How well does regulation work? The cases of paediatric medicines, orphan drugs and advanced therapies

Final report

Client: Ministry of Health, Welfare and Sport

Rotterdam, 9 November 2015
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1 Introduction

The health policy of the European Union (EU) is based on the principle that good health of the EU population is a precondition for meeting the objectives of prosperity, solidarity, and safety. All citizens should have access to universal, quality health care, including preventive healthcare, and healthcare should be patient-centred and based on scientific evidence.

There is a consensus that timely and equal accessibility to high-quality medicines in general should be given high priority. People suffering from disease, especially those with high unmet medical need (i.e. rare diseases, children), need effective medicine to provide them with appropriate treatment, to avoid complications, adverse drug reactions and –possibly– death. The lack of (timely) access to medicines confronts patients with a potential and actual risk of suffering undesirable health effects; these drugs therefore have to be developed, tested, and produced.\(^1\)

The European Commission (EC) and several EU Member States (MSs) have recognised that the current regulatory framework for marketing authorisation of pharmaceutical products may need improvement. The main challenge is to balance earlier access of medicines to patients with unmet medical needs and the greater risks that this may pose, including the risk of the unknown when it comes to ultimate efficacy and safety.\(^2\)

In this dynamic environment, the Dutch Ministry of Health, Welfare and Sport (VWS) has asked Ecorys to study the European regulatory framework for marketing authorisation of pharmaceutical products. More specifically it concerns the Regulations of Advanced Therapies Medicinal Products (ATMPs)\(^3\), orphan drugs and paediatric medicines.

The study focuses on:

- The results of the three regulations in terms of (number of) products that meet a real unmet medical need;
- The extent to which these regulations meet their initial goals;
- The barriers and areas/topics in the regulatory system that are in need of improvement;
- The financial impact of (an increase in) pharmaceutical products due to the regulations, especially for the Netherlands;
- Lessons to be learned from other jurisdictions.

The methods used include:

- Desk research;
- Interviews with relevant national, European and international stakeholders (n=21);
- Financial analysis.

In the following Chapter we describe the regulations under study. In Chapter 3 we provide an overview of whether the regulations led to products that meet a real unmet medical need, have met their initial goals; and the barriers and areas/topics in the regulatory system that are in need of improvement. In Chapter 4 reflections from other jurisdictions with a particular focus on Canada, South Korea and the United States (US) are given. Chapter 5 provides information of the economic

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3 ATMPs are regulated as (chemical-based) medicinal products in the EU.
impact of the regulations for the Netherlands. In Chapter 6 we balance the cost and benefits of the regulations and provide recommendations on how to move forward.
2 The regulations under study

Access to health technology can be accelerated by optimising the process of regulatory approval. In this Chapter we provide an overview of the pharmaceutical regulations under study that are part of the EU regulatory framework, as depicted below.

Figure 2.1 EU regulatory framework

The European Medicines Agency (EMA) is responsible for the scientific evaluation of applications from pharmaceutical companies for EU-wide single marketing authorisations for human and veterinary medicines for preventive, diagnosis and treatment purpose (centralised procedure). Pharmaceutical companies are obliged to apply for a scientific evaluation of their medicinal product before they are allowed to launch their product onto the European pharmaceutical market. The evaluation assesses the degree to which the drugs fulfil the scientific criteria of quality, safety and efficacy. Ultimately, the drugs should demonstrate a positive benefit-risk ratio.4

Alternatively, pharmaceutical companies might choose to apply for the decentralised procedure within a single European country where national competent authorities are responsible for the authorisation of drugs. Thereafter, pharmaceutical companies can enter the market of other EU MSs through the mutual-recognition procedure. EMA is in charge of the resolution of possible disputes in this matter.5

After market authorisation based on the benefit-risk assessment, MSs can assess the ‘relative effectiveness’ and the financial costs of a drug (i.e. national assessment). The pricing and reimbursement policy of drugs is the remit of national governments or health authorities of individual countries.

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The EU pharmaceutical legislation has consistently pursued the protection of public health as well as the free movement of medicinal products. These overarching aims are reflected in the three regulations, which are described in more detail below.

2.1 Paediatric Regulation

The first regulation under study is the Paediatric Regulation. This section describes the context of the Regulation, the regulatory process, and its goals and system of obligations, rewards and incentives.

2.1.1 Towards Paediatric Regulation in the European Union

In 1997, a round table discussion with leading experts in the field of paediatrics was organised to discuss the implementation of a new paediatric rule in the US. The US regulation requires pharmaceutical companies to supply data on the effects of new drugs and biologics in children if the product is expected to be frequently used for children or when it could demonstrate a meaningful benefit. In the EU, there was no paediatric regulation at that time.

The experts at the round table concluded that within the EU there was a general lack of information and appropriate pharmaceutical formulations to support administration of many medicinal products for children. This was due to the lack of well-designed clinical studies in the paediatric population. Over 50 percent of medicines used in children were never tested for use in this population, leading to a lack of appropriate dosage recommendations for children and eventually resulting in frequent off-label use of licensed medicines and the use of unlicensed medicines in children. This situation was in contrast to the general goal of providing high-quality health care to the population in the EU.

Therefore the recommendations of the experts regarding pharmaceutical formulations were “A strengthening of EU legislation should be considered by the European Commission in order to impose requirements on pharmaceutical companies to conduct paediatric studies for medicinal products that are widely used in paediatric patients or that are indicated for a very significant or life-threatening illness.”

2.1.2 European legislative process

In 2000, under the French EU presidency, the topic of medicines of children was discussed as a main public health priority. Afterwards, the Council of Ministers requested the EC to draw up a regulation on paediatric medicines.

The Better medicines for children consultation paper was published by the EC in 2002. This paper was one of the first steps of the Commission to address the problem(s) regarding paediatric medicines. It describes six objectives for European regulatory action: Increase the availability of authorised medicinal products; adaptation of pharmacovigilance mechanisms; facilitate the avoidance of unnecessary studies; prioritization of research areas; develop European excellence in the field of paediatric medicines.
regarding research, development and assessment of clinical trials and assure that the highest ethical criteria are met.9

In 2004 the Regulation on medicinal products for paediatric use was drafted, and later a first proposal were released by the EC. After the first proposal was modified due to the European Parliament’s feedback, the Regulation was agreed upon in December 2006 and became effective on 26 January 2007.10

2.1.3 Goals of the Paediatric Regulation

Market forces alone have proven insufficient to stimulate adequate research into, and the development and authorisation of, medicinal products for the paediatric population. Therefore, the regulation aims to:

1. Facilitate the development and accessibility of medicinal products for use in the paediatric population;
2. Ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population; and
3. Improve the information available on the use of medicinal products in the various paediatric populations.4

2.1.4 Incentives and other measures of the Paediatric Regulation

There are several measures within the regulation designed to achieve the goals, including obligations, rewards, incentives, and measures targeting research and development of paediatric medicines:

- when a marketing authorisation application for a new medicine and certain line-extensions for certain existing patent-protected medicines are submitted, they should contain data regarding the use of the medicine in children as a result of an agreed paediatric investigation plan (PIP). The PIP aims to ensure that paediatric data are generated in the R&D phase and needs to be accepted by the EMA;
- a completely new type of marketing authorisation, referred to as paediatric use marketing authorisation (PUMA). This provides the applicant with 10 years of market protection for innovation (new studies) on off-patent drugs. Data protection extends only to paediatric use;
- a reward for compliance with the requirements in the regulation in the form of a six-month extension to the supplementary protection certificate (SPC), i.e., a six-month patent extension on the active substance. This can be extended in the form of an additional two-years market exclusivity for orphan drugs, added to the existing ten-years awarded under the Orphan Regulation (see section 2.2.4);
- a referral procedure that can be triggered by a marketing-authorisation holder when applying for a new indication, new pharmaceutical form or new route of administration for use in children;11
- a system of waivers from the requirement for medicines unlikely to benefit children;
- a system of deferrals of the timing of the requirement to ensure medicines are tested in children only when it is safe to do so and to prevent the requirements delaying the authorisation of medicines for adults;

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within EMA an expert paediatric committee (PDCO) was set up to provide opinions on the development of medicines for use in children. The PDCO should also establish an inventory of therapeutic needs, in particular with a view to identifying research priorities;

any legal or natural person developing a medicinal product intended for paediatric use may, prior to the submission of a paediatric investigation plan and during its implementation, request free scientific advice from EMA on the design and conduct of the various tests and studies necessary to demonstrate the quality, safety and efficacy of the medicinal product in the paediatric population;

funds for research into medicinal products for the paediatric population shall be provided by the Community budget in order to support studies relating to medicinal products or active substances not covered by a patent or a SPC;

EMA shall, with the scientific support of the PDCO, develop a European network of existing national and European networks, investigators and trial centres with specific expertise in the performance of studies in the paediatric population;

partial exemption from payment of fees for PUMA applications submitted under the centralised procedure;

retain the name of another medical product. This is possible for a medicinal product for which a PUMA has been granted. The product should contain the same active substance and the same holder has been granted an authorisation for use in adults;

measures to maximise the impact of existing studies on medicines for children, including a public database of paediatric studies.\textsuperscript{12,13}

These measures go beyond the mechanisms of the Orphan Regulation and the ATMP Regulation, which is limited to providing incentives as described in the two subsequent sections.

\section{2.2 Orphan Regulation}

\subsection{2.2.1 Towards Orphan Regulation in the European Union}

There are different definitions of rare diseases and orphan drugs in existing legislation (of different countries) and in the literature. In general, a rare disease, including those of genetic origin, is defined as a disease with a very low prevalence that is life-threatening or chronically debilitating. In the EU, low prevalence is defined as not more than 5 per 10,000 in the EU.\textsuperscript{14}

It is estimated that between 5,000 and 8,000 different diseases can be classified as rare diseases. In addition, it is estimated that about 6-8 percent of the EU population is affected by a rare disease, which is about 27-36 million people.\textsuperscript{15}

Because of the low prevalence, rare diseases have traditionally not been on the priority list of the pharmaceutical industry due to a high probability that the return on investment will be insufficient.\textsuperscript{16}

\textsuperscript{14} ISPOR. Special Interest Group Rare Diseases. Rare diseases: terms, definitions, and challenges in assessing and appraising diagnostics and treatments. 5 November 2013. Available at: http://www.ispor.org/congresses/Dublin1113/presentations/ISPOR-Rare-Disease-all-speakers.pdf
\textsuperscript{16} Rinaldi A. Adopting an orphan. Incentives to develop drugs for rare diseases raise hopes and controversy. EMBO Reports. 2005;6(6):507-510.
For this purpose, the EU offers a range of incentives, specified in the Regulation, to encourage the research, development and marketing authorisation of orphan medicines.\textsuperscript{17}

2.2.2 European legislative process

As with the Paediatric Regulation, the US had already developed legislation regarding orphan medicines. The US promulgated the US Orphan Drug Act in 1983 and its success encouraged other countries to enact similar legislation.\textsuperscript{18}


In addition, in the late 90’s the Commission published a programme for community action in the period 1999-2003 to address rare diseases. The aim of the programme was “to contribute, in coordination with other Community measures, towards ensuring a high level of health protection in relation to rare diseases by improving knowledge (...) by promoting the setting-up of a coherent and complementary European information network on rare diseases (...) facilitating access to information about these diseases.”\textsuperscript{19}

2.2.3 Goals of the Orphan Regulation

The goals of the Orphan Regulation are two-fold:

1. Encourage the pharmaceutical and biotechnological industry to develop and market orphan drugs;

The regulation establishes “a Community procedure for designating orphan medicinal products and introduces incentives for orphan medicinal products research, development and marketing, in particular by granting exclusive marketing rights”.\textsuperscript{20} To be eligible for the incentives, orphan drugs should be identified through a Community procedure of designation for which objective criteria should be established.

