaceuticals have both benefits and risks, also leads to the acknowledgement that the information about the benefit-risk balance of a pharmaceutical is limited at the time of licensing and may change after approval. Regulators and scientists increasingly recognize the need for an ongoing assessment of the benefit-risk balance of new medicines. They agree that the point of approval should not be the last call for major regulatory action, but that the benefit-risk assessment is an ongoing activity, ideally spanning the full life cycle of a pharmaceutical (32, 37). Regulators therefore also focus their attention to the post-approval period of development of medicines including more attention for surveillance and post-marketing clinical trials (37).

The proactive EU risk management strategy (2003) and the European legislation on the requirement of risk-management plans with commitments for post marketing pharmacovigilance (since 2005) are the results to calls for a greater focus on safety aspects of pharmaceuticals after licensing (32). Zomerdijk *et al.* show that since this new legislation, significantly more risk management activities took place and conclude that the proactive pharmacovigilance approach is evolving (55). However, the pharmacovigilance system also appears to show some weaknesses (30, 56). The frequency of reporting adverse effects in Europe is mainly based on spontaneous reporting from patients and doctors. Besides, there are concerns about the quality and completeness of the post marketing data and the straightforwardness of the interpretation of these studies. In addition, despite that companies are requested to submit risk management plans, it seems difficult to conduct post marketing studies and post marketing data may never come available (30, 57).

An illustration of the increasing attention to pharmacovigilance is the establishment of The Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicines Agency (July 2012). The PRAC is responsible for assessing and monitoring safety issues for human medicines. It also has responsibility for the design and evaluation of post-authorization safety studies and pharmacovigilance audit (58).

Box 4; Rimonabant (Acomplia®)
In 2006, Acomplia® was authorized in the EU for the treatment under certain conditions of obesity or overweight in adult patients. New data on both side effects and efficacy in daily life became available post marketing. Especially, psychiatric side effects raised concerns and CHMP recommended restricted use of Acomplia® in 2007. On request of the European Commission, CHMP assessed all available data from launch of Acomplia® until September 2008 and advised to suspend the marketing authorization because of the elevated risk of developing psychiatric disorders when using Acomplia®. After suspension, Sanofi-Aventis voluntarily withdrew the marketing authorization of Acomplia® in December 2008, which was confirmed by the EU Commission in January 2009 (59, 60).

Drotrecogin alfa (activated) (Xigris®)
Xigris®, gained a marketing authorization under Exceptional Circumstances in 2002 for the treatment of adult patients with severe sepsis with multiple organ failure. In 2007, CHMP concluded that further clinical studies could not reproduce the initial efficacy of Xigris® and requested the company Ely Lilly to conduct a new placebo-controlled clinical study in patients with septic shock to collect data for reassessment of the benefit-risk balance of Xigris®. This new study failed to meet the primary endpoint of a statistically significant reduction of in 28-day all-cause mortality in patients treated with Xigris® compared to placebo. Eli Lily decided to withdraw Xigris® from the market worldwide in 2011 (61).

4.3 Innovation

4.3.1 Current issues

The relatively low number of new pharmaceuticals that have reached the market (and the patient) in recent years is a concern for both public health and for manufacturers of pharmaceuticals. Innovation is necessary in order to improve already existing therapies and to counter existing (and future) unmet medical needs. However, over the past two decades, increased spending on research and development did not lead to a corresponding increase in new pharmaceuticals (29, 32, 62, 63). On the contrary, there is an obvious downward trend (64, 65). The number of newly marketed chemical or biological entities in Europe declined from 89 in the period 1992-1996 to 52 in the period 2007-2011.

Figure 4.3 shows the level of innovation of pharmaceuticals approved in Europe between 1999 and 2011 (35). Over time, there is no apparent pattern of more innovative drugs being approved, although it may be of some concern that the overall proportion of innovative drugs is lower than reported in 2006. However, it should be taken into account that these numbers refer to pharmaceuticals approved via the centralized procedure and does not cover all important new pharmaceutical approvals across the various European countries (62). This finding fits in the debate about the declining efficiency in drug development, drug approval success rates and lack of truly novel drug products (63, 66, 67)

Between 1994 and 2004 the investments of the pharmaceutical industry rose with 70%, while output of new molecular entities decreased by 40% (68). Ongoing technological, scientific and managerial advantages should have raised the efficiency of commercial research of pharmaceuticals. However, according to some experts, the number of new products approved is not equivalent to the time and costs spend on research and development (48, 68, 69). Woodcock & Woosley are even suggesting that the pharmaceutical industry is suffering from a productivity crisis (69).

Furthermore, the innovative products that are registered, do not necessarily meet the needs of the 'end-user': the patient and his physician. The focus in drug innovation seems to lie on three main therapeutic areas: oncology, infectious and parasitic diseases, and blood and endocrine disorders. The most neglected conditions at the European level (based on their attributable health losses) are neuropsychiatric diseases, cardiovascular diseases, respiratory diseases, sense organ conditions, and digestive diseases, while globally, they are perinatal conditions, respiratory infections, sense organ conditions, respiratory diseases, and digestive diseases (70-72).

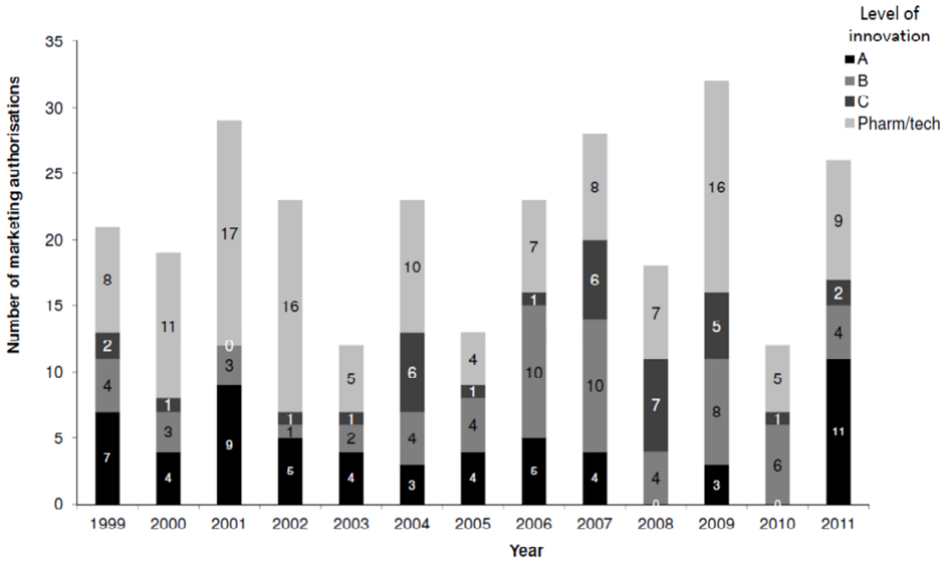

Figure 4.3 Level of innovation of pharmaceuticals approved in Europe between 1999 and 2011. All pharmaceuticals are new active substances that are approved through the centralised procedure in Europe. Classification of innovation according to Motola (73) A) important, B) moderate, C) modest or as Pharm or Tech) merely pharmacological / technological innovations. Source: (35).

4.3.2 Potential causes

Increasing regulatory requirements and attrition rates

Many experts are of the opinion that one of the most important reasons for the decline in innovation in the pharmaceutical sector is the ever tightening regulatory ratchet (see: safety). In other words, the cautious regulator is hampering innovation (37, 48, 63, 74). Development of innovative medicines has become more challenging and more costly due to higher requirements for evidence regarding efficacy and safety. Manufacturers of pharmaceuticals have to carry out more and longer clinical trials, which are very time-consuming and expensive, especially in the later stages of pharmaceutical development.

At the moment, the average time needed by the industry to bring a new pharmaceutical on the market is estimated between 10 and 15 years (64, 74-76). According to the European Federation of Pharmaceutical Industries and Associations (EFPIA), only one or two of every 10.000 substances synthesized in laboratories will, on average, successfully pass all stages needed for market authorization (64). The Centre for Medicines Research also mentioned the high rate of clinical failure at global level, varying from 70% to 90% for all new chemical entities (75). Especially the high rate of late stage clinical failures, at the end of a full development program is of particular concern and raised

questions about the efficiency of the development of pharmaceuticals and of the regulatory system (63, 77).

In 2003 DiMasi *et al.* estimated that the overall clinical success rate of all new chemical entities tested in humans, was 21,5% (78). In 2008 this situation improved: for all new chemical entities tested in the most expensive phase-3 trials, the clinical failure rate was 50% (69). Still, between 2007 and 2012 the attrition rate of phase-3 trials did not improve significantly (79, 80). Whether these attrition rates are primarily caused by increasing regulatory requirements is doubtful (see figure 4.4). Recent analyses of all marketing applications for new active substances for approval at the EMA in 2009, show that most negative outcomes are primarily caused by a failed development strategy and/or immature application (63, 77). Putzeist *et al.* also found that deficits in the initial learning phase are more strongly associated with non-approval than deficits in any of the confirmatory studies. For this reason, they conclude that relevant learning phase studies are of great value to reduce the number of failed dossiers, to increase the quality of the design for phase 3 studies and to speed up pharmaceutical innovation (77).

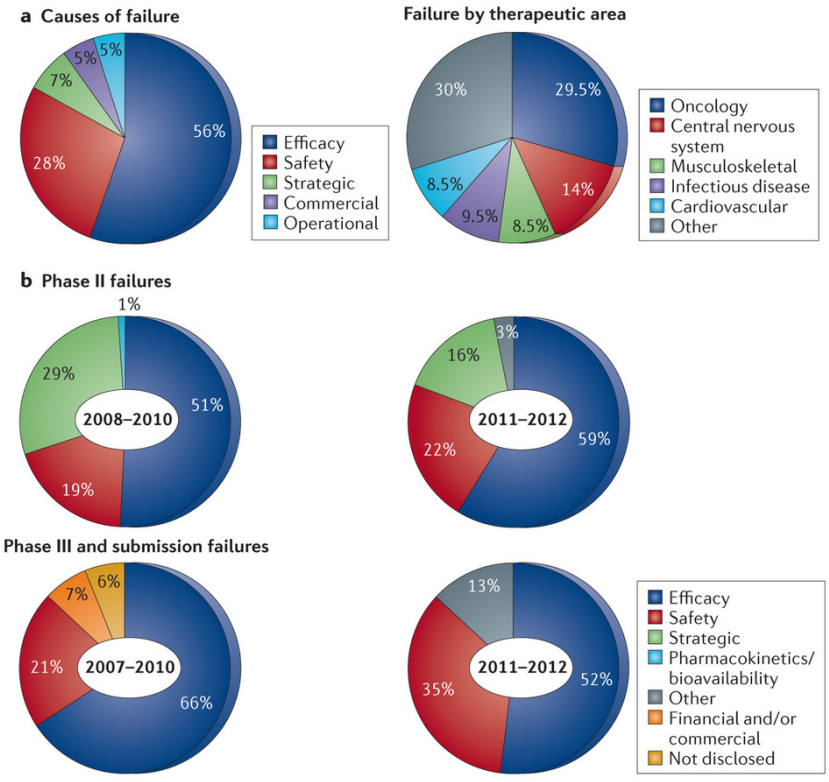

Figure 4.4 Causes of non-approval Of the 148 failures between Phase II and submission in 2011 and 2012, reasons were reported for 105; the majority of failures were due to lack of efficacy, as shown on the left. On the right, the 105 reported failures are broken down according to therapeutic area. b | Comparison of the reasons for failures in Phase II and Phase III trials in 2011 and 2012 with those in earlier periods. Source: (80).

Box 5; Drisapersen®
The Dutch biopharmaceutical company Prosensa is developing Drisapersen®, an investigational antisense oligonucleotide for the treatment of Duchenne Muscular Dystrophy (DMD). For further phase III clinical development of Drisapersen®, Prosensa entered into a collaboration with GlaxoSmithKline (GSK), a global pharmaceutical company in 2009. Unfortunately, in 2013, a phase III placebo-controlled study of Drisapersen® could not meet its primary endpoint of a statistically significant improvement in the 6 Minute Walking Distance test compared to placebo. Based on this outcome, GSK returned the rights Drisapersen® to Prosensa, which intends to continue its clinical development.
Source: GSK website (www.GSK.com), Prosensa website (www.prosensa.eu)

Development strategy: 'better than the Beatles'
The accumulation of regulatory requirements is not believed to be the only reason behind the decline in innovation. According to Lumpkin *et al.*, another important reason is the current lack of ability of drug developers to translate scientific discoveries routinely into innovations (31). Unlike the 20th century, which showed many scientific breakthroughs, there is hardly any progress the last decades, even for some of the most widespread diseases.