2. Create a Committee of Orphan Medicinal Products (COMP) within EMA.

The Regulation determines that a committee composed of experts appointed by the MSs should be established to examine applications for designation.\textsuperscript{21} The main responsibility of this committee is to examine the scientific quality of applications, before consideration of the designation of an orphan medicinal product.

2.2.4 Incentives of the Orphan Regulation

The incentives for orphan drug development are:

\textsuperscript{17} http://www.ema.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000034.jsp&mid=WC0b01ac058002d4eb
\textsuperscript{21} Orphanet. Orphan Drugs in Europe. Available via: http://www.orpha.net/consor/cgi-bin/Education_AboutOrphanDrugs.php?lng=NL&stapage=ST_EDUCATION_EDUCATION_ABOUTORPHANDRUGS_EU_R
\textsuperscript{22}
How well does regulation work?

- Ten year market exclusivity after authorisation for designated products – this is considered to be the main incentive for industry;
- Fee waivers with regard to:
  - marketing-authorisation applications;
  - inspections before authorisation;
  - applications for changes to marketing authorisations made after approval;
  - protocol assistance.
- Scientific advice from EMA on how to conduct various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product prior to the submission of an application for marketing authorisation;
- Possibility of a Community marketing authorisation;
- Marketing authorisation may be achieved through exceptional circumstances when the applicant can show that he is unable to provide comprehensive data on the efficacy and safety under normal conditions of use. The marketing authorisation may be granted when the applicant completes a set of studies within a specified time period. The results form the basis of a reassessment of the benefit/risk profile;
- Incentives to support scientific research through Community programmes, such as Framework Programmes.

These incentives are more extensive compared to those provided under the Advanced therapy Medicinal Products Regulation as described below.

2.3 Advanced Therapy Medicinal Products Regulation

2.3.1 Towards Regulation of advanced therapy medicinal products in the EU

Advanced therapy medicinal products (ATMPs) are based on genes, cells and tissues, but there is no common definition available in the literature. Often a distinction is made between cells or tissues of human or animal origin intended to be used in humans (cell-based medicinal products and tissue-engineering) and biological products involving the use of recombinant DNA (gene therapy medicinal products). In addition, the therapy can include a combination of devices, procedures and therapies, e.g. cells embedded in a biodegradable matrix or scaffold. These products – also called advanced therapies - can provide revolutionary treatments for a number of diseases with high unmet need, including Alzheimer disease, skin burns and cancer. In the field of advanced therapies the main actors are SMEs, academic spin-offs, not-for-profit organizations, and academia, since it is a research-intensive field, while the traditional pharmaceutical companies are not (yet) strongly involved because of the perception of high risk by this industry.

Developments in cellular and molecular biotechnology are essential for developing advanced therapies that could offer new treatment opportunities that were not available in the past.

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However, ATMP is a challenging field from a scientific and technical point of view due to the very low number of patients as well as to the nature of the products. Before the EU Regulation became effective in 2008 (see section 2.3.2. below), products derived from genes and cells were mostly classified as pharmaceuticals, while tissue-engineered products were not explicitly covered by the existing legal framework. As a consequence these products were only partly classified as pharmaceuticals or as medical devices.\textsuperscript{30} The lack of EU regulation in this field led to different approaches at the MS level. These varying approaches were counterproductive for the access to ATMPs and for the growth and competitiveness of the industry.\textsuperscript{31}

2.3.2 European legislative process

Advanced therapies are regulated as (chemical-based) medicinal products in the EU. Regulation (EC) No 726/2004 and Directive 2001/83/EC were eventually amended by Regulation (EC) No 1394/2007, which is the basic legislation for ATMPs.\textsuperscript{32}

The Regulation was adopted in 2007 and became effective on 30 December 2008\textsuperscript{33}. The Regulation was accompanied by a series of guidelines issued by EMA. It contains special rules with respect to the Directive on the creation of a Community code relating to medicinal products for human use (Directive 2001/83/EC) and the Regulation defining Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency (Regulation (EC) No. 726/2004).\textsuperscript{34, 35}

In addition, advanced therapies can be used without a marketing authorisation in domestic hospitals under the so-called hospital exemption (to be described below).

2.3.3 Goals of the ATMP Regulation

The main goals are:

1. Ensure the free movement of advanced therapies within the Community, and the effective operation of the internal market in the biotechnology sector;
2. Distribution and use of products must safeguard public health;\textsuperscript{36, 37}
3. In addition, a Committee for Advanced Therapies (CAT) should be set up within EMA that should become responsible for preparing a draft opinion on the quality, safety and efficacy of each advanced therapy for final approval by EMA’s Committee for Medicinal Products for Human Use (CHMP).\textsuperscript{38}

\textsuperscript{31} http://ec.europa.eu/health/human-use/advanced-therapies/index_en.htm
\textsuperscript{32} http://www.genetherapy.net.com/europe.html
\textsuperscript{36} http://ec.europa.eu/health/human-use/advanced-therapies/index_en.htm
2.3.4 Incentives of the ATMP Regulation

The incentives applicable to ATMPs include exceptional circumstances, (partial) exemption from payment of fees, hospital exemption, optional certification procedure, scientific advice and a classification procedure.39

- An exceptional circumstance could be provided when an applicant cannot show that he is able to provide comprehensive data on the efficacy and safety under normal conditions of use. Marketing authorisation may be granted when the following conditions are met:
  - the applicant completes an identified programme of studies within a time period specified by the competent authority;
  - the results shall form the basis of a reassessment of the benefit/risk profile;
  - the medicinal product in question may be supplied on medical prescription only and may in certain cases be administered only under strict medical supervision.40

- Hospital exemption can be gained; the medication should only be used under the exclusive professional responsibility of a medical practitioner. In addition, the product should be prepared and used within the same MS and an individual medical prescription for a custom-made product for an individual patient is needed;

- The (optional) certification procedure provides the developer with feedback about the quality and preclinical aspects in relation to the regulatory requirements. This procedure is meant as an incentive to SMEs in attracting capital and to facilitate the transfer of research activities to organisations that have the capacity to market medicinal products. In addition, SMEs will receive a 90% fee reduction.

- The classification procedure allows the developer to get a scientific recommendation from EMA, so developers know whether their product is classified as an ATMP. The advantages of this procedure is that the advice is EU-binding and free of charge;

- Partial exemption from payment of fees, for instance a 50% reduction for the marketing authorisation fee.41

- The ATMP developer can obtain scientific advice from the European Medicines Agency (EMA) as early as the development phase so that the authorisation procedure has the greatest possible chance of success

The incentives and other measures regarding the three regulations under study are summarised in Table 2.1.

<table>
<thead>
<tr>
<th>Incentive</th>
<th>Paediatric</th>
<th>Orphan</th>
<th>ATMP</th>
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<tbody>
<tr>
<td>1</td>
<td>Supplementary protection certificate</td>
<td>X</td>
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<tr>
<td></td>
<td>This certificate extends the protection conferred by the basic patent beyond the term for six months for products that are covered by a patent or by a SPC</td>
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<td>2</td>
<td>Marketing Authorisation specific use (PUMA)</td>
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<td>X</td>
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<tr>
<td></td>
<td>Exclusively use in the paediatric population, retain the existing brand name of the corresponding product authorised for adults, data exclusivity.</td>
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<table>
<thead>
<tr>
<th>Incentive</th>
<th>Paediatric</th>
<th>Orphan</th>
<th>ATMP</th>
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</thead>
<tbody>
<tr>
<td>3 Market exclusivity:</td>
<td>X*</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>10 years market exclusivity + 2 years*</td>
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<td>4 Waivers</td>
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<tr>
<td>Some requirements and fees can be ‘waived’ in order to stimulate paediatric development of medicines for which is no paediatric indication.</td>
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<tr>
<td>5 Deferral</td>
<td>X</td>
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<tr>
<td>A deferral is used when paediatric information may be submitted until after approval, e.g. when paediatric studies should be delayed because safety and/or effectiveness data in adults would delay the availability of a product to adults.</td>
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<td>6 Referral</td>
<td>X</td>
<td></td>
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<tr>
<td>The Commission issues a decision, which directs the MSs to update their authorisations with regard to specific wording on paediatric use</td>
<td></td>
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<tr>
<td>8 Exceptional circumstances</td>
<td>X</td>
<td>X</td>
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</tr>
<tr>
<td>Marketing authorisation for applicants who finish a programme of studies on medicinal product(s) within a specified timeframe - drugs only supplied on medical prescription and in certain cases administered only under strict medical supervision</td>
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<td>9 Partial exemption from payment of fees</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>On inspections, applications, annual fees, etc.</td>
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<tr>
<td>10 Retain the name of another medicinal product</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>When PUMA granted - retain the name of another medicinal product containing the same active substance and in respect of which the same holder has been granted an authorisation for use in adults</td>
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<td></td>
<td></td>
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<tr>
<td>11 (free*) Scientific/protocol advise</td>
<td>X*</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Request advice from the Agency on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product</td>
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<td></td>
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<tr>
<td>12 Incentives for micro-, small- and medium-sized enterprises (SMEs) – optional certification procedure</td>
<td>X</td>
<td></td>
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<tr>
<td>13 Research funds (e.g. FP)</td>
<td>X</td>
<td>X</td>
<td></td>
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<tr>
<td>In order to support studies relating to medicinal products or active substances not covered by a patent or a supplementary protection certificate</td>
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<tr>
<td>14 Research network</td>
<td>X</td>
<td></td>
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<tr>
<td>To coordinate studies relating to paediatric medicinal products to build up the necessary scientific and administrative competences at European level</td>
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<tr>
<td>15 EU inventory of therapeutic needs</td>
<td>X</td>
<td></td>
<td></td>
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<tr>
<td>Identifying research priorities</td>
<td></td>
<td></td>
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<tr>
<td>16 Compliance statement</td>
<td>X</td>
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<tr>
<td>Is received if the application complies with all the measures contained in the agreed PIP and product characteristics reflects the results of studies conducted via the PIP</td>
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<tr>
<td>Incentive</td>
<td>Paediatric</td>
<td>Orphan</td>
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<td>17 Hospital exemption</td>
<td></td>
<td></td>
<td>X</td>
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<tr>
<td>For custom made ATMPs when provided that the product is used for individual patients in a hospital and under the professional responsibility of a medical practitioner.</td>
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</tr>
<tr>
<td>18 Classifications</td>
<td></td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>EMA gives scientific recommendations as to whether a given product should be considered an ATMP</td>
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3 Assessing the effectiveness of regulation

In this Chapter we describe:
- the results of the regulations in terms of (number of) products that meet a real unmet medical need;
- the extent to which these regulations meet their initial goals;
- the barriers and areas/topics in the regulatory system that are in need of improvement.

Our findings are based on both desk research and interviews with relevant national and European stakeholders. In addition, we conducted a case study for each of the regulations under study to illustrate the findings. In conducting the case studies, we closely collaborated with health professionals.

3.1 Unmet medical need

In order to determine whether the regulations have led to medicinal products that address diseases with unmet medical need, a description of the term is needed. In the section below, we provide a definition that is used by the FDA in the US and clarify why it is difficult to present a list of medicinal products that fulfil a real unmet medical need.

3.1.1 Addressing unmet medical need

Unmet medical need exists when a disease is not effectively addressed by the current/available therapy. There are two types of unmet medical need:

1. when no therapy exists for a certain disease; and
2. when a disease is not adequately addressed by available therapies. If there is a therapy available for a disease, a new therapy can only address unmet medical need if the new therapy:
   - has a substantial effect on an outcome of the disease that is not known to be affected by available therapies;
   - when it is superior to other therapies targeting the specific disease;
   - has a substantial effect on an outcome of the disease, when patients do not respond to or do not tolerate the available therapies;
   - can be used effectively with other critical agents that cannot be combined with available therapy;
   - when it is just as safe and effective as the golden standard, but provides more benefits;
   - is not or less toxic compared to the available therapies;
   - addresses a public health need.42

Unmet medical need also can be viewed from different time perspectives: (1) instantaneous need to address a serious condition with no or limited treatment in a well-defined population; and (2) longer-term medical need for a population based on serious threats to public health (e.g. antimicrobial resistance).

Our search strategy that was used to support the desk research has not resulted in an overview of medicinal products or a study that mentions a specific medicinal product that addresses unmet

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medical need. Unmet medical need in general, however, is mentioned in several studies. These studies describe the status of unmet medical need in a broader sense. For instance with regard to orphan drugs, we found that: *the unmet medical need is far from over. It is estimated that just 1% of rare diseases are currently covered by approved treatments in the EU (...). the incentives of the orphan drug legislation are necessary and are responsible for facilitating the development of elegant and sophisticated treatments for patients with real unmet needs.* In addition: *Regarding the paediatric regulation in general, critics emphasize the system fails to stimulate research in areas of unmet medical need, and instead has resulted in companies adding paediatric information to medicines developed for adults in lower priority areas.*

Based on our findings, we conclude that overall the regulations have been rather successful in addressing diseases with unmet medical need. This is especially true for orphan drugs, while the number of newly developed paediatrics and ATMPs is still modest. Below, this conclusion is explained.

### 3.2 Effectiveness of the Paediatric Regulation

In the subsequent sections, we provide an overview of the goal attainment of the Paediatric Regulation. The goals were listed in Chapter 2 (section 2.1.3). In addition, we provide an overview of the regulatory hurdles, the areas/topics in the Paediatric Regulation that may need to be improved, and the views of relevant stakeholders.

#### 3.2.1 Goal 1: Facilitate the development and accessibility of medicinal products for use in the paediatric population

One of the explicit goals of the Paediatric Regulation is to increase the number of products that are researched, developed and authorised for use in children and to reduce the off-label use of medicinal products in the paediatric population. The paediatric investigation plan (PIP) is the main tool to achieve this goal. The Regulation obliges companies to make a PIP for products that are new or for products that are already authorised, under patent protection, but are extended (new indication, new route of administration or formulation). The PIP is meant to ensure that the necessary research data are generated. It also describes the conditions to determine whether a medicinal product may be authorised for use in children. When the PIP is completed and all requirements are met, the developer will be awarded a 6 months extension of patent protection (SPC).

In 2013, the Commission released a progress report that describes the first five years of the application of the Regulation. In addition, there are annual reports that provide an overview of companies and medicinal products that have benefited from the incentives and other measures provided under the Paediatric Regulation. From these sources it is clear that at the end of 2014 around 790 PIPs have been approved, of which less than 10% have been completed to date and the vast majority are still on going. The main reason for this is due to the long development cycle of a medicinal product, which is often more than a decade.

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Since the Paediatric Regulation entered into force, 31 out of 152 new medicines have been centrally authorised for paediatric use, 10 of which met the conditions of the general authorisation requirements of Article 7 in the Regulation. This figure is likely to increase in the future, as a considerable number of the new, already authorised, medicines are subjected to an investigation plan where completion was deferred to avoid delays in the authorisation of the adult product. Also, 72 new paediatric indications were approved regarding variations on medicines that were already authorised. Finally, 26 new pharmaceutical forms were authorised for paediatric use in medicinal products that had already marketing authorisation.

While the Paediatric Regulation has led to some new authorisations that include paediatric indications, the regulatory instrument is still quite recent. Because of that, it will probably take some more years before it can be judged in terms of its output. In 2017, the Commission will provide a further report on the (economic) impact of the Regulation, but in terms of number of medicines that became available, there is already a visible positive impact.

At the end of 2013, 9 medicinal products had received the SPC (6 months extension) award in 16 MSs during that year. As not all medicinal products received the 6 months extension in each country, the total number of extensions was 123 for 2013. In 2014, 13 products benefited from this award. In addition, the PUMA (8 years of data exclusivity and 2 years of market protection) is also perceived as a disappointment by stakeholders, as only two products have been granted this award. With regard to the impact of the Paediatric Regulation on orphan drugs, two medicinal products have been granted 12 years market exclusivity (first granted in 2014). Kreeftmeijer-Vegter et al (2014) conclude that the Regulation "added complexity to the research and development and regulatory process of orphan medicinal products, exemplified by the applicant’s investment time and effort in drafting a PIP." This complexity has led to a minor impact on the availability of orphan drugs for children and has increased time to marketing authorisation.

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3.2.2 Goal 2: Ensure that medicinal products used to treat the paediatric population are subject to ethical research of high quality and are appropriately authorised for use in the paediatric population

Many pharmaceutical companies considered the adult population their number one market before entry of the Regulation. Research in the paediatric population was not very interesting for pharmaceutical companies due to the factors described in Chapter 2. This situation has changed due to the Paediatric Regulation. Every new adult product has to be screened to determine whether it is feasible for paediatric use. Companies have given feedback on this requirement, which indicates that a change of culture has occurred. Paediatric development is now considered to be a regular step in the process of product development.\(^56\)

The requirement of the Regulation to develop and discuss a PIP with the PDCO forces companies to think about paediatric use early on. This early consideration is useful, as it avoids any delays in general product development. To ensure that enough and adequate data are generated for paediatric authorisations, research and development is part of the plan.\(^57\)

One of the goals in the Regulation is that medicines for children need to be tested in order to ensure their safe and effective use. One would expect this requirement would lead to more clinical trials in children. The EudraCT database does not show an increase in paediatric trials. Between 2006 and 2012 the number of clinical trials remained stable, about 350 trials on average per year. For a subpopulation, however, there has been an evident increase in the number of paediatric study participants; the age group from 0 to 23 months. The inclusion of neonates is a positive sign; these had been the most neglected paediatric group.\(^58\)\(^59\) However, according to Kreeftmeijer-Vegter et al, the impact of the Regulation on research quantity and quality in children through PIPs is not yet clear.\(^60\)

3.2.3 Goal 3: Improve the information available on the use of medicinal products in the various paediatric populations

Articles 45 and 46 of the Paediatric Regulation require that existing and newly generated paediatric data (study data) must be submitted to Competent Authorities to assess, for example, whether amendments need to be made to the Summary of Product Characteristics (SmPC).

In addition, the Paediatric Regulation includes incentives to stimulate new research that can improve the information base on the use of medicinal products in paediatrics. For this purpose, a paediatric clinical research network: the European Network for Paediatric Medicines Research at EMA (Enpr-EMA) was set up in 2009. It is an international network for paediatric research and focuses also on research quality criteria. In addition, EU funding is provided to 15 projects focusing


on at least 20 off-patent medicines (active substances) with a total budget of at least €75 million.61,62

3.2.4 Regulatory hurdles and areas for improvement

Companies have raised concerns regarding the PIP, the core of the Regulation. The companies are obliged to submit the PIP before submitting a market authorisation application. This requirement could be problematic for pharmaceutical companies, because there is uncertainty about the benefit-risk profile during the drug development phases, which could result in an increase in the probability that downstream modifications need to be made on the proposed study design. Also, it is not uncommon that products fail between the end of Phase I of the application and market authorisation. This could result in products that fail to reach the market. Finally, there is a risk of misalignment between the development of paediatric products in the EU and the US, since the FDA requests a paediatric development plan after Phase II of the application63 (see next Chapter).

Regarding neonates, there has been progress in their inclusion in drug development, but there are limitations surrounding the incentives that lead to market failure. This is reflected by poorer market signals for this age group. Market failure, though, can be overcome by legislation, as is shown by the older age groups.64 The literature suggests to measuring PIPs against a benchmark of paediatric needs, because the therapeutic areas covered by (the current) research gives a better reflection of adults needs instead of those of children. It might be difficult to identify a suitable benchmark. A topic that remains under-studied is long-term safety and effectiveness. To improve this situation, new EU pharmacovigilance legislation or checking the relevancy of studies in children might help.

Both the US and EU governments have made investments in research regarding off patent medicines. In Europe PUMA acted as stimulation with EU funding, but the yields of licensing are not yet noticeable.

The fact that only two PUMA’s have been granted could indicate limited effectiveness of this incentive. It takes time to conduct studies with off-patent medicines in children, but since the years that passed since the introduction of the regulation, a higher number of PUMA requests might have been feasible. Financial prospects could be a limitation to license off-patent medicines for paediatric indications. It has been suggested that the target population for a PUMA is too small. National reimbursement rules may not offer rewards that cover research costs for off patent medicines and investment sources for paediatric research among generic companies may be lacking.65

Regarding the paediatric regulation in general, critics emphasize that the system fails to stimulate research in areas of unmet medical need, is too complex and burdensome, is inconvenient in its timeline regarding submission of the PIP, has administrative issues, does not reach the goal of bringing more medicines to children, and instead has resulted in companies adding paediatric

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information to medicines developed for adults in lower priority areas. In addition, critics suggest that scientific advice should be provided free of charge, no matter the size of the company.

3.2.5 Experts’ opinion
For this study we consulted several experts, including experts in the field of paediatrics. These experts included both researchers and representatives of governmental agencies. According to these experts, the incentives for paediatric drug development are perceived as very limited. The costs for research and development are excessively high and the incentive of 6 months additional market protection is insufficient to make up for these costs. Still, the number of applications for waivers and deferrals is growing, which indicates that research on paediatrics is growing.

Although the period of additional market exclusivity is limited, it is still interesting for big companies with blockbusters receiving large revenues to develop a paediatric drug based on the same molecules. Each additional month with extra revenues is interesting, as long as the costs of developing a child-friendly dose are low. Without the additional period of market protection, large companies would not be willing to develop paediatric drugs. For smaller companies (SME’s) without blockbusters, incentives such as free scientific advice and waivers make an important difference.