One of the underlying phenomena is – rather poetically – called the 'better than the Beatles'-problem. The pharmaceutical industry has to compete with its own successes: an ever-improving back catalogue of approved pharmaceuticals (yesterday's blockbuster is today's generic). This increases the complexity of the development process for new products, and raises the evidential hurdles for approval, adoption and reimbursement. Furthermore, it deters research and development in some areas, crowds research and development activity into hard-to-treat diseases and reduces the economic value of as-yet undiscovered pharmaceuticals (48, 53).

Smits & Boon argue that the traditional linear model of innovation in pharmaceutical industry – 'science finds, industry applies, man conforms' – has lost its meaning. In this linear model, basic science findings will automatically translate into medicines that will reach the market. The context for innovation has changed, caused by rising costs, increased competition, new scientific and technological developments, but also by users that are more demanding. Since the development process of pharmaceuticals increasingly involves many stakeholders (like the industry, academia and patient organizations) who all have their own expectations and goals, they suggest that innovation would benefit from systematic stakeholder participation (72).

Me too's, generics and the lack of comparative evidence
Several studies show that the degree of therapeutic innovation of new pharmaceuticals, submitted for approval through the Centralized Procedure, is low. Most products cover needs that are already met, without substantial improvement (62, 73, 81). A point of attention is that the EMA does not have a clear definition of 'innovative medicinal products'. The current definition of innovation, the number of new molecular entities entering the market, is controversial because it does not make a distinction between real innovative pharmaceuticals and products that are similar to existing ones (30, 71, 82).

Market authorization of new medicines does not demand a systematic comparison of the new product with products that are already on the market. As a result, the marketplace is crowded with so-called 'me too'-drugs that offer modest or no therapeutic benefits, compared to existing therapies (56). Furthermore, less data is required to apply for market approval of generic and biosimilar pharmaceuticals. Manufacturers of generics or biosimilars have to prove that their product is essentially similar to a pharmaceutical authorized in

the Member State. This makes it more attractive for manufacturers to develop these kinds of products (19).

Some experts, like Barbui & Garattini (2007), emphasize the importance of introducing the concept of 'added value' into the market authorization procedure. Comparison with reference products makes it possible to determine the relative benefit of a new pharmaceutical. They expect that the concept of 'added value' will advance innovation, because a higher threshold for the entry of new medicines would force investigators towards the development of truly innovative products (56). However, the introduction of requirements for comparative evidence will make the approval of new pharmaceuticals more difficult and time-consuming. Not surprisingly, manufacturers claim that 'added value' would also discourage investment and hinder the development of new medicines (56, 82).

Origins of innovation: large companies are falling behind

Although large and intermediate-sized companies still represent the main engine for commercializing new pharmaceuticals, Small and Medium Enterprises (SMEs), academic institutions, public bodies and public-private partnerships (PPP) represent an important source of innovation and enrich the product pipelines of larger companies. A summary of the originator and the marketing authorization holder for all 94 approved products between 2009 and 2010 is shown below in figure 4.5. A regulatory framework under which new pharmaceuticals are supported throughout their development already exists for SMEs in the EU but it is recommend that new regulatory incentives are developed to facilitate engagement with academic institutions (83).

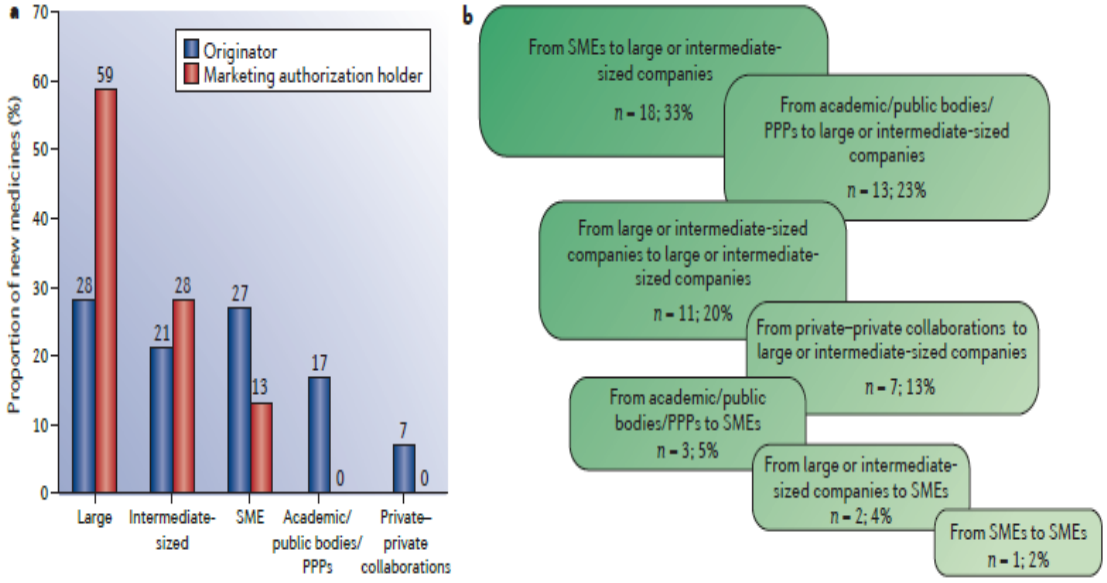

Figure 4.5 Origin of new medicines in the European Union (2010–2012). a | Originator and the marketing authorization holder for all 94 approved products evaluated, divided according to organization type. b | Direction of product transfers between organization types during development; the size of the lozenges is representative of the proportion of transfers. PPP, public–private partnership; SME, small or medium-sized enterprise. Source: (83).

4.3.3 Government reactions

Regulations to stimulate innovation

Traditionally, the main task of the European regulatory system for pharmaceuticals is the scientific evaluation of the safety, quality and efficacy of medicinal products. In recent years, regulators expanded their role as facilitators of public health by supporting and/or directing innovation, such as regulations on:

- Orphan Drugs
- ATMP's

Regulation on Orphan Drugs

In 2000 the European Commission issued a Regulation on Orphan Drugs (Regulation 141/2000) which contains several economic and regulatory incentives (such as market exclusivity, EMA-fee reductions, etc.) to stimulate the development of pharmaceuticals for rare diseases ('orphan diseases') (84). The regulation addressed the complaint that the development of medicines for small populations is not financially viable for pharmaceutical companies because of a low return on investments. Recent studies show that this regulation is quite successful. More than half of the products that have been granted an Orphan Drug-designation seem to be real innovative products (85).

Box 6; Taliglucerase alfa (Elelyso®)

Elelyso® was designated as an orphan medicinal product intended for the treatment of type-I Gaucher disease in March 2010. When applying for a marketing authorization in November 2010, Pfizer Ltd submitted a critical report on the possible similarity of Elelyso® with two already authorized orphan medicinal products, Zavesca® and Vpriv®. After assessment of the application, the CHMP considered the risk- safety balance of Elelyso® favourable for the requested indication. However, CHMP also considered Elelyso® similar to Vpriv® and had to recommend refusal of granting MA because of Vpriv's® orphan market exclusivity (86).

Regulation of ATMP's

Advances in molecular genetics and molecular biology offer the possibility to identify new substances that have the potential to prevent, cure or treat diseases that are classified as an unmet medical need (31, 87, 88). At the same time, advanced therapies and new technologies challenge the current regulatory system. Most advanced therapies have difficulties to meet the criteria for market approval, mainly due to the fact that the obligatory clinical trials require a large population of patients to gain statistical significance. Advanced therapies, however, are based on the principle of adjusting treatment to a specific patient (88). These advanced therapies continue to get more complex and targeted and therefore ask for clearer guidelines and pathways by regulatory agencies (31, 53, 88, 89).

Regulation 1394/2007, issued by the European Commission in 2007, tries to address these concerns. The regulation states that products based on gene therapy, somatic cell therapy or tissue engineering product (or a product that combined one of these therapies with a medical device) will be eligible for classification as a 'advanced therapy medicinal product'. The ATMP classification will help developers to clarify the applicable regulatory framework and offer some 'fasttracking'. It is envisaged to function a useful tool for applicants to initiate an early dialogue on the product development with regulators (90). The Regulation itself is supported by an amendment of the medical code (Directive

2001/83/EC), which contains updated definitions of gene therapy medicinal products (GTMPs) and cell therapy medicinal products (CTMPs).

There are some doubts as to whether the aim of the Regulation matches the practice of ATMP-production. At the end of 2013 there were only four ATMPs that had successfully applied for market approval. Several reasons have been put forward to explain this. The industry that produces ATMPs is still young and cell, gene and tissue based products are not easily suitable for industrial manufacturing. ATMPs cannot be controlled as precisely as chemically synthesized small-molecule products, especially when it comes to impurities. In addition, the mechanisms of action for most applications are not well established making pharmacokinetic studies less relevant (91).

Early dialogue & scientific advice

To stimulate innovation, regulators increasingly rely on early dialogue: the possibility for companies to gather scientific advice from regulators at an early stage in drug development. This procedure has become an important regulatory tool for effective development of pharmaceuticals (53). It requires early dialogue like informal briefing meetings, qualification of novel methodologies and the support of new or small companies. Companies that make use of scientific advice seemed to be more likely to receive a successful registration (29, 53, 92). Regnstrom *et al.* show that particularly smaller companies and those developing orphan drugs, are engaging in a dialogue with European regulators via the scientific advice-procedure. Factors related to compliance with scientific advice are company size and orphan drug status (25, 60 and 84% for small, medium-sized, and large companies, respectively; 77 and 38% for non-OD and OD status, respectively) (93).

Compared with 2010, there was a significant increase (52%; from 33 to 50 applications) in the number of stand-alone (i.e. non-generic/hybrid/biosimilar) initial marketing authorization applications with an outcome in 2011. The use of scientific advice among stand-alone applications increased to 76% (38/50) compared to the rather stable 55-60% reported during the previous three years. This analysis does not include the generic applications where scientific advice is generally lower than for applications with a more comprehensive development. The use of Scientific Advisory Group (SAG) or ad hoc expert group meetings was 20% (10/50 applications, vs 21% in 2010) (94).

Box 7; Becaplermin (Gemesis®).

Gemesis® is a product to regenerate tissue around the teeth with becaplermin, a recombinant human platelet-derived growth factor, as active substance. In the EU, the product is considered a medicinal product because of its claimed properties. However, Gemesis® is marketed as a medical device in the USA and Canada since 2005, resp. 2006. During product development, the company, BioMimetic Therapeutics Ltd, did not seek scientific advice at EMA. In 2008, they applied for marketing authorization through the centralized procedure. In July 2009, CHMP issued a negative opinion based on serious clinical and quality shortcomings. After re-examination of the opinion as requested by the applicant, the CHMP confirmed its negative opinion in November 2009 (95).

Public-Private Partnerships

In the 2004 WHO-Report *Priority Medicine for Europe and the World*, public-private partnerships (PPPs) were identified as a promising solution for addressing challenges in pharmaceutical innovation (96). In the EU, public-private partnerships are defined as: ‘partnerships where private sector partners, the Union and, where appropriate, other partners, commit to jointly support the

development and implementation of a research and innovation programme or activities' (97).

PPPs are envisaged to play an important role as technology platforms in high priority disease areas. A few examples of such platforms are the Top Institute (TI) Pharma in the Netherlands, which was launched in 2006 with total funding of €260 million and which has used the 2004 Priority Medicines Report as the foundation for its research program (98), and the Innovative Medicines Initiative (IMI). The latter was founded in 2008 by the European Commission and EFPIA in order to boost the development of new medicines across Europe.

Both of the IMI's founding members are equal in terms of their level of investment and their rights. With a total budget of 2 billion euro – to be spent over a 10-year period – the IMI is the largest public-private partnership in R&D in the field of the life sciences. It aims to create collaborative frameworks between large pharmaceutical companies, academic institutions, small and medium enterprises, patients, and regulatory agencies (99). The IMI has funded a large number of research projects, ranging in topic from antibiotic resistance and the development of new antibiotics to schizophrenia, diabetes and Alzheimer's disease (99, 100).