Criticism of the regulation stating that pharmaceutical companies engage in paediatric research for indications which are rare among children to obtain additional market protection for the same drug used for adults is not shared by the researcher who was involved with the paediatric committee.

Not many pharmaceutical companies conduct Phase I research in the Netherlands. The strict Dutch interpretation of the European norm stating that research should bring significant and positive therapeutic benefit makes it very difficult to comply.

An important improvement could be realized if the effectiveness of current (off-label) medicines used by children were closely monitored and used in the registration procedure. Many drugs have been prescribed to children off-label for a long period of time and information about these practices is available. According to the regulation this does not suffice. Instead, the regulation requires that patients are enrolled in a formal study at an average cost of €10,000 per patient. Changing this obligation would greatly contribute to the registration of paediatric medicines.

Currently, a license for market entry is granted at a certain point in time. A question which then remains is whether and how the drug will fulfil its promise. If not, there should be a mechanism for price negotiations. However, this mechanism is not dealt with in the regulations because this is the mandate of MSs.

3.3 Effectiveness of the Orphan Regulation
The extent to which the two goals of the Orphan Regulation (see section 2.2.3) are achieved is provided below, as well as an overview of the regulatory hurdles and the areas in need of improvement. In addition, we also present the views of relevant stakeholders.

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3.3.1 Goal 1: Encourage the pharmaceutical and biotechnological industry to develop and market orphan drugs

This goal has been met. In 2006 the EC stated “the orphan legislation in the EU has far exceeded initial expectations; more than 450 applications for orphan designation have been submitted in the period between April 2000 and April 2005. Of those, more than 260 have been designated and 22 have gone on to receive a marketing authorisation.” Since then these numbers have steadily increased. Currently, 117 orphan medicines have received marketing authorisation. As stated in Chapter 2, the incentives for developers include incentives such as fee waivers for the regulatory procedures or 10 year market exclusivity. Furthermore, 1202 products have currently received an orphan designation. To receive orphan designation, developers may benefit from incentives such as protocol assistance that supports the development and authorisation of the products. The use of scientific advice/protocol assistance has increased the probability of approval. Sponsors have made use of these services: the uptake is extensive and has increased over time. For example, the number of requests for protocol assistance increased from five in 2001 to 35 in 2004, and over 80 procedures were completed during the first five years of the EU Orphan Regulation.

It seems that the Orphan Regulation has been a success, especially when we look at orphan drugs that can be considered a real breakthrough. An example is lenalidomide (Revlimid) a drug with considerable added therapeutic value for the treatment of multiple myeloma.

In addition, various orphan drugs are developed for diseases for which treatment already exists. For example, Bosentan (Tracleer) is prescribed for pulmonary arterial hypertension (PAH), but there are various other drugs prescribed for PAH as well. This contradicts the unmet medical need criterion. On the other hand there is always a need for alternative products in case of non-response, contra-indications or intolerance regarding the first product.

3.3.2 Goal 2: Create a Committee of Orphan Medicinal Products (COMP) within EMA

The Committee for Orphan Medicinal Products (COMP) was established and has – according to the EC “taken on an important role in stimulating the development of orphan medicinal products and in implementing the legislation. This legislation has been applied without any major difficulties, achieving outstanding results and public health benefits. The COMP, together with the Commission and in consultation with stakeholders and interested parties, has developed appropriate guidance to establish a sound EU process to designate orphan medicinal products eligible for incentives as provided by the legislation.”

The COMP, along with other tasks, is responsible for reviewing applications from companies seeking orphan medicinal product designation. The COMP makes use of an expert network to assist in the review of orphan designations. As a follow up for all designations, COMPs opinions are published every month on EMA’s website. By this time, all relevant documents should be finalized and forwarded to the Commission for the designation process. After the opinion on the designation is made, a public summary will be available on EMA’s website.

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3.3.3 **Regulatory hurdles and areas for improvement**

It remains important to plan strategies for rare diseases on the research and regulatory agenda in order to ensure that patients suffering from these diseases have access to timely and high-quality care.

With respect to research activities, funding and the scope of research should be identified on both the national and the Community level, to determine the state of the art with regard to the knowledge base and improve the coordination of research within the Community. It is important that MSs actively contribute to common diagnostic instruments, screening, European guidelines and medical care. Assessment reports are also important, in which therapeutic added value of orphan medicinal products is estimated. Such measures could contribute to faster price negotiations at the national level, which could reduce the delays for access to orphan drugs.73

3.3.4 **Experts’ opinion**

Interviews conducted as part of this study revealed that the regulation on orphan drugs is considered as a tremendous success by representatives of governmental agencies both at national and European level. However, it could turn into a victim of its own success. In the early days of the regulation, the COMP received about 5-6 applications per month. This has increased to about 30 per month. Applicants range from small companies and universities to pharmaceutical companies. Applications seem to be market-driven with a focus on a few orphan drugs. Developing orphan drugs, however, requires cutting edge science and often provides input for widely-used medicine. As a result, also big pharmaceutical companies are now involved. Still, it remains unclear how to stimulate the development of innovative products. During the designation phase, more attention should be paid to the innovative character of the medicine.

An important characteristic of the legislation is the fact that only the first applicant working on a specific molecule can receive market exclusivity, hampering the development of a number 2 and 3, while it is still important to develop initiatives in addition to the initial medicine. Legislators hoped this element would stimulate cooperation instead of competition between researchers. As this cooperation has not taken place, it may be time to evaluate this part of the regulation.

An important issue is the fact that once a drug has been registered, little further research takes place. The drug developed for cystic fibrosis, for example, focusses on only 8 to 9 possible mutations of the protein involved. Patients with other mutations still will get this medicine off-label prescribed by their physician. As a result, there is no incentive for the pharmaceutical company to research the effectiveness of the drug on other mutations.

The Orphan Regulation is sometimes used for registering low-cost magistral formulae74 to bring high-priced specialty drugs to the market if the costs are not justified by the registration requirements. It is also clear that due to the availability of magistral formulae there is no unmet medical need as is the case for other orphan drugs. This strategic use of the regulation should be evaluated to prevent turning well intended regulations into perverse incentives. An interviewee from the NHS stated: “The regulation dealing with orphan drugs focusses on rare and disabling diseases. It does well and is successful in stimulating research in this area. However, it also does

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lead to rather “unhealthy behaviour” by pharmaceutical companies”. The level to which this kind of rediscovery/ repurposing happens is not known.

The element of high prices paid for orphan drugs touches the very core of the Regulation itself: The regulation was introduced to induce companies to develop medicines, through a set of incentives, which under normal market conditions were not developed. Given the high prices of sometimes €200K-€400K per year, it is doubtful if these ‘normal market conditions’ still exist. Even without incentives, a company should be able to invest in research given the profits made, even for ultra rare diseases.

The high prices, along with the growing utilization, is increasing health care costs. The increasing utilization can be explained by situations in which medicines first intended to be used in a late stage of treatment are increasingly being used in an early stage of treatment. An example is Lenalidomide (Revlimid), which was initially developed as a third-phase drug, but is now being used as a first-phase drug including far more patients. Still the price is unchanged: €5.000 per patient per year. The same might be true for a similar new drug, developed by the same company: Pomalidomide, which is promoted as a third-phase drug, but probably will shift towards the first phase.

Meanwhile, initial orphan drugs are losing their commercial protection. Due to their high complexity, it remains to be seen if these drugs will be replaced by generic ones. If not, it can be concluded that orphan drugs have some kind of natural monopoly, diminishing the need for long periods with commercial protection.

The success of the Regulation combined with the relatively high prices for orphan drugs pose a threat to affordability and the sustainability of health care. Although some countries are rather successful in negotiating agreements with pharmaceutical companies, better results might be achieved at a European level.

### 3.4 Effectiveness of the Advanced Therapy Medicinal Products Regulation

The ATMP Regulation has two goals as described in section 2.3.3. Below we describe the extent to which the goals are achieved, the regulatory hurdles and the areas in need of improvement. We also present the views of relevant stakeholders. The case study of IMPACT, provided in Annex B, gives more details on the issues at stake.

#### 3.4.1 Goal 1: Ensure the free movement of advanced therapies within the Community, and the effective operation of the internal market in the biotechnology sector

The ATMP Regulation provides the tools to adopt specific requirements regarding the content of marketing authorisation applications, good manufacturing practices, good clinical practice, and the traceability of ATMPs. Later on, an amendment was made in terms of the content of marketing authorisation applications for ATMPs. Also, a revised Guideline on good manufacturing practice containing specific adaptions for ATMPs applies since 31 January 2013. The adoption of specific requirements regarding good clinical practice and traceability is still pending as additional experience was deemed necessary to better understand the type of adaptions required.\(^\text{75}\) In this sense, the ATMP Regulation provides a clear regulatory framework for the approval of these

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products in the EU. However, to date only five products have been granted marketing authorisation in the EU. The number of ATMPs that are applied under the so-called hospital exemption is not known, but there are indications that this exemption is not extensively used in the EU.

3.4.2 Goal 2: Distribution and use of products must safeguard public health

There are no indications indicating that good quality, efficacy and safety regarding authorised products are not safeguarded by the requirements of the ATMP Regulation. However, it needs to be considered if the Regulation achieves a high level of public health protection, as it is undermined by the marketing of products exhibiting the characteristics of ATMPs, but which are marketed outside the framework of the ATMP Regulation. Also, with regard to the hospital exemption rule, there is no overview of what is going on in each individual MS.

3.4.3 Goal 3: To create within the Agency, a Committee for Advanced Therapies

The implementation of the ATMP Regulation inherently formed the basis of the CAT. Since 2009, the CAT has assessed the quality, safety and efficacy of ATMPs applications and discusses developments in the field. Currently, the CAT consists of a multidisciplinary scientific expert committee, representing all EU MSs and Norway and Iceland, as well as patient and medical associations. Also, regulatory expertise is included in the CAT.

3.4.4 Regulatory hurdles and areas for improvement

In 2014, the EC published a report on the experiences with the first five years of the Regulation. In addition, a public consultation took place that was reported. It shows a number of areas in which the legislation could be improved, as described below.

The current marketing authorisation procedure is considered complex, especially for SMEs and non-for-profit organisations. There is a need to improve the evaluation procedure for ATMPs within EMA. If this procedure is revised to be less complex, it would provide clarity for both the applicant and the evaluator. In addition, developers not only need to comply with the ATMP Regulation but also with national legislation, as not all phases of the ATMP manufacturing process fall within the scope of the EU Regulation (e.g., donation, procurement and testing of the human tissue or cells), leading to an extensive administrative burden for the developers.

The first years of the Regulation show that there are some issues to be solved, including the complexity of product classification. Good measures should be developed to avoid disparities in the classification of ATMPs. Also, the scope of the Regulation could be clarified when the definitions of ATMPs were re-defined. In order to streamline applications for hospital exemption, those conditions...
should also be clarified. The role of data obtained in the context of marketing authorisation procedures could be sharpened. The requirements for the authorisation of ATMPs should be revised with a view to ensure that applicable requirements are proportionate and well adapted to the specific characteristics. Another point for improvement is streamlining the marketing authorisation procedures, so that the certification procedure is extended and the link between the certification and the marketing authorisation procedure is clarified. Academic or non-for-profit developers could benefit from early contacts in the development process with authorities. This could be the result of the application of the fee reduction for scientific advice. Finally, to reduce the financial impact of post marketing obligations, considering fee incentives is recommended.81

In addition to process improvements, the decision-making itself may be more effective. Currently, the CAT consists of representatives from every MS which – according to some stakeholders – does not reflect the scientific excellence that is needed to assess ATMP applications, sometimes resulting in decisions coloured by personal opinions; the process is often perceived as a social process instead of a scientific assessment. Summarizing, there is a need to improve the evaluation procedure for ATMPs and the availability of expert knowledge.

3.4.5 Experts’ opinion

At present, the CAT consists of members from every MS. These may change frequently and not every member is an expert from the field of ATMP. The result can be that decisions are influenced by personal opinions of non-experts. Decision-making should be based on expert knowledge rather than one vote for every MS.

In addition, expert panels could be organized for specific registration-related issues. For example, the process could profit from a panel in the area of research methodology. Research methods differ in terms of applicability, but the members of the CAT seem unaware of this. An expert panel could help resolve this issue. In addition, diminishing the administrative burden and shortening procedures could help to facilitate the registration process.

With respect to the effectiveness of the incentives, it is noted by a researcher in the area of ATMPs, that the impact differs depending on the characteristics of the pharmaceutical company. For a publicly owned firm, for example, market protection as a financial stimulus is more important than for a researcher working in a clinical setting. For these individuals, communication with EMA, e.g. as part of free scientific advice, is considered as very important during the registration process of an ATMP.

The norm of conducting a Randomized Controlled Trial (RCT) for ATMP is applied a very stringent manner. An example: The University Medical Center in Sweden that was first in applying cartilage treatments had to stop these activities because they were financially unable to conduct a RCT and as a result could not qualify. This outcome seems unfortunate, since they were offering the only treatment with documented and positive results over a period of 20 years.

Hospital exemptions can be considered as a pragmatic instrument to prevent the high costs that are incurred for registration by EMA. In Germany, hospital exemptions are widely used. One hospital obtains a hospital exemption for an ATMP. Through contracts and by establishing legal entities with other hospitals, these ATMPs are made available to other hospitals as well.

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In addition to the growing use of hospital exemptions in some countries, researchers are increasingly facing an intellectual dilemma in response to the stringent application of complex and demanding rules: In Asia regulators focus primarily on safety of the new ATMP. When minimal safety norms are met, the product can be used in the market for further research. As a result, the gap between Europe and Asia is growing. In Europe the costs of conducting trials are extremely high, leading to high prices. Physicians in turn are hesitant to apply these ATMPs in their treatment and health insurers are reluctant to pay the costs. These factors lead to a vicious circle which is hampering instead of stimulating the development of ATMPs.
4 Reflections from other jurisdictions

4.1 Paediatric Regulation

Desk research and interviews with key international experts have been conducted to derive lessons with respect to the Paediatric Regulation from different jurisdictions, including South Korea, Canada and the United States.

4.1.1 South Korea

Very few legislative and regulatory initiatives regarding paediatric medicines have been undertaken in countries other than the USA and Europe. This is also the case in South Korea, where no specific legislation and regulation exists regarding patent extensions for paediatric medicines. Orphan drugs may include drugs to be used in paediatrics.

4.1.2 Canada

In Canada a 6 month extension for data protection is granted to innovator companies providing evidence to support a paediatric label indication. The Paediatric Data Protection in Canada is organized as follows: An additional six-month extension to the eight-year term of data protection will be applied if an innovator includes, in its new drug submission, or any supplement to that new drug submission filed within the first five years of the eight-year data protection period, results of paediatric clinical trials. These should be designed and conducted with the purpose of increasing knowledge about the use of the drug in paediatric populations and will lead to a health benefit for children. To qualify, the drug must be an innovative drug and qualify for the eight-year term. The extension of data protection for submitting the results of paediatric studies is to encourage sponsors to submit trial data pertaining to the use of the drug in paediatric populations. Therefore, it must be clear that the goal of such studies was to increase knowledge about the use of the drug in paediatric populations that will assist health professionals, parents, caregivers and patients in making informed choices about drug therapy. The additional knowledge of the use of these drugs for these populations must be publicly available through additions to the labelling and/or Product Monograph for the drug. Where the clinical studies demonstrate that the drug should not be used in paediatric populations, the addition of contraindications and/or other warning statements in the labelling of the drug may be sufficient to warrant granting of the six-month extension. This goal of increasing knowledge of the use of the drug in one or more of the paediatric populations should be reflected in the study hypothesis, objectives, design and conduct of the clinical trial.

4.1.3 United States

The United States historically has a long history in promoting paediatric drug development.

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Table 4.1 gives an overview of the major milestones of paediatric legislation in the US.88

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<tr>
<th>Year</th>
<th>Milestone</th>
<th>Details</th>
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<tr>
<td>1994</td>
<td>Paediatric Labelling Rule</td>
<td>Drug manufacturers were required to survey existing data and determine whether those data are sufficient to support additional paediatric use information in the drug's labelling.</td>
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<tr>
<td>1997</td>
<td>Paediatric Rule</td>
<td>This required a manufacturer to submit a supplemental new drug application to the FDA seeking approval of the label change.</td>
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<tr>
<td>2002</td>
<td>BPCA: Best Pharmaceutical For Children Act</td>
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<tr>
<td>2003</td>
<td>PREA: Paediatric Research Equity Act</td>
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<tr>
<td>2007</td>
<td>FDAAA: Food and Drug Administration Amendments Act</td>
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The first initiative took place in 1994 when the Paediatric Labelling Rule was issued. This required drug manufacturers to survey existing data and to determine whether those data are sufficient to support additional paediatric use information in the drug's labelling. Under the Paediatric Labelling Rule, if a manufacturer determines that existing data permit modification of the label's paediatric use information, the manufacturer must submit a supplemental new drug application to the FDA seeking approval of the label change. Since the approach under the Paediatric Labelling Rule was entirely voluntary, and did not substantially increase the number of products with adequate paediatric labelling, the FDA introduced in 1998 the Paediatric Rule.

The rule was designed to ensure that new drugs and biological products that are likely to be commonly used in children, or that represent a meaningful therapeutic benefit over existing treatments for children, contain adequate paediatric labelling for the approved indication at the time of, or soon after, approval. The rule would require a manufacturer of a new drug to submit, before approval, safety and effectiveness information in relevant paediatric age groups for the claimed indications. The submission of information could be deferred, e.g., if paediatric studies should not begin until information on adults had been collected, or in case the collection and filing of paediatric data would delay the availability of a product that provides a significant therapeutic advantage in adults. The requirement would be waived for some or all paediatric age groups if, e.g., the product did not represent a meaningful therapeutic benefit over existing treatment or the product would likely be unsafe or ineffective in paediatric patients.

Also in 1997, the Food and Drug Administration Modernization Act (FDAMA) introduced a process in which the FDA would develop a list of drugs for which additional paediatric information might be beneficial, agree on necessary studies, and issue to sponsors a Written Request for paediatric studies. The Written Request includes a timeframe for completing such studies. In addition, the FDAMA provided an incentive for pharmaceutical companies to study products which would yield a health benefit in the paediatric population. If companies submitted studies responding to a Written Request, six additional months of marketing exclusivity were granted. Many drugs have received paediatric labelling under this provision, such that the FDAMA could be considered as the major legislative initiative that progressed paediatric drug development in the US.

In 2001, the FDA's Report to Congress identified some drawbacks, for example, that the incentive legislation was only applicable to some drugs. These drawbacks were partially addressed by the Best Pharmaceuticals for Children Act (BPCA) in 2002. The BPCA renewed the exclusivity incentives, created a process for on- and off-patent drugs involving government contracts for paediatric studies, and mandated public disclosure of study results. In 2003, the Paediatric Research Equity Act (PREA) was enacted, putting into legislation most components of the

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Paediatric Rule. It required paediatric assessment for certain applications unless waived or deferred and a paediatric plan that outlines the paediatric assessment (including timelines) and addressed development of an age-appropriate formulation. In summary, there are two separate legislations for paediatric drug development in the US: the PREA defining the requirements and the BPCA defining the incentives. The PREA covers drugs and biologics and the studies are mandatory (only for indications under review, exempting orphan indications), whereas the BPCA covers only drugs and the studies are voluntary, relate to the entire moiety, and might expand indications (including orphan indications). PREA and BPCA request paediatric studies to be labelled and paediatric safety data to be presented publicly to an advisory committee one year after study conduct. Both acts are clearly designed to encourage more paediatric research and more development of paediatric medicines. In 2007, within the scope of the Food and Drug Administration Amendments Act (FDAAA), the PREA and the BPCA were amended and re-authorised. The reauthorisation extended the BPCA incentive and the PREA authority until October 2012 (Table 1). In addition, the FDAAA introduced the Paediatric Review Committee (PeRC). The PeRC includes employees of the FDA with expertise in paediatrics, clinical pharmacology, statistics, chemistry, legal issues, paediatric ethics, and appropriate expertise pertaining to the product under review as well as other designated individuals. The PeRC provides the framework for the preparation of consultation on and general review of paediatric information in paediatric plans, assessments, and paediatric studies to help ensure quality and consistency. The PeRC reviews all WRs, all deferrals and waivers, and submitted studies in response to a Written Response. 89, 90, 91

An expert interviewed for this study commented very positively with respect to the paediatric legislation and its effects for new medicines. As of August 2015, about 500 medicines now carry specific paediatric labels which grant these medicines a six months patent extension. However, the respondent warns that the success comes with a cost. The work on the paediatric programme is very labour intensive and poses a high administrative burden for the FDA.