4.4 Costs

4.4.1 Current issues

Overall figures about the costs of research and development of pharmaceuticals in Europe show a significant increase. In absolute terms, the total R&D-investments in 1990 in Europe alone amounted to 7.766 million euro, rising to 17.849 million euro in 2000 and 27.796 million euro in 2010 (64). To what extent inflation plays a role in the increase is unclear. On the other hand, studies by DiMasi *et al.* and the Tufts Center of Drug Development (an independent non-profit research group) show that this cost increase is not a purely European phenomenon. Both groups used samples of multinational pharmaceutical companies from both foreign and US-owned firms. The approach used to estimate development costs is similar for all studies (101).

Estimates of average costs for research and development of a new pharmaceutical show an obvious increase over time. In the period 1963-1975, these costs - in real terms - were 137 million dollar, rising to 319 million dollar in the period 1970-1982 (both in year 2000 US$-rates). In the period 1983-1994, the estimated costs increased to 802 million dollars (in year 2000 US$-rates) (78, 101, 102). The most recent estimates show a further increase, namely 1.059 million dollar for the development of one pharmaceutical (in year 2005 US$-rates). Although both the cost of preclinical and clinical studies have increased in real terms, the growth rate for clinical studies, was nearly twice as high as that of preclinical studies (78). At the same time, the figures mentioned above have to be interpreted with some caution. Differences in methods, data sources and periods, but also by a lack of transparency of data from pharmaceutical companies make it difficult to give accurate estimates of the cost for research and development of pharmaceuticals (78, 103). Morgan *et al.* further point that despite three decades of research in this area, no widely used standard is available for estimating the costs of the development of pharmaceuticals (103).

4.4.2 Potential causes

Requirements for marketing authorization

According to many experts, the increasing costs involved in research and development are directly related to compliance with regulatory requirements (see: safety) (37, 50, 76, 101). Especially the increasing demands and rules concerning clinical trials is seen as a driver of cost increase (19, 37, 50). Scannell calls this phenomenon 'the multiple clinical trial problem': the 'cautious regulator' is currently less prepared to assume that the safety and efficacy of new pharmaceuticals can be generalized across the heterogeneous and fragmented patient population, so more and costlier trials are needed (48). Breckenridge *et al.* mention that the high costs of performing large-scale randomized clinical trials have made this development model financially unstable (29).

Not only have the demands concerning clinical trials made them costlier, it also extended the time it takes to get market approval (the so called 'long cycle time problem'). Longer development and regulation processes lead to decrease of time that has to be used to maximize the return on investment before the patent expires. In previous decades, the regulator was less cautious and requirements for marketing authorization were lower, which resulted in faster innovation processes, resulting in lower costs for research and development (48).

Development strategy

Yet, the tightening of the regulatory ratchet is not the only reason behind the rising costs of research and development. There are some issues with the development strategy of pharmaceutical companies as well. The rejection of numerous products in a late stage of the development process – after the use of many economic resources and the exposure of thousands of subjects to investigational products – is driving up the R&D-costs as well. The need to compensate these financial losses partly explains the high costs of new pharmaceuticals (31). That makes the average investment costs of 800 or 1.059 million dollars per pharmaceutical – as mentioned by DiMasi *et al.* – a somewhat misleading figure (76). It does not give a clear figure of the money involved to develop one single pharmaceutical. The money needed to recoup the losses of 'failed products' is also included these investments figures (see also: innovation).

Advanced therapies

Technological advances and conceptual foresight gained from the life sciences have increased the quality of patient care, but at a considerable costs [see: innovation](88). Industry analysts have recently examined the impact of genomics and other new technologies on the research and development process. They suggest that these new approaches may lead to a significant rise of costs (78). Moreover, the growing discordance between costs and clinical benefits has led to increasing concerns. Most stakeholders agree that urgent improvements in cost to benefit ratios are required (88). The standard model of research and development of pharmaceuticals is becoming less financially viable owing to factors such as the unsupportable growth in the cost of development, a regulatory environment that does not yet reflect the latest scientific advances and uncertainties over price and reimbursement (104).

Reimbursement requirements

While the EU – through the EMA – has a well-established position in the field of market approval, drug pricing and reimbursement policies are considered to be

an integral part of the national competence of EU-member states. This leads to a tension between market approval and reimbursement which has repercussions throughout the system, especially when it comes to the costs of pharmaceuticals. In daily practice, regulatory approval gets its true value to industry and patients after a pharmaceutical has passed the requirements for reimbursement. At the same time, rising healthcare costs have put restrictions on reimbursement of new pharmaceuticals (105). Health insurance authorities are increasingly turning towards health technology assessments, which provides them a more evidentiary approach to their decision making process (106).

One of the effects is that, next to the requirements of regulatory agencies, like the EMA, national reimbursement authorities often require additional information on the added value of new pharmaceuticals. Pharmaceutical companies have to satisfy the sometimes divergent needs of both regulators and reimbursement agencies (105). According to Naci *et al.*, manufacturers have expressed their concerns about the requirement of providing comparative evidence [see: innovation] (82). These additional requirements call for new trials that are expensive and time-consuming. Delays in launching new products may have a negative impact and increase costs, as companies lose exclusivity periods and receive potentially lower returns for research and development.

Box 8; Lapatinib (Tyverb®).
In the Netherlands, the pharmacotherapeutic report on lapatinib in combination with an aromatase inhibitor for the indication 'metastatic HR+ HER2+ breast cancer' concluded that primary care treatment with Tyverb® in combination with an aromatase inhibitor has a therapeutic value equal to that of trastuzumab in combination with an aromatase inhibitor in specific patients. However, including Tyverb® on list 1B (reimbursement list for medicines with an incremental therapeutic benefit) will lead to added costs at the expense of the pharmacy budget that could amount to €2 million per year. If Tyverb® is also used outside the indication for which the CFH has determined that it has an equivalent therapeutic value, i.e., for patients with the indication metastatic HER2-positive breast cancer after lack of success with trastuzumab, the additional costs could amount to €1.5 million more. It was decided to reimburse Tyverb® only under strict conditions (107).

4.4.3 Government reactions

Questioning the cost effectiveness of regulations
EMA guidelines are expected to provide both the industry and the assessors with sufficient and appropriate guidance in order to guarantee good efficacy, quality and safety of pharmaceutical products at all stages of development as well as after their introduction on the market. They contribute both to the promotion of public health and to the harmonization of European evaluation and medicine development practices. Between January and December 2009, Ernst & Young conducted the evaluation of the EMA (108). In the questionnaire administered to national agencies, most respondents thought that the number of guidelines is appropriate (27 out of 37) and their topics fit the needs (34 out of 37), see figure 4.6. This opinion is generally shared by the industry. However, some interviewees stress that guidelines' adequacy with needs may vary widely depending on the therapeutic area: there are for instance many guidelines in the central nervous system or cardio-vascular therapeutic area, but maybe less in other domains, like gastro-enterology, endocrinology or medicines for elderly people.

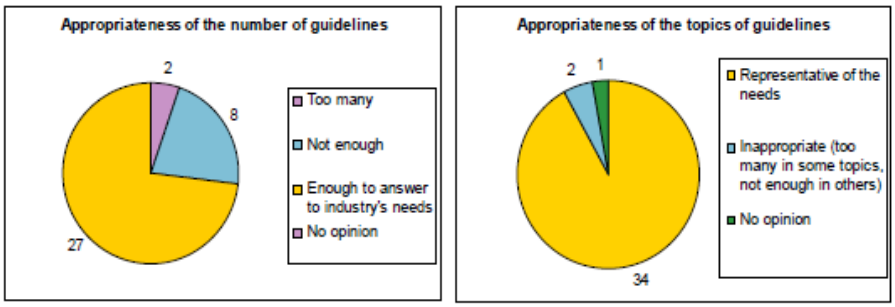

Figure 4.6 Opinion members national agencies on appropriateness of the number of EMA guidelines (108)

However, due to the high requirements for licensing and the high amount of applications that are not approved for marketing authorization, the efficiency of the regulatory system is increasingly questioned (63). According to Bouvy *et al.*, the exponential cost increase of pharmaceutical research and development during the last four decades are directly related to compliance with regulatory requirements (50). Although the regulatory framework aims to strengthen public health by setting requirements for market authorization, ineffective and costly regulatory requirements can, at the same time, be seen as barriers (50).

For example, the cost-effectiveness of mandatory QT/QTc-studies for all pharmaceuticals under development was doubtful. The incremental cost-effectiveness ratios of regulation vs. no regulation were €2,4 million per sudden cardiac death prevented and €187,000 per QALY (quality-adjusted life year) gained in users of antipsychotic drugs (109). A similar study showed that the cost-effectiveness of all Periodic Safety Update Reports (PSURs), submitted for biologicals in Europe from 1995 to 2009, was relatively low. During this period, PSUR reporting resulted in the detection of two out of 24 urgent safety issues for biologicals. The incremental cost-effectiveness ratio of full regulation (PSUR reporting) vs. limited regulation (no PSUR reporting) was €342,110 per QALY gained (110).

It is likely that the withdrawal of certain guidelines would decrease total costs for research and development and reduce time for clinical development. Bouvy *et al.* furthermore showed that the general public was willing to accept a small increase of insurance premium in order to be protected from a risk caused by pharmaceuticals. For that reason, they emphasize the importance of an evaluation of the cost-effectiveness of the guidelines in order to determine whether adding a requirement to the development process of pharmaceuticals offers value for money. According to them, this would be an essential step toward a more sustainable regulatory system (50).

Furthermore, according to the evaluation carried out by Ernst & Young, the production of EMA-guidelines is highly resource-consuming. It is the main activity of some Working Parties. Some Working Parties were responsible for less than 10 guidelines, but other dealt with dozens. In 2008, the CHMP Biosimilars Working Party managed 19 documents and guidelines, the Blood Products Working Party dealt with 26 and the Pharmacovigilance Working Party with 25. The CHMP Efficacy Working Party managed as many as 227 documents and guidelines. Maintaining, updating and creating new guidelines thus represent an important workload for the Agency (108).

Convergence between market approval and reimbursement

That independent assessment of one product by different authorities is not efficient, is a view that is shared by virtually all actors in the regulatory system.

Therefore, more attention is given to the improvement of the interaction between health insurance and regulatory authorities (28, 53, 57). There's an increasing agreement across sectors that improved communication and coordination could contribute to facilitating timely patient access to effective, affordable treatments that offer value to the health system (28). There is a need to align these evidence needs (82).

Breckenridge *et al.* also argue that it would be desirable if regulation and health technology assessment complement to each other and work more closely together (29). However, as put forward by de Jong *et al.*, regulatory authorities and health technology assessors work independently and have limited interaction on what evidence they consider appropriate for market authorization and reimbursement of new pharmaceuticals respectively. Because this is not efficient, they recommend these agencies to share information and make use of each other's standards and methods (111).

In 2010, the EMA undertook a pilot study to parallel scientific advice with HTA bodies that allowed developers to receive simultaneous feedback from both regulators and HTA bodies on their development plans for new medicines. The EMA has so far conducted 25 parallel scientific advice procedures, a further six procedures are expected to start in 2014. Based on the experience gained by all stakeholders, guidance for EMA-HTA parallel scientific advice will be developed and published for public consultation in early 2014 (112).

Box 9; Prucalopride (Resolor ®)

The CHMP recommended that Resolor® be given a marketing authorization based on three main studies in which Resolor® was compared with placebo (a dummy treatment) involving 1,999 patients with chronic constipation, 88% of whom were women. The patients had not responded well enough to previous treatment with laxatives. The Dutch CFH concluded that that the therapeutic value of Resolor® is lower for women in whom laxatives fail to provide adequate relief due to insufficient data on this group of patients. They stated that it is not clear whether the patients included in the phase 3 studies are refractory to optimum doses of the standard laxatives. For example, no data are available on the laxatives used, it is not clear whether different laxatives were used and/or whether the maximum doses of laxatives were given (113).

Collagenase Clostridium histolyticum (Xiapex®)

The condition 'Dupuytren's contracture' causes the patient's fingers to bend forward towards the palm, which means that the fingers cannot be straightened anymore. In 2011, Xiapex® received an EU marketing authorization for the treatment of Dupuytren's contracture. The clinical efficacy of the product was demonstrated in phase 3 double blind, randomized, placebo-controlled studies. The company planned further clinical development to obtain data to compare Xiapex® treatment with currently available treatment options, i.e. surgery and percutaneous needle aponeurotomy (PNF). In The Netherlands, the National Health Care Institute advises the Minister of Health on the reimbursement of medicinal products by health insurances. In 2012, they concluded that the therapeutic value of Xiapex® treatment has to be established in comparison to treatment by surgery. Since no data were available yet, they issued a negative advice on the reimbursement of Xiapex®. As a result, Xiapex® is not included in the basic coverage of the health insurance in The Netherlands (114, 115).