Statistics published by the FDA show the success of these regulations. The Paediatric Exclusivity Statistics shows that by the end of May 2015 the FDA received 884 Paediatric Study Requests and issued 470 Written Requests. The FDA granted paediatric exclusivity for 211 drugs, as of May 2015. Table 4.2 gives a breakdown of all completed paediatric studies (469) over the period between September 27, 2007 and November 18, 2013.92

<table>
<thead>
<tr>
<th>Type of Study</th>
<th>BPCA</th>
<th>BPCA + PREA</th>
<th>PREA</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy/Safety</td>
<td>45</td>
<td>31</td>
<td>201</td>
<td>277</td>
</tr>
<tr>
<td>PK/Safety</td>
<td>9</td>
<td>40</td>
<td>20</td>
<td>69</td>
</tr>
<tr>
<td>PK/PD</td>
<td>14</td>
<td>8</td>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td>Safety</td>
<td>6</td>
<td>4</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>10</td>
<td>45</td>
<td>57</td>
</tr>
<tr>
<td>Total</td>
<td>76</td>
<td>93</td>
<td>300</td>
<td>469</td>
</tr>
</tbody>
</table>

An important contrast between the framework in the EU and the US is the timing of the paediatric development plan. The European Paediatric Investigations Plans (PIPs) should be agreed at the end of Phase I, while the American Paediatric Study Plans (PSPs) should be agreed at the end of Phase II. The theoretical advantages for early engagement are often outweighed by the fact that studies included in PIPs are deferred for considerable periods. According to Turner 2014, global development would benefit from a harmonised approach across the two jurisdictions. Even if it brings higher requirements to industry, the Paediatric Regulation retains the principle of rewards (an extra 6 months of patent protection, i.e. extension of the duration of its Supplementary Protection Certificate, for unauthorised and/or patented medicines and an extra two years of market exclusivity for orphan medicinal products. The Paediatric Regulation has also established a new type of marketing authorisation (not foresen by the US legislation), called the Paediatric Use Marketing Authorisation (PUMA), and intended to stimulate the development of off-patent products for use in the paediatric population. Most of these compounds are widely used daily in children of all age groups and mostly not adequately tested in this population. PUMA guarantees 10 (8 + 2) years data protection.93

According to the interviewee, identifying “equivalent” incentives programs across EU and US regulations is not straightforward. The differences in incentive programs are largely due to clear differences in statutes and regulations that govern paediatric drug development between EU and the US. Many of the paediatric EU incentives are not directly comparable to paediatric programs or incentives in the US. Moreover, the PREA requires drug companies to study their products in children under certain circumstances. When paediatric studies are required, they must be conducted with the same drug and for the same use for which they were approved in adults. Thus, although PREA has led to a substantial increase in studies of drugs and biological products in children, it is not considered an incentive programme.

The interviewee listed three important incentive programs applicable to paediatric drug development in the US:

- **Best Pharmaceuticals for Children Act (BPCA)** – This law, enacted in the US 2002, provides an incentive for drug companies to conduct FDA-requested paediatric studies by granting an additional six months of marketing exclusivity.
- **Orphan Drug Act** – The law, enacted in 1983, provides financial incentives to develop drugs intended to treat rare diseases or conditions (i.e., affecting less than 200,000 persons in the US). This program is directly intended to incentivize paediatric product development but many of the products approved under this program are for rare diseases or conditions that also affect paediatric patients.
- **Hatch/Waxman Amendments** – The amendment to the Federal Food, Drug, and Cosmetic Act, enacted in 1984, provides 5-year marketing exclusivity following approval of a new chemical entity product and 3-year marketing exclusivity for an application containing new clinical investigations. This incentive is also not specific to paediatric drug development; these exclusivity provisions are applicable to a supplements or new drug applications.

Mandates for the creation of paediatric research networks are not included in US incentive programs. FDA recognizes the importance of paediatric research networks and is actively engaged in efforts with interested stakeholders to develop research networks to increase the efficiency of paediatric product development. For example, recently, FDA, in collaboration with the Critical Path Institute has begun discussions with interested stakeholders on the creation of an international neonatal research consortium.

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A cohort study by Li et al (2007) showed that there can be a significant economic return from the US incentives for paediatric drug development. They evaluated nine programmes that were submitted for six months of additional exclusivity as a result of studies in children, ‘paediatric exclusivity’, reflecting a range of therapeutic areas between 2002 and 2004 were selected for detailed economic evaluation. Among the 9 programmes net economic return of the 6 months of paediatric exclusivity ranged from $−8.9 million to $507.9 million and the net return to cost ratio ranged from−0.68 to 73.63. The authors concluded that the economic return for paediatric exclusivity is variable. As an incentive to complete much-needed clinical trials in children, paediatric exclusivity can generate lucrative returns or produce more modest returns on investment.94

### 4.2 Orphan Regulation

Table 4.3 makes a comparison of some distinct aspects of the regulation of orphan medicines in South Korea, the EU and the US.95

<table>
<thead>
<tr>
<th>Items</th>
<th>United States</th>
<th>EU</th>
<th>Australia</th>
<th>Japan</th>
<th>South Korea</th>
<th>Taiwan</th>
<th>China</th>
</tr>
</thead>
<tbody>
<tr>
<td>Criterion for prevalence of rare diseases (&lt;‰)</td>
<td>0.75</td>
<td>0.5</td>
<td>0.11</td>
<td>0.4</td>
<td>0.4</td>
<td>0.1</td>
<td>prevalent &lt; 1/500,000, or neonatal morbidity &lt; 1/10,000**</td>
</tr>
<tr>
<td>Affected population</td>
<td>25–30 million</td>
<td>27–36 million</td>
<td>1.2 million</td>
<td>N</td>
<td>N</td>
<td>more than 2,000</td>
<td>16.8 million**</td>
</tr>
<tr>
<td>Financial subsidies</td>
<td>government grants for clinical research</td>
<td>framework programs plus national measures</td>
<td>N</td>
<td>Governmental grants for clinical and non-clinical research</td>
<td>N</td>
<td>Governmental grants and awards from the central competent authority</td>
<td>NSFC research grants</td>
</tr>
<tr>
<td>Market exclusivity (years)</td>
<td>7</td>
<td>10</td>
<td>5 (similar to other drugs)</td>
<td>10</td>
<td>6</td>
<td>10</td>
<td>N</td>
</tr>
<tr>
<td>Tax credits</td>
<td>up to 50% for clinical</td>
<td>managed by MSs</td>
<td>N</td>
<td>15% tax credits, up</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

### How well does regulation work?

<table>
<thead>
<tr>
<th>Items</th>
<th>United States</th>
<th>EU</th>
<th>Australia</th>
<th>Japan</th>
<th>South Korea</th>
<th>Taiwan</th>
<th>China</th>
</tr>
</thead>
<tbody>
<tr>
<td>expenses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>to 14% corporate tax reduction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fast track approval</td>
<td>Yes</td>
<td>Yes - centralized approval</td>
<td>Yes</td>
<td>Yes</td>
<td>N</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Protocol assistance</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>N</td>
<td>Yes</td>
<td>N</td>
</tr>
<tr>
<td>Regulatory fee waivers</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Pharmaceutical pricing</td>
<td>market-driven</td>
<td>depending on MSs</td>
<td>same as general drugs</td>
<td>price negotiation</td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Medical expense reimbursement</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>for 56 diseases</td>
<td>Yes</td>
<td>70% for patients, up to 100% for low-income families</td>
<td>N</td>
</tr>
</tbody>
</table>

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**4.2.1 South Korea**

In South Korea, rare diseases are defined as diseases that affect fewer than 20,000 people or diseases for which an appropriate treatment or alternative medicine has yet to be developed. The Orphan Drugs Guideline was established in 2003 and stipulates exclusive marketing rights for 6 years to encourage the research and development of orphan drugs. It was revised in 2013 according to the interviewees. Support measures include medical expense reimbursement and nationally funded research programs along with support from the Ministry of Health and Welfare and the Korean Centers for Disease Control and Prevention as well as a discount for registration (2000 USD in stead of 4000 USD). Since the introduction of the Orphan Drugs guideline there has been an increase in the number of orphan drugs in South Korea.

**4.2.2 Canada**

According to Health Canada, the definition of rare diseases is conditions affecting less than 5 in 10,000 persons. They have concluded that new rules and approaches to the development, evaluation and approval of orphan medicines are needed to address the fact that the small size of the patient population makes it scientifically difficult and most often commercially impractical for drug companies to develop and market orphan drugs. Health Canada is therefore developing a modern framework for the designation, authorisation and monitoring of orphan medicines that will provide a significant benefit to Canadians with rare diseases and spur research and innovation in

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Canada. A key focus of this new approach will be on international information-sharing and collaboration for the development and regulation of orphan drugs. Enabling Canadian scientists and regulators to participate with trusted global counterparts will make better use of scarce resources and benefit Canadian patients. The new framework will maintain evidence requirements based on clinical trials and will be supported by greater information sharing amongst international partners who are committed to pooling scarce resources for maximum benefit. Once authorised, drugs will continue to be closely monitored for effectiveness and safety while in use.97

4.2.3 United States

The FDA Office for orphan products development provides incentives for sponsors to develop products for rare diseases. The following are the three most important incentives for orphan drug development:

- Seven years of market exclusivity available for certain orphan-designated and approved drugs and biologics;
- FDA funds clinical trials of products (e.g., drugs, devices, biologics, medical foods) for rare diseases with an annual budget of ~$15M/year;
- Sponsors of orphan-designated drugs and biologics are eligible to receive tax credits of up to 50% of the costs of qualified clinical testing.

The program has successfully enabled the development and marketing of more than 400 drugs and biologic products for rare diseases since 1983. In contrast, fewer than 10 such products supported by industry came to market between 1973 and 1983. The Orphan Grants Program has been used to bring more than 45 products to marketing approval. The Humanitarian Use Device Program has been the first step in approval of more than 50 Humanitarian Device Exemption approvals. The Orphan Drug Designation program provides orphan status to drugs and biologics which are defined as those intended for the safe and effective treatment, diagnosis or prevention of rare diseases/disorders that affect fewer than 200,000 people in the US, or that affect more than 200,000 persons but are not expected to recover the costs of developing and marketing a treatment drug.98

Cohen cited differences in licensing and reimbursement of orphan medicines between the EU and the US as presented in Table 4.4.99

<table>
<thead>
<tr>
<th>Total number of US approvals</th>
<th>151</th>
<th>Total number of European approvals</th>
<th>140</th>
</tr>
</thead>
<tbody>
<tr>
<td>US payer coverage</td>
<td>97%</td>
<td>Average European payer coverage</td>
<td>94%</td>
</tr>
<tr>
<td>Average percentage of drugs with conditions of authorisation, quantity limits, step therapy</td>
<td>84%</td>
<td>Average percentage of drugs with conditions of reimbursement: restrictions, coverage with evidence development</td>
<td>37%</td>
</tr>
<tr>
<td>Co-insurance for physician-administered drugs</td>
<td>20%</td>
<td>Co-insurance for physician-administered drugs</td>
<td>Between $2-$15 per prescription</td>
</tr>
</tbody>
</table>

In the period 1983-2013 more orphan medicines were licensed in the US (151) than in the EU (140). The number of orphan medicines licensed first in the US was 76 and in the EU 64. According to Cohen, more orphan medicines are reimbursed in the US than in the EU, but co-payments are higher in the US. In general, differences between the US and the EU can be summarized as follows:

- Since enactment of the Orphan Drug Act in 1983, 7% more orphan drugs approved in the US than in the EU.
- Since 1983, 17% more orphan drugs approved first in US than approved first in the EU.
- More denials of orphan drug coverage in the EU than in the US.
- Prices of orphan drugs are approximately 15% higher in the US than the EU.

According to the FDA, the facts show that the orphan programme has been very successful in the US. To grant an orphan designation during the development phase and additional market exclusivity is very helpful. For the near future FDA sees a mixture of two categories of orphan medicines coming to the market. On the one hand these are 'true orphans' for (very) rare diseases. On the other hand, thanks to the genetic research, there will be much more targeted therapies directed at patients with very specific mutations only, like in lung cancer, or at patients who are resistant to the standard therapy. The respondent doesn't consider this as 'salami slicing' of indications, but as true orphan indications. The respondent neither acknowledges the problem of converting compounded pharmacy products into very expensive registered orphan medicines. On the contrary, the respondent points out that in the US there have been incidents with compounded products. In 2012 there was an outbreak of severe fungal meningitis which has led to the death of about 50 patients. It was caused by epidural steroid injections, prepared and nationally distributed by a compounding pharmacy in Massachusetts. According to the respondent, overseeing compounding pharmacies is not the jurisdiction of the FDA, but of the Regional Board of Pharmacy.

### Advanced Therapy Medicinal Products Regulation

4.3

Until now, five Advanced Therapies Medicinal Products (ATMPs) have been licensed by EMA:

- ChondroCelect (tissue engineered product) licensed on 4 October 2009;
- MACI (tissue engineered product) licensed on 27 June 2013, suspended on 17 December 2014;
- Provenge (somatic cell therapy product) licensed on 6 September 2013;
- Glybera (gene therapy product) licensed on 25 October 2014;
- Holoclár (tissue engineered product) licensed on 17 February 2015.

The availability of advanced therapies is reportedly much greater in countries with less restrictive regulations than in the EU, albeit that the efficacy and safety of the treatments offered may not have been proven. For several different reasons it is worthwhile to explore whether there are lessons to be learned in this respect from South Korea, Canada and the United States.
4.3.1 South Korea

East Asia is witnessing a remarkable growth in advanced therapies. South Korea is perceived as a country with a strong advanced therapy sector in spite of the fact that advanced therapies are subject to substantial regulatory oversight.

In South Korea, different organisations are involved in the regulatory process and pricing and reimbursement of drugs. These organisations include the National Evidence-based healthcare Collaborating Agency (NECA), the Ministry of Food and Drug Safety (formerly known as Korean Food and Drug Administration), Health Insurance Review and Assessment Services (HIRA), National Health Insurance Corporation and the Ministry of Health and Welfare. NECA is the health technology assessment (HTA) agency that was established in 2008 to provide authentic and quality information about medical devices, medicines, and health technology through objective analysis of evidence through comparative assessment of health technologies. NECA was established by the Korean government as an independent agency collaborating with the Korean Ministry of Health and Welfare.100 It consists of two bodies: a research body (focuses on Health Technology Assessment, Collaboration Research, and RAPID) and Center for New Health Technology (supporting the Committee for New Health Technology Assessment). The agency serves a population of 50 million inhabitants, and has approximately 120 staff.101

The Korean government is investing substantial amounts of money in stem cell research and product development. Overall, six different ministries were investing 100 billion won (=83 million euro) in stem-cell research in 2012.102

According to Ancans 2012, during the last decade Mesenchymal Stem Cell (MSC)-based therapy clinical trials have been conducted for at least a dozen of different medical conditions.103 The results of clinical studies have led to the conclusion that MSC applications have been safe and feasible. However, the efficacy often could not be convincingly demonstrated as the therapies advanced along with the clinical development. This is also illustrated by the absence of MSC-based products in the European market.

Currently, 13 cell therapy products are approved in Korea. One of them (Queencell) is a minimally manipulated product and the other 12 products would be ATMPs according to the EU definition. South Korea is leading with four MSC products registered and the first authorisation granted in 2011. These registrations might be linked to the procedure of a conditional marketing approval in the regulatory framework of South Korea that allows commercial sale after Phase II trials for orphan disease products on the condition that Phase III trial results to be delivered afterwards. There is also a procedure of conditional marketing authorisation in the EU prescribed by the Regulation (EC) N° 507/2006, but differences exist in the regulatory systems. With the approval from the Korean FDA in January 2012, Cartistem has become the world’s first allogeneic, off-the-shelf MSC-based product. The product contains the umbilical cord blood (UCB)-derived MSCs and it is indicated for the treatment of traumatic and degenerative osteoarthritis. In 2011 the Korean company FCB PharmiCell received Korean FDA approval for commercial sale of HeartiCellgram indicated for post-acute myocardial infarction treatment. It is an autologous bone marrow-derived MSC therapy product. The regulatory approval for HeartiCellgram was granted after 6 years of clinical trials. The company has announced that the patients displayed a 6% improvement in the left ventricular

ejection fraction 6 months after one dose of HeartiCellgram. However, the company has not published the results in a peer-reviewed journal, according to Ancans.\textsuperscript{104} The third MSC product was also approved in 2012: Cupistem.\textsuperscript{105} This is an autologous adipose tissue-derived mesenchymal stromal cell-based product for anal fistula (Crohn’s disease). The fourth MSC product that was granted marketing authorisation concerns a product for amyotrophic lateral sclerosis or ALS (Lou Gehrig’s disease). The two products in Crohn’s Disease and ALS received conditional approval from the KFDA, while the other two went through regular approval process after Phase III trials.

Concerns are expressed about the political trend towards further simplification of the authorisation process for cell therapeutics in South Korea. An employee of a cell therapy centre warned, for example, against a legislative proposal pending in the National Assembly of Korea that proposes that stem cell therapeutics targeting rare diseases should be approved solely based on the Phase I and investigative clinical trials.\textsuperscript{106} Another proposal suggested that stem cell therapeutics from autologous donors should be exempted from Phase III clinical trials in order to increase the efficiency of industrializing stem cell therapeutics. However, under such regulatory systems, governmental agencies would be forced to stamp the approval of documents without having sufficient opportunity to verify the therapeutic effects (efficacy) or long-term toxicities of a treatment. Insufficient inspection of new cell therapies for improving efficiencies of industrial processes can also pose risks. Interestingly, the industrial sectors in Korea that deal with cell therapeutics are generally opposed to such legislative proposals. The companies are concerned about the possible decline of the credibility of their cell therapy products in international and domestic markets.

According to Oh, further industrial competitiveness for cell therapeutics in Korea should be sought from technological advances and proven therapeutic efficacy of the products rather than from simplification of regulatory systems. Loosening of the regulatory system would likely impede industrial benefits as well as public health security rather than augmenting the efficiency of industrialization of cell therapy products of Korean companies. The author pleads that “efficacy” is much more important than “efficiency” with regard to stem cell therapeutics.\textsuperscript{107}

\subsection*{4.3.2 Canada}

According to Ancans 2012, it seems that in Canada a similar regulatory decision regarding MSCs as in South Korea has been adopted for Prochymal which consists of allogeneic MSCs. The company was granted an authorisation for the treatment of acute graft-vs-host disease (GvHD) in children under Health Canada’s Notice of Compliance with conditions (NOC/c) in May 2012. This is an authorisation to market on condition that the manufacturer undertakes additional studies to verify the clinical benefit. Such a regulatory pathway provides access to treatments for unmet medical conditions and that have demonstrated that the benefits outweigh the risks in the clinical trials. Overall this may represent a regulatory trend to consider evaluation procedures that could address medical needs more efficiently. Adaptive licensing, e.g., conditional approvals, would be based on stepwise learning in circumstances of acknowledged uncertainty, with iterative phases of data gathering and regulatory re-evaluation.\textsuperscript{108}

\begin{thebibliography}{100}
\end{thebibliography}
4.3.3 United States

The United States is the most important market for pharmaceuticals, with more than 50% of the world market. Many established manufacturers and also many new biotechnology firms are based in the United States.

The Center for Biologics Evaluation and Research (CBER) of the Food and Drug Administration regulates cellular therapy products, human gene therapy products, and certain devices related to cell and gene therapy. CBER uses both the Public Health Service Act and the Federal Food Drug and Cosmetic Act as enabling statutes for oversight. Although some cellular therapy products (Provenge, Carticel) have been approved, CBER has not yet approved any human gene therapy product for sale. However, the amount of cellular and gene therapy-related research and development occurring in the United States continues to grow at a fast rate. CBER has received many requests from medical researchers and manufacturers to study cellular and gene therapies and to develop cellular and gene therapy products. In addition to regulatory oversight of clinical studies, CBER provides proactive scientific and regulatory advice to medical researchers and manufacturers in the area of novel product development.\(^{109}\)

From a US perspective, a report from the Pharmaceutical Research and Manufacturers of America (PhRMA, 2013), which lists all US industrial sponsored biologics in clinical trials, identified 69 cell therapies in clinical trials or under review by the US Food and Drug Administration (FDA). Fifteen were in Phase III clinical trials, of which six were autologous.\(^{110}\)

The first tissue engineered product was licensed by the FDA in 2012. It was Gintuit for oral soft tissue regeneration to treat oral mucogingival conditions in adults. Until mid 2014 in the US. Three autologous cell therapies have been approved. Carticel (autologous chondrocytes for cartilage repair) was the first approved in 1997. An autologous treatment for prostate cancer (Provenge) was approved in 2010. An autologous fibroblast product for filling wrinkles (Fibrocell) was approved in 2012.\(^{111}\) In total, ten cell therapy products and related devices are approved. Until now, gene therapies have not been approved in the US. From the interview, it appears that there is still some hesitation with regards to gene therapy due to safety concerns. Several patients, most of them children, have died in early experiments caused by immuno-response reactions, infections and leukaemia.

According to Rehmann, the European regulation is similar to the regulatory framework set up in the US under the authority of the FDA, although in the EU it is much more standardized, systematic and comprehensive.\(^{112}\) One point of interest will be to review whether this standardised strategy is successful in Europe, given that it is very much the type of approach the FDA has decided is not easily applied to products such as ATMPs. The regulatory approach in Europe is (or has the potential to be) in marked contrast to the situation in the US. The FDA has very much adopted a case-by-case analysis of ATMPs with little product “class” guidance to instruct compliance. The relevant department of the FDA that deals with ATMPs is the CBER and, within this section, the Office of Cellular, Tissue and Gene Therapies. This office will typically arrange a pre-IND (investigational new drug) meeting with prospective applicants and agree a specific protocol, which will eventually lead to a biologics license application for approval of the product. Although this


sounds straightforward, recent history has demonstrated that the data required in order to complete a BLA to the requisite standard could cause problems for ATMPs. Contained within the BLA is a section that requires the applicant to demonstrate that the production process for the ATMP is sufficiently controlled as regards characterization and quality. Clearly ATMPs that involve modifying a patient’s own cells have a variable content that makes compliance with the above FDA requirement difficult. Most notably, for the prostate cancer vaccine product Provenge (sipuleucel-T) complying with the requirement took some time.\textsuperscript{113}

According to Hourd, comparing the regulatory landscape in Europe and the US, there are several disconnects in expectations between the FDA and the EMA. The requirements for Good Manufacturing Practices (GMP) compliance are not always interchangeable, with subtle differences in the sterile processing, documentation and quality control requirements. Disparities exist in the control of starting materials, sterility testing and the environmental monitoring of GMP suites, in particular the terminology and specifications for allowable levels of particulates and the measurement of microbial contamination. In terms of clinical trial regulation, there are differences between the clinical trial authorisation procedure in the EU and the Investigational New Drug application in the US. In contrast to the EU, GMP facilities for manufacturing of Phase I/II and Phase II trials in US are not subject to inspection. A manufacturing authorisation is required in the EU for the manufacture of investigational medicinal products. Under the manufacturing authorisation, each batch of a medicinal product must be released by a Qualified Person who must assess release criteria and adherence to GMP regulations and guidelines. In the U.S, there is no such requirement. In fact, guidance provided by the FDA for the manufacture of some drugs and biologics for Phase I trials provides a more graded approach to GMP in which manufacturers may be exempt from many of the requirements in CFR Part 211 of the regulation.\textsuperscript{114}