4.5 Availability

4.5.1 Current issues

The availability of medicines is dictated by supply and demand-side factors, such as levels of pharmaceutical use, overall expenditure on medicines, medicines

prices, as well as more wide-ranging factors including market structure, regulatory policies, and cultural practices. As a result of variation in these factors, pharmaceutical availability varies between Member States.

The supply of medicines is the responsibility of the pharmaceutical industry. Commercial interests play an important role in determining which choices are made. History shows that these choices are not automatically the choices that benefit public health or individual patients the most and may lead to limited access to medicines (19). There's an unequal availability of new pharmaceuticals and some diseases seem to be neglected, i.e. become an 'unmet medical need' (70).

The Global Forum for Health Research reported that at global level less than 10% of the available resources is invested in studies for diseases that contribute to 90% of the global burden of disease and vice versa (116). In addition, Hoebert *et al.* show that innovative medicinal products are not equally available in the EU (117). One important reason for this inequality seems the different economic situations in the European countries and a lack interest of pharmaceutical industry to market approved EU products in low resourced markets.

There's broad consensus in the literature that the theme's discussed in the previous paragraphs, such as increasing safety requirements, declining innovation and rising costs, all contribute to a decline in availability of new pharmaceuticals on the European market (53, 87). Many believe that the main cause of limited availability is the current regulatory regime. According to this view, cautious regulators are hampering innovation, driving up costs and limiting the amount of products that can enter the market.

Box 10; Alemtuzumab (MabCampath®)

The marketing authorisation holder (MAH) responsible for MabCampath® was Genzyme Europe B.V. The European Commission was notified by letter of the MAH's decision to voluntarily withdraw the marketing authorization for MabCampath® for commercial reasons as of august 2012. The MAH has committed to ensure that patients who need treatment with MabCampath® will continue to receive it through patient access programmes. The Dutch CFH stated that MabCampath® has a therapeutic benefit in patients with B-cell chronic lymphocytic leukaemia (BCLL) for whom fludarabine combination chemotherapy is not appropriate. Nevertheless, the MAH, now a unit of Sanofi, planned to market alemtuzumab for the indication Multiple Sclerosis that needs a much lower treatment dose of alemtuzumab than BCLL but could be priced higher based on the price of competitor products. By withdrawal of MabCampath®, Genzyme and prepared the way for the higher priced medicine Lemtrada® that is, essentially, MabCampath® by another name, but is indicated for the treatment of Multiple Sclerosis. Off label use of MabCampath®, which would be cheaper for the treatment of Multiple Sclerosis, was prevented by the withdrawal (118, 119).

Somatropine (Valtropin®)

The MAH responsible for Valtropin® was BioPartners GmbH. The European Commission was notified by a letter dated 31 October 2011 of the MAH's decision to voluntarily withdraw the marketing authorisation for commercial reasons. Valtropin® was not marketed in any EU country. In 2012 Biopartners GmbH introduced Somatropin Biopartners®; identical active substance, other therapeutic area (120).

4.5.2 Potential causes

European procedures versus national procedures

The establishment and expansion of a common system for the evaluation and approval of new pharmaceuticals reaching the European market [see chapter 'Background'] had positive implications for both the industry and the patients. Drug developers only had to file a limited number of applications, shortening the time for EU-wide approval. For patients, the simultaneous approval in all EU member states reduced potential inequalities for patients in the availability of new pharmaceuticals (5, 30, 121)

Still, centralized marketing authorization does not necessarily guarantee that medicines are actually marketed in all EU member states. Barbui & Garattini emphasize that some EMA rules also have a negative impact on the evaluation and availability of new pharmaceuticals (122). Despite harmonization, the central procedure is not compulsory for all pharmaceuticals. Companies still use the national procedures for market approval, for various reasons. This dual system creates competition between the EMA and national regulatory agencies and heterogeneity between countries in terms of approved indications and availability of pharmaceuticals (122).

Despite being approved at European level, a pharmaceutical may not be available at national level, because of a negative reimbursement decision (5, 70, 106, 121). Regulatory authorities look at the sufficient balance of benefit to risks, while health technology assessors look at the effects of the pharmaceutical in an unselected population, in which patients it works best, what the costs are and how it compares to alternatives (29). As we have seen in the previous paragraph on costs, the additional requirements for reimbursement make it more difficult for drug developers to bring new pharmaceuticals on the market (106). In some cases, there are even discrepancies in evidence requirements for market access versus reimbursement, which may result in conflicting decisions by regulatory agencies and health insurance authorities. These discrepancies also indicate lack of harmonized HTA requirements.

Box 11; Drisapersen®

EU Clinical Trials Directive 2001/20/EC aims to harmonize the requirements for the conduct of clinical trials with medicinal products in the EU. Nevertheless, requirements for conducting a clinical trial still may vary between EU member states. For example, clinical trials with minors are in principle forbidden in The Netherlands. The Medical Research Involving Human Subjects Act only makes an exemption for research of direct benefit to the research subject or research with negligible risk and minimal objections. The Dutch biopharmaceutical company Prosensa is developing Drisapersen®, an investigational antisense oligonucleotide for the treatment of Duchenne Muscular Dystrophy (DMD) patients. As the company experienced problems in getting approval for a phase I /II clinical trial due to this prohibition, they decided to conduct the trial in Belgium and Sweden (123).

Source: CCMO website (www.ccmo.nl), Prosensa website (www.prosensa.eu)

External reference pricing

The way European countries handle the health policy objectives of sustainability, equity and quality of care can differ substantially between countries. There are several pricing and reimbursement policies used in the EU, such as external reference pricing (124). The impact of these policies on the price of medicines, the availability of and access to medicines, and pharmaceutical expenditure vary. In some cases, these policies can have adverse effects, such as creating shortages or inappropriate incentives. In other cases, more efficient allocation of

resources can create “headroom for innovation” by allowing budget savings elsewhere to be invested in innovative medicines that address medical needs.

Policies in one Member State can influence those in another. For example, pricing policies in one country can have an impact on parallel trade or external reference pricing. Therefore, there is limited incentive for pharmaceutical companies to offer lower prices to lower-income countries when this would subsequently decrease prices (through external reference pricing) or lost sales (through parallel trade) in other European markets. Companies frequently offer confidential discounts or rebates to get around this issue. The interaction between price referencing policies and marketing strategies of companies (and impact on patient access) should be recognized (125).

Box 12; Effects between member states: example of Greece
Greece is facing a serious shortage of medicines and claims that pharmaceutical multinationals have halted shipments to the country because of the economic crisis and concerns that the medicines will be sold by Greek wholesalers to other European countries because prices are higher in other European countries. Regulators in Athens have been trying to tackle the problem with fines and export bans (126).

4.5.3 Government reactions

Steering innovation
Catalá-López *et al.* recommend pharmaceutical industry leaders and policy makers to get more involved with the future priorities of drug development and steer towards a more public health oriented perspective and ‘unmet medical needs’ (70). Projects like ‘Priority Medicines’ carried out by the WHO have identified a number of pharmaceutical gaps, areas where pharmaceuticals are needed, but not developed yet (96, 125). As a result, these areas will have more attention in future research programs, partly sponsored by the European Union, like IMI [see: innovation] (19).

Fast-tracking access: Conditional Approval and Exceptional Circumstances
With regard to the availability of pharmaceuticals there are conflicting interests. On the one hand there is the societal pressure for safe pharmaceuticals. On the other had there is a group of patients that wants to have quick access to promising new products that are still under development. In order to find a balance between these two interests, new authorization models (often referred to as types of ‘adaptive licensing’ are being tested. Adaptive licensing entails a more flexible way of market authorization, in which stepwise approval stages replace the current one off marketing authorization (28, 32, 98). According to Eichler *et al.*, adaptive licensing offers a more favourable alternative to the current licensing paradigm. It facilitates earlier access to innovative, pharmaceuticals and it reduces costs and time needed for initial market authorization (32). In response to the 2001 Review (see: background) two adaptive licensing procedures were installed: Exceptional Circumstances and Conditional Approval. Both procedures are meant to speed up access to innovative pharmaceuticals.

On the other hands, both procedures also involve more uncertainties about the benefit-risk profiles of new products (71). These procedures require a different approach by regulators, which involves more focus on active surveillance and post marketing clinical trials and a continuous evaluation of the benefit risk balance over its entire life cycle (37, 44). A study by Arnardottir *et al.* looks at whether Exceptional Circumstances and Conditional Approval procedures resulted in more medicines with a post marketing safety alert or

safety related withdrawals (see: figure 4.2, safety) (44). They concluded that this was not the case. At the same time, they argued that their findings do not mean that the accelerated procedures are appropriate for all pharmaceuticals. With respect to risk tolerance of society, different ways of risk management and enforcement of compliance may apply when introducing accelerated pathways for less serious diseases.

Granting initial market authorization on reduced level of evidence, requires thorough insight into what an appropriate level of evidence should be. This will be difficult and challenging to determine. Good communication about benefit and risks by regulators and companies will be very important (111). However, according to Forda *et al.*, there is not yet an agreement regarding suitable benefit-risk methodologies, its conclusions and outputs (104). A multiple benefit-risk assessment framework could be a solution, as opposed to applying a single approach in every situation. Advanced methods like modelling and simulation can improve the planning and interpretation of clinical trials and may have solutions for small patient populations with limited data available. However, flexibility of trial design also brings costs, requires time and gives additional complexity for regulators to assess the results and to perform health technology assessments for reimbursement (53).

Box 13; Pralatrexate (Folotyn®)

In November 2010, Allos Therapeutics Ltd submitted an application for a conditional marketing authorisation to EMA for its orphan medicinal product Folotyn®, indicated for the treatment of relapsed or refractory peripheral T-cell lymphoma (PTCL). The application was based on a pivotal clinical study designed as a single-arm trial with response rate as primary endpoint. However, CHMP considered a randomized, controlled trial design with overall survival as endpoint to be essential as was already advised during CHMP's protocol assistance in 2008. During the assessment process, the applicant proposed to perform a randomized, controlled clinical trial post-approval. After re-examination of its initial negative opinion, CHMP issued a majority recommendation to refuse the granting of a marketing authorization in January 2012. However, a CHMP minority had a divergent opinion and favoured a Conditional approval taking into account the high medical need for new medicines for the treatment of patients with PTCL and the ongoing clinical development program providing the required additional data within a reasonable period of time (127).

Extrapolation: 'learning' studies and medicine classes

A first form of optimizing evidence generation concerns extrapolation between medicines. This can be done within and between medicine classes. The Escher Project has shown this could be a valuable way to reduce uncertainty without requiring additional data generation (98). They showed in a study that focused on learning between same class medicines during marketing approval, that adverse drug reactions of first in class medicines were not always included in the Summaries of Product Characteristics of second in class medicines.

Another example showed that for HIV medicines safety issues were taken into account in the approval process of other medicines in the same class. Improving this kind of learning could help to achieve a proper level of safety knowledge while requiring less data to be collected preapproval. A second form of extrapolation investigated within the same Escher Project concerns relying more on preclinical and early clinical data. One study distinguished 'confirmatory' studies (late-stage trials) and 'learning-phase studies' (e.g. mode of action, proof of concept, pharmacokinetics, dose finding and safety pharmacology), and found that both types of studies are important for

marketing authorization. Analysis of the 'learning-phase studies' showed that in cases where outcomes of efficacy studies were problematic, sufficient evidence on the mode of action, proof of concept and dose finding studies were important factors for successful marketing authorization. The study suggests that assessors might rely more on extrapolation of the results of early clinical studies (in healthy individuals) to increase the degree of confidence about 'real' clinical effects in patients. This could be a way to optimize evidence generation in the confirmatory phase.

4.6 Transparency and Accountability

4.6.1 Current issues

The European regulatory system for pharmaceuticals has been criticized for fostering an environment of insufficient transparency and accountability. In 2003 Abraham argued that the secrecy involved in drug testing and regulation made it virtually impossible to assess how bad or good the system was in protecting public health. He concluded that 'the current drug regulatory systems lack adequate public accountability, exhibit extensive conflict of interests and are dominated by drug testing at the service of commercial interests' (128). His views were shared by others. According researchers like Bassi, Wieringa, Garattini and other, the fact that CPMP opinions were kept secret in case of a withdrawn applications, was not in the interest of public health: information on the potential problems of new drugs is important for potential patients, physicians and interested parties and should be made public (40, 56, 121). The 2010 evaluation of the European Medicines Agency by Ernst and Young showed that pharmaceutical companies were asking for more transparency of the work of Scientific Advisory Groups (108).

Still, the EMA was not the only institution being criticized for a lack of transparency. Taylor *et al.*, for example, pointed towards an evident industry bias in the economic evaluation of pharmaceuticals. Studies funded by the pharmaceutical industry less likely to reach unfavourable qualitative conclusions as non-profit funded studies (106). Furthermore, the 2009 Seroxtat®-incident (in which GSK was accused of withholding unfavourable clinical trial data) showed there were significant gaps in the duty of candor which had been assumed to exist between pharmaceutical companies and regulators (129).

Box 14; Oseltamivir (Tamiflu®)

In 2009, there was widespread concern about a new flu pandemic (H1N1), and billions were being spent by governments around the world stockpiling Tamiflu®. Looking back, it seems that, faced with the sudden threat of pandemic flu, parties behaved opportunistically and irresponsibly. Pharmaceutical companies exploited a window for rapid sales. Regulators approved medicines with insufficient scrutiny (as exposed now by the forensic approach of Cochrane researchers) and politicians were desperate to act, to do something in the face of a perceived crisis, whether it was based on evidence or not. It seemed that patient welfare didn't matter, although it was the excuse for these decisions. Roche, the pharmaceutical company behind Tamiflu®, withheld vital information on its clinical trials for half a decade. This example of Tamiflu® perfectly illustrates the need for full transparency around clinical trials (130, 131).

4.6.2 Potential causes

Interdependency regulators and industry

The inherent mutual dependency of regulators and the industry in the pharmaceutical chain, and the shroud of confidentiality that surrounds this relationship, has been a source of public concern for some time. Both the EMA and national regulatory agencies are mainly financed by fees charged from the pharmaceutical industry. In 2009, roughly 76% of the EMA's 194 million euro budget was financed by fees. The national authorities of the involved European countries show a similar distribution (56, 132)

According to some, this financial dependency affects the independence of the EMA and other regulators. In 2011, Gotzsche and Jorgensen of the Nordic Cochrane Centre (NCC) raised their concerns over the fact that the EMA unfailingly refused access to documents regarding authorization decisions, just because disclosure would threaten commercial interests of the pharmaceutical company (133). After a four year struggle, this high profile conflict was decided in favour of the NCC (13). As of 2014, the concerns about the 'close ties' between industry and regulators – for example in the with regard to early dialogues and/or scientific advice (see: innovation) – have not completely disappeared (134-136).

Box 15; The case of Oseltamivir (Tamiflu®)

In 2009, there was widespread concern about a new flu pandemic (H1N1), and billions were being spent by governments around the world stockpiling Tamiflu. Looking back, it seems that, faced with the sudden threat of pandemic flu, parties behaved opportunistically and irresponsibly. Pharmaceutical companies exploited a window for rapid sales. Regulators approved medicines with insufficient scrutiny (as exposed now by the forensic approach of Cochrane researchers) (131). And politicians were desperate to act, to do something in the face of a perceived crisis, whether it was based on evidence or not. It seemed that patient welfare didn't matter, although it was the excuse for these decisions. Roche, the pharmaceutical company behind Tamiflu, withheld vital information on its clinical trials for half a decade. This example of Tamiflu perfectly illustrates the need for full transparency around clinical trials(137).

4.6.3 Government reactions

Increasing transparency

These concerns did not go unnoticed by the EU. As a reaction to the concerns about transparency and accountability, Regulation 726/2004 introduced new rules. National authorities were obliged to make rules of procedure publicly accessible and after granting approval, authorities were required to make available, without delay, the marketing authorization, the Summary of Product Characteristics, the assessment report and reasons for the opinion. Furthermore, it was decided that the majority EMA documentation would fall under existing EU legislation governing public access to documents. (105).

At the same time, the freedoms of the applicants were curtailed. Under decentralized procedure applicants were no longer permitted to withdraw an application. Information on serious adverse drug reactions and other pharmacovigilance data should be made publicly accessible. Therefore, the EudraVigilance, the common European electronic data reporting system of pre and post approval safety data, was made more accessible for the general public (30).

Partially due to the 'Cochrane affaire', the Council of the European Union proposed a new regulation on clinical trials. It states that the clinical trial data

submitted in support of a clinical trial application should be based only on clinical trials recorded in a publicly accessible and free of charge database (138). Yet while the quantity and quality of data that inform benefit to risk profile decisions is rising dramatically, the methodologies for synthesizing the information and balancing the good and the bad remain largely unchanged and poorly described. According to Lumpkin *et al.*, 'the transparency of public advisory committees and online availability of regulatory documents helps, but to many the regulatory thought process still remains a black box' (31).

5 Interview results

> *All values* [safety & efficacy, innovation, costs and availability] *are important, but they are not always compatible with each other. (…) It is of great importance to acknowledge the legitimacy of each of these values and the existence of tensions between them. - Expert 6*

5.1 Introduction

In this chapter we present the results of our interviews with national experts in the field of pharmaceutical regulation. These findings are grouped according to their major theme: Safety & efficacy, Innovation, Costs, Availability and Transparency & Accountability. The methodology behind the review is explained in chapter 3: Methods. The numbers in the text between square brackets […] refer to individual experts.

5.2 Safety & efficacy

5.2.1 Public trust and the perception of risks

When asked about their opinion on how the current regulatory regime for pharmaceuticals performs in terms of safety, all respondents agreed that it functions well. Yet, at the same time they acknowledge the increasing public attention to incidents like those with Vioxx® or Diane 35®. According to some interviewees, the commotion that these incidents caused, can be explained by the tension between the different way patients, regulators and society perceive risk. According to Expert 2, there are different ways to look at risks when dealing with pharmaceuticals. *There's risk on the level of the population. This is how producers and regulators think about risks. Yet, at the same time, there is risk on the individual level as well, and that's a specific risk for an individual patient.*

Regulators try to fulfil society's demand for safe pharmaceuticals. However, some interviewees question the viability of this aim, since there is – as Expert 5 put it: *no such thing as a 100% safe pharmaceutical*. Four out of nine interviewees stressed the fact that the willingness among patients to use pharmaceuticals which are not yet authorized is much higher than among non-patients [2,4,5,6,9]. How should regulators address this tension? Three interviewees suggested that the choice whether or not to use 'risky' pharmaceuticals is something that should be left to patients and their physicians [2,4,5]. At the same time, the government and regulators should invest more in education and advice: make society aware of the fact that there is always risk involved when using pharmaceuticals [4,5].

With the current focus on risk minimization, regulators seem to have lost touch with daily medical practice. *Decisions are made by people who don't see patients anymore. (…) This has changed the way of thinking and reasoning about pharmaceuticals. Compliance with regulations and guidelines has become more important. (…) It's all about risk reduction, while risk reduction and good quality of care are not per definition compatible* [Expert 2].

5.2.2 *Cautious regulators*

Regulators have become more wary to accept even a limited amount of risk. More rules and guidelines are introduced, yet they are rarely abolished [2,4,5,8]. According to Expert 8, there are more than 600 guidelines. However, by increasingly intensifying the regulatory regime, governments may have assumed too much responsibility. Expert 2: *when something goes wrong, all fingers point towards the government, even though the mistakes usually weren't made by the government, but in the daily healthcare practice; for example due to wrong off-label use.* It is therefore not surprising that regulators have become more careful. Accountability has shifted from the producer of a 'faulty product' and physicians who use the 'wrong product' to the regulator who has granted market authorization. Regulators are therefore also protecting themselves. *Various new rules are introduced of which some protect public health and some only protect the regulator* [Expert 8].

However, most interviewees agree that the 'cautious regulator'-problem is not easily solved. A clear division in responsibilities might help, according to Expert 2. He states that, when it comes to the safety of pharmaceuticals, there are several aspects one has to take into account. There is the quality of the product itself. That is the responsibility of the producer. There is the physician who prescribes and the pharmacist who's responsible for the delivery of the product. How pharmaceuticals are ultimately used, is also the responsibility of the patient. Yet, at the same time, Expert 5 points out that the 'cautious regulator'-problem is also rooted in the fact that some actors do not take their responsibility. *The pharmaceutical industry has public trust issues and politicians have to address these issues, in this case by intensifying the regulatory regime* [Expert 5].

5.2.3 *Excessive regulations*

While the phenomenon of the 'cautious regulator' might be caused by the interplay of various factors, most interviewees agreed this does not mean that legislation should not be screened for excessive regulations. To illustrate the existence of 'unreasonable legislation' the respondents came up with three examples:

1. Compulsory QT studies. There are serious doubts about the cost-effectiveness of these studies [4,8]. *These resources would have been better spent on innovation* [Expert 4].

2. The regulations concerning the transmission of Creutzfeld-Jakob disease through the use of bovine materials in pharmaceuticals or other medicinal products. There are no indications this ever happened, according to Expert 8. Furthermore, studies have shown that the reduction of this already minimal risk with only 1% would cost about 46 billion euros [8].

3. The rules regarding social media in the *Guideline on good pharmacovigilance practices*. These rules demand that the industry screens the internet and social media under their management or responsibility for potential reports of suspected adverse reactions. According to Expert 2, it is doubtful that this will indeed result in new information that is not picked up otherwise.

5.2.4 *Post market approval: pharmacovigilance*

Pharmacovigilance – the collection, assessment, monitoring and prevention of adverse effects with pharmaceuticals – is divided over various stakeholders

within the EU pharmaceutical chain, like regulators, pharmacovigilance agencies, the industry and medical professionals. All respondents agreed that pharmacovigilance plays an important role in minimizing the risk of adverse events. During the interviews, three aspects of pharmacovigilance were often highlighted: the division of responsibilities, underreporting and the use of pharmacovigilance data.

With regard to the division of responsibilities, the case was made that pharmacovigilance and market authorization should remain in the hands of separate institutions. Like it is the case in the Netherlands, authorization is something best left to the government – as the guardian of the common good – while the detecting and monitoring adverse events is best guarded by health care professionals; they work with pharmaceuticals on a daily basis. According to Expert 2, *there's an inherent tension between market authorization and pharmacovigilance that just doesn't work when they're carried out by the same institution. Just imagine: if pharmaceuticals are withdrawn from the market, it would immediately appear as if mistakes were made during the authorization procedure, which doesn't necessarily have to be the case*. The role of the industry – which according the EU-legislation also has the obligation to collect reports on adverse events – should be abolished [2,8]. This data should be given to independent pharmacovigilance agencies that can assess this information and make it public to everyone, including the industry [2].

In the literature (see: literature results) there is doubt whether or not the system of 'spontaneous reporting' on which most pharmacovigilance systems rely, is the most reliable system [8]. This concern seems to be valid, especially when looking at the (lack of) reports filed by hospitals and patients [2]. Expert 8 put forward that the relative underreporting from hospitals is probably caused by 'red tape'. *When a physician wants to report an adverse event with a biological, the producer immediately asks him to fill out a multitude of forms. This stimulates the fact that the second time this physician is confronted with an adverse effect he'll probably pretend not to have seen it* [Expert 8]. He suggests that hospitals should be obliged to hire someone whose sole job is to detect and report adverse events. This problem is acknowledged by Expert 2, but at the same time he claims that there's no evidence that the system of 'spontaneous reports' has missed any of the important safety concerns of the past decades. Expert 2: *As long as the system itself can differentiate between signals and 'noise' it doesn't really matter* (…) *It's not about the quantity, but the quality of the reports*.

His main concern lies with the way data collected by pharmacovigilance agencies is used. According to him, most safety signals reach the regulator, but do not reach the physician's consultation room. Information that might benefit the quality of care is put in a European circuit and disappears in a fog of bureaucracy [2]. Similar concerns were raised by Expert 1 and Expert 5. Data collected through pharmacovigilance systems could be beneficial for innovation, but *in order to use this data in a scientific way, it would be necessary to link these reports with biological material* [Expert 1].

5.2.5 Premarket approval: the RCT and efficacy

Several checks and balances are built into the development stage of a pharmaceutical. The core around which the assessment of the safety and efficacy of a pharmaceutical product is built, is the Randomized Controlled Trial. Regulators rely heavily on this data, since – as Expert 8 states *you don't learn a lot about safety from animal experiments*.

According to our respondents, the role of medical ethical research committees (MERCs) is paramount during the start-up phase. Both Expert 1 and Expert 3 agree that not every trial-proposal that reaches the MERC is up to par.

Still, the share of proposals that has been rejected only lays around 7% (or less). That the compulsory review by the MERC is not always appreciated is understandable. Expert 1: *it's only logical that individual researchers think that the process is complicated, bureaucratic and unnecessarily time-consuming. They've already thought long and hard about their protocols and are – in this phase – eager to get to work.*

Still, there is room for improvement. Expert 3 state that researchers will benefit from more interaction between regulators and MERCs. This would prevent that, at the end of the authorization process, trials which have been approved by a MERC are rejected by the regulatory agency. On the other hand, MERCs and regulators should have distinct competences. The idea to separate the scientific and ethical review as has been laid down in the new European Regulation on Clinical Trials is not applauded, especially since the Medicines Evaluation Board claims the competency of scientific review. *It would not be beneficial if ethical aspects of research trailed behind the scientific review* [Expert 3]. This concern is shared by Expert 4. Furthermore, he states that this new Regulation is a threat to the legal position of patients that participate in an RCT. There's no court or other institution of arbitration to which patients can turn in case of conflicts.

There are concerns about the central place the RCT has in the authorization procedure. With regard to personalized medicines, the *trial of the future* might look different. Expert 1 states that in the current 'state of the art' in oncology pharmaceuticals are being developed on the basis of a certain genetic mutation. It would stand to reason to only include patients in a trial with that specific mutation. This means that the efficacy of a product can be proved much quicker and with fewer patients than in a standard RCT. According to Expert 5, regulators should investigate the possibility of using tissue sampling and other simulation techniques as a basis for new trials. Expert 5 has other concerns: *trials are also very much focused on the production of scientific output. There are examples in which this bias has led to the continuation of RCTs with products of which it was known that they didn't work* [5]. Expert 4 points out that by giving the RCT such a prominent position, other sources of information about the safety and efficacy of pharmaceuticals are not used. Such as data collected by pharmacovigilance agencies. This hampers our knowledge about the (off-label) use of pharmaceuticals and it ultimately obstructs innovation [4].

When touching upon the point of innovation, the tension between the use of placebos versus comparators was mentioned by various respondents. Regarding this question, the interests of producers, regulators and health care professionals diverge. Health care would benefit more from comparator studies [1,4]. Regulators prefer placebo-controlled trials, since it (usually) provides them with a clear outcome [3, 4]. Furthermore, Expert 4 points out, *when you look at the superiority of a certain new medicinal product, you also have to face the inferiority of the previous standard medication. That's a difficult thing to do*.

5.3 Innovation

5.3.1 Decreasing innovation

That the pace of innovation is slowing down, is not contested by any of the respondents. When asked for the reasons behind this decrease, the term 'return of investment' often surfaced. Expert 8 and Expert 2 both pointed towards the commercial motive behind pharmaceutical development [2,8]. *The pharmaceutical industry is particularly focused on shareholder value (…)*

Innovation has become less important, since it demands long term investments which don't have an immediate effect on the short term profit that shareholders value so much [Expert 2].

Expert 5's explanation differs slightly. According to him, innovation was initially slowed down by excessive regulations. The return of investment time became longer, especially in the innovative biotech sector. These companies relied heavily on venture capital. Due to the 'credit crunch', the suppliers of venture capital laid down stricter rules in order to shorten the return of investment time. As a result, biotech companies became less attractive for investment, etc. *It's a vicious circle that is slowly strangling the pharmaceutical sector* [Expert 5].

5.3.2 Patents

However, it's not only about investments. The pharmaceutical industry strongly focuses on the protection of intellectual property rights, in which patents play an important role. According to Expert 8 and Expert 4, patents have a negative effect on the pace of innovation and the social behaviour of producers. The latter can be illustrated by the sluggish way AIDS-pharmaceuticals were made available to poor regions where AIDS was (and is) a major public health concern, such as Africa and Asia [4].

Concerning the former, Expert 4 points out that innovation in the area of pharmaceuticals is a spasmodic process governed by 'patent blindness': if it cannot be patented, it is not worth the investment. Furthermore, once a chemical entity has been granted market authorization, the development process stops. Producers have little interest in improving an already authorized product, since: a. it would only help the producers of generics; b. it is not really necessary since physicians will use it 'off-label' if the product proves to be beneficial for something other than the original indication [4].

Expert 5 endorses this viewpoint. Even though Expert 5 and Expert 1 think there is a lot to say in support of the current patent system, the extent of protective measures on the pharmaceutical market is extreme [1,5]. A more open and transparent market – one that fosters competition – would be beneficial for innovation [5]. Expert 8 refers to an EU-investigation which analysed the way the pharmaceutical industry uses the system of patent protection (139). *It's mainly used to minimize competition (…). Several studies show that there's a negative relation between the innovativeness of a company and the amount of patents it has* [Expert 8].

Whether the current patent system is ready for the future, is doubtful. Expert 1 points out that the patenting of the body's own mutations will probably raise serious ethical concerns. According to Expert 5 it is not unlikely that future treatments will consist of various pharmaceutical components, developed by different companies or institutes, which will make the question of ownership and value more pressing [5]. Expert 8: *it would be wise to think about the way people get compensated for their intellectual properties. Maybe* [financial] *incentives aren't always necessary. Real innovations come from the academic world: scientists are more concerned with publications than with patents.*

5.3.3 Purchasing innovation

Most interviewees agree that the era in which pharmaceutical innovation was driven by the pharmaceutical industry is over. To compensate the faltering R&D-strategy, large pharmaceutical companies increasingly turn to academic institutions and small or medium sized biotech enterprises [1,2,4,5,8]. This does not mean large companies have no expertise. On the contrary, Expert 5 states: *they have a tremendous amount of expertise, especially in the field of*

compliance, setting up phase 3 and 4 trials and marketing & sales. The function of large companies, however, has changed from a driver of innovation to something resembling bank and broker for smaller companies or research institutes. The focus on blockbuster-drugs is not entirely illogical, since the sheer size of most companies means that they need to turn over a lot of money just to function.

Purchasing promising innovations is therefore extremely important for the survival of large companies. On the other hand, universities and small companies also need them. Expert 1: *new products and concepts are being developed in (academic) hospitals. In a later stage, for example after completion of phase 1 and 2 trials, the patents of these products are sold to pharmaceutical companies, because the necessary phase 3 studies has become so expensive that it is an impassable road for hospitals*. According to Expert 8 and Expert 1, this situation is far from ideal. While innovation is being 'outsourced' to public sectors like universities, hospitals or small private companies, the large companies reap the most financial benefits. In a sense, society pays twice: first by financing universities and secondly by paying the retail price of the product [1,4]. Expert 2 claims that this commercial aspect of this phenomenon is often (wrongfully) downplayed. In the interest of public health, the government demands cheap pharmaceuticals, while at the same time the government also wants to support the industry for economic reasons [2].

Expert 4, Expert 6 and Expert 8 are concerned about this development and want the government to take a more active role. Expert 4: *if you pay for it, why wouldn't you try to influence what you pay for?* Expert 6, on the other hand, warns against direct government investments. *It would create an equally flawed system.* Some countries experiment with price funds, which more evenly distribute the costs and risks of return on investments. This lessens the need for all actors, including the industry, to build up a large amount of safeguards [6].

5.3.4 Stimulating innovation

There are several other ways to stimulate innovation. Firstly, there is the possibility of special legislation, like the EU-regulations on Orphan Drugs or Advanced Therapy Medicinal Products. Both offer certain financial or regulatory incentives. Expert 4 states that in the case of Orphan Drugs the promised market exclusivity is not really an incentive at all: *it's a guarantee of market exclusivity on an already extremely exclusive market*. He has similar concerns about the Regulation on ATMPs. Traditionally, cell and gene therapy were treated as conventional pharmaceuticals. Since the introduction of the ATMP-Regulation, only four products have been registered as an ATMP. *All innovation in this area seems to have stopped* [Expert 4].

Expert 5 suggests that the pharmaceutical sector could learn from the idea of 'fast prototyping', a common phenomenon in the world of ICT and consumer electronics. By testing and adapting the prototype in a limited but 'real life'-setting, fast prototyping allows companies to turn innovative ideas into successful end products more rapidly and efficiently. This would especially be beneficial for serious (orphan) disorders. However, it would mean that the regulatory regime should make a more clear distinction between 'regular disorders' and 'serious disorders'. At the same time they should allow for a more adaptive form of market authorization and a less formalized way of gathering evidence [5].

According to Expert 6, early dialogues between the industry and regulators could also stimulate innovation. It allows for producers to hear on which grounds market authorization or reimbursement decisions will probably be taken at an early stage of development. This helps them to optimize their

research strategy and choose the right set of end points. As a quid-pro-quo, the industry has to give some indication on the intended price of the product. Early dialogues create an instrument through which society can steer the activities of the industry [6].

5.4 Costs

5.4.1 Price setting: a black box

The steadily increasing costs of pharmaceuticals during the last few decades are a source of worry, even though pharmaceuticals do not take up a large share of the total health care expenditure (yet). Medical technology, for example, has a much higher impact on the costs of health care, than medicines – according to Expert 1. When asked about the reasons behind the price increase, most respondents agree that this question is not easily answered. It is assumed that the growing amount of regulations is one of the main drivers [1,4,9]. The requirements that have to be met when conducting a clinical trial are so complicated, that most pharmaceutical companies hire specialized firms to set up their phase-3 trials, so called Contract Research Organizations (CROs). Expert 4: *these companies can charge up to a 100% of the original trial budget*.

Though compliance with regulatory requirements probably plays an important role in the price setting of pharmaceuticals, this cannot be tested. Pharmaceutical companies are not transparent how they compile their prices. In some cases, high prices are understandable; for example with orphan drugs. With these products, the industry only has a small patient base out of which they have to recoup their investment (and make a profit). In other cases, it is unknown what share of the price of a single product is spent on marketing, R&D or profits. *It's more or less a black box*, states Expert 2.

Expert 8, Expert 1, Expert 9 and Expert 6 support this claim [1,6,8,9]. The major 'consumers' of pharmaceuticals are governments. Through health insurance schemes, governments pay for the majority of pharmaceuticals. Expert 6: *It's extremely difficult for governments to deny reimbursement of pharmaceuticals only on grounds of its price. Society would not accept it*. This gives the industry a lot of leeway in their price setting. Expert 1 illustrates this with the example of a pharmaceutical (for a neurological disorder) developed by a university medical centre. *We couldn't register it due to the complexity of the registration process. As a result, the company that eventually licensed it as an orphan drug and marketed the product charged a much higher price: 30.000 euro instead of a 1.000* [Expert 1]. Furthermore, he points out, once a product is 'on the market', health insurers do not reimburse a magistral preparation made in a pharmacy, even though it's exactly the same and cheaper. Expert 8 thinks this problem can only be tackled efficiently on the European level [8].

5.4.2 Synergy between authorization and reimbursement

In order to curb the rising costs of pharmaceuticals, the decision-making process concerning market authorization and reimbursement should become more closely intertwined. For producers, the decision about reimbursement is source of larger concern than the decision about market authorization [8]. Producers and regulators should pay attention to the cost-effectiveness of a product in an early stage of the authorization process [8]. Only products with a clear superior cost/benefit ratio should be registered. After all, once a product is on the market, it is virtually impossible to remove it [8]. Expert 4, on the other hand, warns against too much synergy. *Reimbursement decisions are, and will remain, political decisions contrary to authorization decisions which are based on a*

scientific assessment. Both the government and politicians have to take that responsibility [Expert 4].

According to Expert 6, there are several major differences between the requirements for market authorization and reimbursement that have to be taken into account. First of all, the indicators used to measure the clinical effect of a certain pharmaceutical – for example a decrease of cholesterol levels – are different than those used to judge its added value, such as its effects on the incidence of cardiovascular diseases, longevity, etc. Secondly, in the world of health insurance it is common to compare different products with each other based on performance and costs. Thirdly, there's a fundamental difference between the contexts of both systems. Safety issues have direct consequences for the patient, while an unfavourable cost-effectiveness ratio is usually shifted on to those who pay the health insurance premiums. *It's a complicated clash of interests, in which one civilian – the payer – is placed against the other – the patient* [6].

It's therefore doubtful that the EMA or other regulators will deny market authorization based on a lack of added value, when the efficacy and safety of a product are scientifically proven. It's not their task. This does not mean that more harmonization would not be welcomed [6].

5.5 Availability

5.5.1 Risk minimization

The availability of pharmaceuticals is a complex issue in which the industry plays an important role. If there are still patented products on the market, there is no incentive to continue the development of an alternative. Expert 5: *the pharmaceutical industry does not always have the ambition to get products on the market as quickly as possible*.

On the other hand, Expert 4 observes that there is also a discrepancy between what people expect – both safe and available medicines – and what regulators and other authorities do [3]. The focus on risk minimization has led to a situation in which certain promising products and/or treatments are not entering the market, either because they failed the authorization procedure or because their development was stopped in an early phase, due to concerns about the outcome of the registration process (see: safety and innovation). Expert 9 underlines this observation: *Currently, regulators are only held accountable when a product has gained market authorization and it turns out that there's something wrong with it* (…) *However, there are no sanctions at all if a product is wrongfully withheld market authorization, whereas this is also a failure* [Expert 9].

The length of the authorization procedure is a point of concern as well. Expert 5 suggest that regulators should have an option to fast-track the procedure in the case of severe disorders. *The fact that the average length of the procedure is 14,8 years is not a problem in itself. The real problem is, that people with, for example, Amyotrophic lateral sclerosis (ALS) cannot wait 14,8 years* [Expert 5]. For those patients a short cycle time is crucial. According to Expert 9, Expert 2 and Expert 8 the length of the authorization procedure is caused by an increasing bureaucracy. Expert 9: *the sense of urgency is not always shared by people in important positions.* This could be amended by giving patients a more actively role in the authorization procedure [2,4,5,9]. Expert 2 and Expert 5 both point to the example of HIV/AIDS in which patient organizations and the gay community played a crucial role by pressurizing both regulators and government [2].

5.5.2 Centralization of production sites

Expert 1 on the other hand, is especially worried about the negative consequences of the ongoing centralization of pharmaceutical production sites on the availability of medicines. *In previous years, if there was a problem with one production site, another site could take over. These days, if there's a problem it's getting more common that products cannot be delivered at all* [Expert 1]. Furthermore, it is not easy for pharmacies to find out different ways to get the product. In the case of oncology, the consequences are even more severe, since most of the time there is no alternative and stopping treatment is not always an option. *It would mean a great deal, if regulators and governments would set certain requirements concerning a guaranteed supply* [Expert 1].

5.5.3 Compassionate Use

Compassionate Use programs are aimed at patients that do not benefit from regular treatments and makes it possible to request permission to use an alternative treatment which is still in its experimental phase. However, there are two major issues with this program, according to our respondents. First of all, there's no solid financial program to back up the Compassionate Use programs. In the Netherlands it usually depends on the goodwill of the health insurer [5,9]. Secondly, the program itself is complicated [9]. Patients have to undergo all available 'regular' treatment options before they become eligible for compassionate use. In some cases, even when it is clear that the other options will not work either [5]. Furthermore, both Expert 5 and Expert 9 think the real strength of a program like Compassionate Use, lies in the gathering of data. *Officially, it's not allowed to use Compassionate Use programs to gather data. This should be altered. Most doctors and patients are willing to do so* [Expert 5].

5.6 Transparency and accountability

5.6.1 Culture of secrecy

According to some respondents, the current regulatory regime is governed by a strong tradition of secrecy [2,4,5,8]. Expert 8: *it's a very tight-lipped system. Who is responsible for what is not always clear* (…) *The regulator who makes the rules is also responsible for their application and is – at the same time – the ultimate court of appeal*. The lack of transparency leads to an unverifiable decision making process which makes regulators unaccountable, warns Expert 4.

The claim that registration dossiers contain sensitive information about compounds, production processes and development strategies which could harm the producer if this information is openly available is contested by Expert 8: *in the case of biotech products, most information in the dossier is really just stating the obvious, but it also contains information about silly slip-ups, for example labelling mistakes*. Expert 5 states that more transparency not only enhances public trust, it might even benefit innovation. *Failing is an integral part of the innovation process, as is learning from your mistakes* (…) *by being transparent about it, you force the industry to become more innovative* [Expert 5].

In the case of regulators, Expert 4 and Expert 2 point out that the tradition of secrecy is rooted in their concern about being held accountable for 'mistakes' made in the past. Dossiers sometimes hold information that in retrospect might indicate a certain adverse event, which would immediately suggest that errors were made during the authorization process. Based on what was known at that time, this does not necessarily have to be a mistake [2,4].

On the other hand, being transparent might also show the arbitrariness of certain decisions. Expert 2 illustrates this with the example of the contraceptives Yasmin® and Diane-35®. Studies have shown that in the case of the (third generation) contraceptive Yasmin®, the risk of thrombosis is three times higher than that of any other second generation contraceptive, but it's just as high as with Diane-35®. *One is withdrawn as a contraceptive, the other one is still on the market. Maybe the EMA was worried about a potential 'pill scare'. That's understandable, but it doesn't negate the fact that it is a rather arbitrary decision* [Expert 2].

While the secrecy seems reasonable from the viewpoint of regulators and the industry, it also fosters unnecessary distrust in the system as a whole [2,4,8]. Public distrust is furthermore fed by an appearance of conflicting interests within the regulatory system. The relation between regulators, governments and industry sometimes appears to be 'warmer' than it should be. One example of this, is the shroud of mystery surrounding risk management plans. Under current EU-legislation, pharmaceutical companies are obliged to draw up risk management plans that give an overview on the possible risks of a certain product. In order to prevent doing the same thing twice, Expert 2 says, pharmacovigilance agencies should have access to these plans as well. Yet, it proves to be extremely difficult to get these plans (which are officially openly available). *It's strange that a producer has more information on possible adverse effects than the pharmacovigilance agency, but it's even stranger that the government has this information and refuses to share it with health care professionals and patients. The only reason not to share this information is to protect the economic interests of the industry* [Expert 2].

The tension between economic interests and public health is a constant factor in policymaking process around pharmaceuticals. The European Union wants to maintain a strong and innovative pharmaceutical industry vis-à-vis the United States of America. The output of this industry however, does not always serve the most pressing needs of public health. Expert 3: *it's a for-profit industry, which means that they put their money where they expect to gain the most. Usually this isn't a product aimed at a small population of patients or antibiotics, but a product aimed at common chronic disorders like diabetes, high cholesterol, hypertension, etcetera.* In order to steer money into those field, governments have to invest huge amounts of money themselves, as is the case with the Innovative Medicines Initiative [2]. By investing this money, the EU facilitates two aims: research in unmet medical needs and a strong position of Europe in the global pharmaceutical industry, but at the same time it also nurtures a system that is more 'industry friendly' than one solely based on the interests of public health. The real question is, whether it is possible to completely avoid this amalgamation of interests [2].

6 Discussion and conclusion

6.1 Key Questions

This report is a data driven investigation of the sustainability of the European pharmaceutical regulatory system in relation to its objectives to minimize risk with respect to pharmaceuticals reaching/being on the market, while maximizing gains in public health by stimulating innovation and availability of pharmaceuticals. Over the past decade, regulators have often been criticized for being overly risk averse by requesting too much data or delaying decisions because of unwillingness to leave room for uncertainty (38). The current European regulatory system is for a large part driven by the societal demand for minimal risks. Incidents generally generate an abundance of media attention, which leads to an increasing distrust by society in the regulatory system (31, 32, 48).

Against this background, two questions became paramount during our study: first, how is the European regulatory system for pharmaceuticals performing in terms of protecting public health from harmful and ineffective medicines (through the scientific evaluation prior to the market authorization of medicines and post market supervision afterwards)? Second, is it possible to obtain an appropriate balance between costs, availability, innovation and safety, taking into account the divergent opinions of different stakeholders? In this discussion, we share our reflections about these two key questions. We examine the consequences of developments in- and outside the system and conclude with what should be taken into account when discussing the possibilities of improvements of the system.

6.2 Public health or economic interests: an ambivalent relationship?

As we have seen in the historic background of the European regulatory regime, the system was built on the pillars 'public health' and 'economic interests': guaranteeing the safety of medicines available on the market, but safeguarding the interest of the European pharmaceutical industry at the same time (5, 25). Both goals were not directly at odds with each other, but were not entirely compatible either. Various experts also highlighted this dual nature of the regulatory regime during the interviews. The tension between economic interests and public health is a constant factor in the policy making process around pharmaceuticals. Whether this amalgamation of interests is something that can be entirely avoided, remains to be seen.

Furthermore, recent developments also cast doubt as to whether it is possible to make a clear distinction between the European and the global market (and industry) for pharmaceutical products (140, 141). While currently, the top-10 of the largest pharmaceutical developers in the world is equally divided between American and European companies, recent bids on EU-companies like AstraZeneca show that the market is continuously in motion (142). Medicines developers from India and China are on the rise, as well. How the European regulatory system has to react to these developments, is something that is still unclear.

6.3 Safety & efficacy: the root of all problems?

Regulatory agencies are tasked to ensure that only those pharmaceuticals are licensed of which the benefits outweigh the risks. In our study, both the reviewed literature and the interviewed experts state that the existing regulatory

system performs well in terms of safety and efficacy. Compared to the number of yearly authorized pharmaceuticals, the number of serious safety incidents is low (35). Yet, at the same time, this is not how it is perceived in 'the outside world', as has been shown by the increasing public attention to incidents like those with Vioxx® or Diane 35® (19, 32). The different way patients, regulators and society define acceptable risks, explains some part of the commotion that these incidents cause (31).

The classic response of regulators to public commotion is an increasing emphasis on medicines safety (48). Our study shows that this has negative effects on innovation, availability and costs. Demanding larger or more sophisticated studies increases costs, which makes innovative research in many therapeutic areas commercially unattractive. At the same time, it is doubtful whether larger and more extensive trials will generate better knowledge of all possible adverse effects. Moreover, the advantages of all safety requirements at the time of registration are often undone in daily clinical practice, e.g. by means of polypharmacy, off label use and/or non-compliance (19, 31, 40, 89). This explains the broad support for focussing more on the post-approval period within the lifecycle of a product by putting more emphasis on post-marketing safety monitoring.

Addressing these issues probably requires changes on several fronts. First, there's a growing need to rethink the balance between ensuring medicines safety on the one hand and the need to promote innovation, ensure availability and limit costs on the other. This rethinking should take into consideration risks perceived by society and patients, benefit-risk communication needs, medical needs and expected risks related to use in daily practice. Second, all experts and decision makers in the marketing approval process should be aware of the balance between the gain in safety versus the feasibility and costs of requesting additional information or data. Third, a continuous dialogue between regulators, the public at large, patients, healthcare professionals and pharmaceutical industry is needed to address both balances and to aim for development of products with greater efficacy benefits for patients. Regulation should keep pace with (fast) changes in society and adopt societal dynamics.

6.4 The less flourishing side of innovation

During the last decades, many innovation-enabling technologies have been developed. We have witnessed impressive innovations in treatment of numerous diseases and there are several (biotech) products in development for serious unmet medical needs (e.g. Alzheimer's disease, cancer, depression, stroke, schizophrenia) (32, 48). However, there are also less flourishing sides to pharmaceutical innovation. Last decennia, fewer new chemical entities reached the market, while there is a still growing need for new products (62, 63). Total R&D expenditure rose sharply as did the costs for a new chemical entity, there is stagnation/decline of output and worsening of attrition rates (64, 65).

The findings in this report show that some of these developments can be attributed to factors triggered by the regulatory system, such as higher regulatory requirements and the fact that more hurdles need to be taken; e.g. cost-effectiveness required by reimbursement agencies or head-to-head comparisons (37, 74, 82). However, these developments can also be attributed to factors outside the regulatory system, such as patent expirations, development strategy of pharmaceutical developers, increasing amount of generic products and me too's, the 'better than The Beatles'-problem and the 'return of investment'-time (30, 48, 73, 81).

The regulatory system does respond to these factors by stimulating innovation and availability through specific procedures, for example adaptive

licensing procedures or guidance to facilitate early dialogue between regulators, health-technology-assessment bodies and medicines developers (29, 31, 32, 53). Despite the awareness and system responds, the lack of real innovation remains difficult to resolve. The results of the experts' interviews underline this complexity, as various opinions were voiced when touching upon possible solutions to stimulate innovation. Progression within this area remains a challenge.

6.5 Costs: the black box

The steadily increasing costs of pharmaceuticals during the last few decades are a source of worry (64, 101). Both the literature and the interviews highlight that the growing amount of guidelines (including a.o. the demands for expensive phase III trials), and the additional requirements for reimbursement (pharmaceutical companies must also show that their products provide "value," both therapeutic and economic) are the important drivers of this development (29, 48, 50). Ultimately, long development times coupled with low success rates translate into high overall R&D costs, which are compensated through higher prices (31, 76).

However, a part of the cost increase is also a response to the vastly expanded research opportunities created by advances in basic science (78, 88). Just how much the compliance with existing and new regulations is costing pharmaceutical companies is hard to point out. Most producers are not transparent about how they compile the prices of their products (78, 103). As stated by one of the interviewees: *it's more or less a black box*. This development is not without consequences. Increasing costs lead to an increasing tension between those who pay for expensive medicines through their insurance premiums – the collective – and the individual patient. Transparency on the amounts of money spent on the various elements that determine the product price (e.g. compliance with regulations, marketing, earlier development failures, scientific progress, and etcetera) may provide insight into the role of regulation in rising costs.

6.6 Availability: a complex issue

The availability of pharmaceuticals is a complex issue in which many stakeholders play an important role. In addition, both system factors and external factors can be linked to variation in availability between products and/or countries. When discussing causes of non-availability, distinction should be made between actual non-availability of medicines; e.g. due to stagnation of scientific discoveries or unmet medical needs; and limited or no access to available medicines, e.g. due to problems at the production site or national policy issues (5, 19, 70, 117, 121).

Policy-makers have vast range of tools to improve medicine availability and affordability for their citizens. Various pricing policies and strategies exist (124, 125). However, it is not easy to determine which to implement. All have strengths and weaknesses, just as all countries/patients have unique medicine needs and challenges. Each country/regulatory agency must therefore assess its own medicines situation and implement different combinations of policies and interventions. Next to this, collaboration and coordination between countries is necessary to avoid situations as illustrated by the example of Greece; serious shortage of medicines due to the economic crisis and price differences between countries (126).

6.7 Transparency and accountability: a culture of secrecy?

The findings in this report furthermore show that insufficient transparency and accountability of the system are inextricably bound up with the four identified goals of the system; safety & efficacy, innovation, costs and availability (106, 121, 129, 133). During the course of the twentieth century, freedom of information has become the cornerstone of democratic societies and the culture of secrecy of the pharmaceutical industry and/or medicines regulatory authorities, leads to an unnecessary distrust in the system as a whole (128). Furthermore, it hinders innovation, raises costs and restricts the availability of necessary pharmaceuticals. This problem is widely recognized. Recent legislation by the European Union, as for example the higher transparency of clinical trial results, is addressing this issue (138). Nevertheless, it would be beneficial to rethink the way in which essential information can be mobilized best from pharmaceutical industry and/or medicines regulatory agencies without injuring any valid interest (141, 143). Accountability is intertwined with transparency; as an interviewee pointed out: *in the case of regulators, the tradition of secrecy is rooted in their concern about being held accountable for 'mistakes' made in the past*. Increased transparency is therefore not expected to be a panacea against distrust. This should be at least supplement with strategic communication on responsibilities of all stakeholders.

6.8 Pharmaceutical regulation: an intricate system of wheels and gears

In the previous section, we have discussed potential vulnerabilities of the pharmaceutical regulatory system. However, we can't ignore the fact that the selected themes are strongly interrelated and cannot be separated. Interventions in one theme will have an effect on another theme or even on multiple themes; e.g. more attention to safety and efficacy will affect costs, innovation and availability of pharmaceuticals. One could present the four major themes as a four gearwheels. When one wheel is being turned, the others are also set in motion (see figure 6.1). In addition, all four themes are influenced by transparency and accountability.

Figure 6.1: Interrelatedness between the four major themes of the regulatory system for pharmaceuticals

6.9 Strengths and weaknesses of this study

Inherent to this topic, there are many (different) views and opinions. However, we have tried to give this report a scientific basis by collecting additional quantitative evidence. The several sources of information used in this report were very useful, with the qualitative findings strongly supporting the quantitative results found or vice versa. The interviewees were Dutch experts. We do not expect that this has any influence on our discussion about the potential vulnerabilities of the European pharmaceutical regulatory system as all interviewees are strongly involved both in the national and European regulatory system.

This project has been commissioned by the organizations that form the Dutch medicines chain; the Dutch Ministry of Health, Welfare and Sport/Department Pharmaceutical Affairs and Medical Technology (VWS/GMT), the Medicines Evaluation Board (CBG-MEB), the Health Care Inspectorate (IGZ), the Central Committee on Research Involving Human Subjects (CCMO) and the Dutch Pharmacovigilance Center (Lareb). These parties have in common that they should have the ability to think on an abstract level (not a patient level). Our results are in line with this ability and presented on a high abstraction level. The pharmaceutical industry has been excluded in our interviews. Not because we are of the opinion that they should not be heard, but because we have primarily looked at the regulatory system from a governmental perspective. Besides, concurrently to the timing of this project, EFPIA commissioned the Escher project to conduct a review of the regulatory system for marketing authorization and the developments in its drivers based from an industry perspective. The Escher project review runs simultaneously with the project as described in this report.

6.10 Conclusions

Although the European regulatory system for pharmaceuticals seems to perform well in terms of protecting public health from harmful and ineffective medicines, a mixture of factors, internal and external to the system, combined with a slow-moving organizational structure, gives reasons to believe that the current regulatory system for pharmaceuticals is not sustainable in the future. The internal factors, such as the system's current focus on safety and efficacy and the ever expanding requirements, and external factors – e.g. patent legislation, reimbursement decisions, commercial strategies concerning investment and drug development – have an adverse effect on development of other areas, such as innovation, costs and availability.

Health care professionals and/or patients react to this by choosing alternative routes to increase access to certain pharmaceuticals, e.g. MyTommorows or off-label use of medicines. The system attempts to respond to these vulnerabilities, largely by expanding the regulatory network and/or corresponding legislation. Although these attempts are mostly aimed at one theme, they affect all themes simultaneously, as these themes are interrelated to each other.

This interrelatedness makes adjustments to the system complex and should always be kept in mind when discussing possible solutions for improvement of the pharmaceutical regulatory system. Thereby, progress can only occur with coordinated (inter)national effort by all relevant stakeholders, including EMA, national regulatory agencies, patient organizations, health care providers, pharmaceutical industry, SMEs, academia, member states as interests differ between various stakeholders. Any future changes to the regulatory system should be made as robust as possible towards plausible national and

international scenarios. Finally, establishing a robust baseline of transparency and accountability is a prerequisite for success.

> [I can‘t say whether it will become better if it will change, but I can definitely say that it must change if it shall come to a good end.]
> - Georg Lichtenberg, German scientist and philospher

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8 List of abbreviations

ABPI	Association of the British Pharmaceutical Industry
ADR	Adverse Drug Reactions
AIDS	Acquired Immunodeficiency Syndrome
ALS	Amyotrophic Lateral Sclerosis
ATMP	Advanced Therapy Medicinal Products
CA	Conditional Approval
CAP	Centrally Authorized Products
CFH	Medicinal Products Reimbursement Committee
CHMP	Committee for Human Medicinal Products
CP	Centralized Procedure
CRO	Contract Research Organizations
CTMP	Cell therapy medicinal products
DHPC	Direct Healthcare Professional Communication
DP	Decentralized Procedure
EC	European Commission
ECs	Exceptional Circumstances
EDQM	European Directorate for the Quality of Medicines
EFPIA	European Federation of Pharmaceutical Industries and Associates
EMA	European Medicines Agency
EMEA	European Agency for the Evaluation of Medicinal Products
EPAR	European public assessment report
ERP	External Reference Pricing
EU	European Union
EUnetHTA	European network of Health Technology Assessment
HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
GTMP	Gene Therapy Medicinal Products
GSK	GlaxoSmithKline
ICH	International Conference on Harmonisation
IMI	Innovative Medicines Initiative
LSE	London School of Economics and Political Science
MERC	Medical Ethical Research Committees
NCC	Nordic Cochrane Centre
OMCL	Official Medicines Control Laboratories
PIL	Patient Information Leaflet
PPP	Public-Private Partnerships
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Reports
RAND	Research ANd Development
RCT	Randomized Controlled Trials
SA	Scientific Advice
SAG	Scientific Advisory Group
SME	Small and medium enterprises
SPC	Summary of Product Characteristics
TiPharma	Top Institute Pharma
QALY	Quality-adjusted life year
WHO	World Health Organization

9 Glossary

Adaptive Licensing: Adaptive licensing is a prospectively planned, flexible approach to regulation of drugs and biologics. Through iterative phases of evidence gathering to reduce uncertainties followed by regulatory evaluation and license adaptation, Adaptive Licensing seeks to maximize the positive impact of new drugs on public health by balancing timely access for patients with the need to assess and to provide adequate evolving information on benefits and harms so that better-informed patient-care decisions can be made (32).

Applicants: parties (e.g. pharmaceutical companies or academic groups) that intend to submit or have submitted a marketing authorization application.

Benefit-Risk assessment: evaluation of benefits (favourable effects) and risks (unfavourable effects) of a medicinal product.

Committee for Medicinal Products for Human Use (CHMP): committee of the European Medicines Agency responsible for conducting the initial assessment of medicines for which an EU-wide marketing authorization is sought. The CHMP is also responsible for several post-authorization and maintenance activities, including the assessment of any modifications or extensions ('variations') to an existing marketing authorization.

Conditional approval: procedure to grant marketing authorization - even though comprehensive clinical data have not (yet) been provided - to (i) medicinal products for treatment, prevention or medical diagnosis of seriously debilitating or life-threatening diseases, or (ii) to medicinal products to be used in emergency situations or (iii) orphan medicinal products, on the basis of less complete data than is normally the case and subject to specific post-approval obligations.

The following requirements are mandatory: 1. The Benefit/Risk balance of the product is positive; 2. It is likely that comprehensive clinical data will be provided; 3. Unmet medical needs will be fulfilled; 4. Benefit to public health of immediate availability outweighs risks. A Conditional Approval is valid for one year (renewable) and is subjected to specific obligations to complete ongoing studies, or to conduct new studies with a view to confirming the positive Benefit/Risk balance.

Council of Europe: is an international organization promoting co-operation between all countries of Europe in the areas of legal standards, human rights, democratic development, the rule of law and cultural co-operation. It was founded in 1949. The best known bodies of the Council of Europe are the European Court of Human Rights and the European Pharmacopoeia Commission. Not to be mistaken with the European Council/Council of the European Union.

European Medicines Agency (EMA): The European Union regulatory authority committed to the recommendation about marketing authorization of medicinal products.

Exceptional Circumstances: Authorization under 'Exceptional Circumstances' can only be granted if the applicant is unable to provide comprehensive clinical data because of: 1.rarity of the disease; 2. present state of scientific knowledge; 3. ethical constraints. There is an obligation to focus on safety studies. The

approval is valid for 5 years (renewable), but there will be an annual re-assessment of the benefit/risk balance by the CHMP.

Food and Drug Administration (FDA): The United States regulatory authority committed to the recommendation about marketing approval of medicinal products.

Health Technology Assessment (HTA) bodies: Health Technology Assessment bodies provide recommendations on medicinal products and other health interventions that can be paid for or reimbursed by the healthcare system in a particular Member State. Their recommendations are based on comparing the 'relative effectiveness' of medicines and taking into account their financial costs.

Marketing authorization: the (first) approval of a medicinal product by a regulatory authority, leading to access to the market.

Marketing authorization application: the submission of a dossier for marketing authorization.

Medicinal products: Any substance or combination of substances presented for treating or preventing disease in human beings. Any substance or combination of substances which may be administered to human beings with a view to making a medical diagnosis or to restoring, correcting or modifying physiological functions in human beings is likewise considered a medicinal product. (Directive 2001/83/EC).

Orphan Drugs: Orphan medicinal products are intended for the diagnosis, prevention or treatment of life-threatening or very serious conditions that affect no more than 5 in 10,000 persons in the European Union.

Pharmaceuticals: See medicinal products.

Pharmacovigilance regulation: regulation aimed at the protection of public health in order to prevent, detect and assess adverse reactions to medicinal products for human use after they have been placed on the market.

Regulatory authorities: authorities committed to the marketing authorization of medicines on a European or a national level; also called **competent authorities or regulatory agencies**.

Regulatory system: the system that regulates the development, marketing authorization and market access of medicines.

Scientific advice: the opportunity for applicants to discuss scientific and regulatory aspects of the marketing authorization application with a regulatory authority.

Scientific guidelines: guidelines on the studies of a medicinal product to demonstrate a product's quality, safety and efficacy.

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