Freeman et al (2012) argued that the primary reason why the cell therapy industry in the US found itself in the midst of a financial funding crisis was due to unrestrained over-regulation by the FDA, rather than any lack of viability of the technologies.\textsuperscript{115} They mention that many medical organisations in the US have noted that the FDA was only granted authority by the US Congress to regulate allogeneic tissue transplants in order to control communicable disease transmission. However, the FDA had no authority to regulate human cells of any type like mass produced prescription drugs. The authors cite the objections of the American Society of Clinical Oncology (ASCO):

- “ASCO objects in the strongest terms to FDA’s proposed regulation of stem cell transplants. This misguided proposal is unnecessary... and exceeds FDA’s legal authority”.
- “…stem cell transplants are medical procedures. Their use is the practice of medicine, not the manufacturing of a drug as FDA asserts”.
- “A striking aspect of FDA’s proposal to regulate stem cell procedures is the virtual absence of any justification for the initiative”.
- “The FDA should not regulate stem cell procedures undertaken within an institution... or in any other setting where the cells are procured from a donor for a preselected recipient under the direction of physicians caring for these patients…. The proposed approach is a threat to good medicine and should not be adopted.” \textsuperscript{116}

\textsuperscript{114} Hourd, P., Chandra, A., Medcalf et al. Regulatory challenges for the manufacture and scale-out of autologous cell therapies, StemBook, ed. The Stem Cell Research Community, StemBook, doi/10.3824/stembook.1.96.1. Published June 30, 2014.
The interviewee from the FDA confirmed that many stem cell transplantations are taking place in hospitals in the US nowadays. However, as this is very difficult to do, these therapies are not regulated by the FDA. The respondent considers ATMPs, especially cell therapies and tissue engineered products, as very important for the therapeutic armamentarium in the near future. Some of these therapies are now already applied unlicensed. From a regulatory perspective, however, devising a controlled strategy is problematic, especially with regards to the consistency of the manufacturing process.
5 Assessing the costs of regulation for the Netherlands

5.1 Introduction

In the previous Chapters, we focused on the effectiveness of the regulations under study. In this Chapter we focus on the costs of the regulations for the society. This is on the one hand related to the actual public expenditures on orphan drugs, paediatric medicines and ATMPs, and on the other hand related to the “societal costs” of the incentives included in the regulations to stimulate the development of these specific types of products. The following research questions are answered in this Chapter:

- What are the actual expenditures on orphan, paediatric and ATMP drugs for the Netherlands (impact on the national health budget)?
- What kind of costs is related to the incentives included in the regulations?
- What is the budgetary impact of these incentives for the Netherlands?

At the start of this Chapter it is important to note that detailed quantitative information about the actual expenditures on especially orphan and paediatric drugs is very scarce. Most publicly available information is based on estimations. For this specific project we received from the Stichting Farmaceutische Kengetallen (SFK) detailed data about the expenditures on outpatient drugs for the period 2007-2014 (see also Annex A, under A1). Regarding the expenditures on inpatient drugs we were dependent on high-level publications (such as the recent report of the Dutch Healthcare Authority – NZa), using aggregated data.117

5.2 Identification of the actual expenditures

In this section we present the actual expenditures on orphan drugs, paediatric medicines and ATMPs in the Netherlands. Where possible, we also present some data about the European situation.

5.2.1 Expenditures on paediatric drugs

The European context

The European Paediatric Regulation came into force in January 2007. Since that moment, almost 800 paediatric investigations plans (PIPs) have been submitted and agreed upon, while also dozens of products have been authorised for mixed use (adult and paediatric) or paediatric use only. Most of the therapeutic areas covered by the PIPs refer to infectious diseases, oncology and immunology-rheumatology-transplantation.118 There seems to be hardly any literature or data on the expenditures on paediatric drugs within the EU. The extended impact assessment stems from 2004 (providing overall cost figures – i.e. not per product) and a further report on the (economic) impact of the Paediatric Regulation is foreseen for 2017.

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Expenditures on paediatric drugs in the Netherlands

The financing of outpatient paediatric drugs in the Netherlands is done via the drug reimbursement system (i.e. GVS). Inpatient drugs are financed via hospital budgets or via specific regulation, which can be the case for very expensive paediatric drugs. In 2010, the EMA published a survey on the paediatric uses of medicinal products in Europe. For the Netherlands, the presented data is quite limited but it does provide an overview of the type of prescriptions per age group. The survey showed also that in The Netherlands the top-50 of prescribed medicinal products cover approximately 75% of all prescriptions for paediatric use (see Table below).

Table 5.1  Overall prescriptions of authorised medicinal products for the paediatric outpatients (2010)

<table>
<thead>
<tr>
<th>Age 0-18</th>
<th>Age 13-18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betalactamines (17%)</td>
<td>Oral contraceptives (14%)</td>
</tr>
<tr>
<td>Inhalative beta-agonists (8%)</td>
<td>Inhalative beta-adrenergic agonists, glucocorticoids (14%)</td>
</tr>
<tr>
<td>Antimicrobials for intestinal use (7%)</td>
<td>Corticosteroids for topical use (6%)</td>
</tr>
<tr>
<td>Betalactam antibiotics (13%)</td>
<td>Antihistamines for systemic use (6%)</td>
</tr>
<tr>
<td>Inhalative beta-adrenergic agonists, glucocorticoids (14%)</td>
<td>Stomatological preparations (5%)</td>
</tr>
<tr>
<td>Amoxicillin (8%)</td>
<td>Inhalative beta-adrenergic agonists (5%)</td>
</tr>
</tbody>
</table>


In 2008 the SFK reported about the use of drugs by children until 11 years (all available drugs). From this monitor it becomes clear that over the period 2004-2008 the expenditures for drugs for children until 11 years old, increased from approximately €41 million in 2004, to approximately €52 million in 2008.\(^{119}\) Palivizumab (€12.3 million) and Somatropine (€11.9 million) were in 2008 the two products with the highest expenditure and covered together 47% of the listed expenditures. For Palivizumab, the EMA granted in 2014 a compliance statement under the paediatric regulation. For Somatropine the decision on the PIP is still pending (latest information 2013).\(^{120}\)

Regarding the actual outpatient expenditures in the Netherlands for drugs with a paediatric indication we received (non-public) data from the SFK. The data shows that for the overall Dutch population the expenditures for ‘drugs with a paediatric indication’ decreased from €689 million in 2008 to €360 million in 2014. The actual expenditures for these products for children (under 18 or U18) are relatively limited: approximately €4.4 million in 2014. The development of these U18-expenditures is shown in the next Figure.

\(^{119}\) SFK, https://www.sfk.nl/nieuws-publicaties/PW/2009/2009-14.html. Within this period the share of “expensive drugs” (> €500 per prescription) rose from approximately 30% to 45%.

With regard to the development of the expenditures it is important to note that there was a change in the regulatory regime in 2012. In that year a number of medicines with a high volume moved from the regular outpatient reimbursement system (no volume cap) to the inpatient reimbursement system (with a volume cap). Examples of these shifted products were Etanercept and Imatinib.

The overall development in the DDDs is shown in the Figure below.

The SFK-data shows that especially in the last three years (2012-2014) the top-15 of most expensive products (in terms of overall costs and U18-use) cover approximately 90% of the overall expenditures. An overview of the top-15 of these U18-expenditures is shown in the next Table.

### Table 5.2 Expenditures on drugs with paediatric indication (U18, outpatient 2014)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Top-15 in 2014 (INN)</th>
<th>Overall costs (x € 1,000)</th>
<th>DDDs (x 1,000)</th>
<th>Costs/ DDDs (€)</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Atomoxetine</td>
<td>2,245</td>
<td>421</td>
<td>5.34</td>
<td>51%</td>
</tr>
<tr>
<td>2</td>
<td>Formoterol with budesonide</td>
<td>616</td>
<td>413</td>
<td>1.49</td>
<td>14%</td>
</tr>
<tr>
<td>3</td>
<td>Formoterol with beclometason</td>
<td>382</td>
<td>281</td>
<td>1.36</td>
<td>9%</td>
</tr>
<tr>
<td>4</td>
<td>Montelukast</td>
<td>203</td>
<td>793</td>
<td>0.26</td>
<td>5%</td>
</tr>
<tr>
<td>5</td>
<td>Nevirapine</td>
<td>143</td>
<td>20</td>
<td>7.08</td>
<td>3%</td>
</tr>
</tbody>
</table>

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How well does regulation work?

<table>
<thead>
<tr>
<th>Rank</th>
<th>Top-15 in 2014 (INN)</th>
<th>Overall costs (€ 1,000)</th>
<th>DDDs (x 1,000)</th>
<th>Costs/ DDDs (€)</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>Calcipotriol, combined products</td>
<td>124</td>
<td>189</td>
<td>0.66</td>
<td>3%</td>
</tr>
<tr>
<td>7</td>
<td>Clindamycine, combined products</td>
<td>90</td>
<td>171</td>
<td>0.53</td>
<td>2%</td>
</tr>
<tr>
<td>8</td>
<td>Esomeprazol</td>
<td>87</td>
<td>571</td>
<td>0.15</td>
<td>2%</td>
</tr>
<tr>
<td>9</td>
<td>Rosuvastatine</td>
<td>81</td>
<td>121</td>
<td>0.67</td>
<td>2%</td>
</tr>
<tr>
<td>10</td>
<td>Valganciclovir</td>
<td>77</td>
<td>2</td>
<td>47.45</td>
<td>2%</td>
</tr>
<tr>
<td>11</td>
<td>Estradiol with nomegestrol</td>
<td>54</td>
<td>203</td>
<td>0.27</td>
<td>1%</td>
</tr>
<tr>
<td>12</td>
<td>Ezetimib</td>
<td>52</td>
<td>43</td>
<td>1.20</td>
<td>1%</td>
</tr>
<tr>
<td>13</td>
<td>Darunavir</td>
<td>51</td>
<td>2</td>
<td>23.25</td>
<td>1%</td>
</tr>
<tr>
<td>14</td>
<td>Tiotropium</td>
<td>47</td>
<td>34</td>
<td>1.38</td>
<td>1%</td>
</tr>
<tr>
<td>15</td>
<td>Rizatriptan</td>
<td>40</td>
<td>28</td>
<td>1.41</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td>Top-15</td>
<td>4,291</td>
<td>-</td>
<td>-</td>
<td>97%</td>
</tr>
</tbody>
</table>

Source: Ecorys. Based on SFK-data

There is no public data available regarding the inpatient expenditures on drugs with a paediatric indication. The main reason for this lack of public information is the fact that the prescription of these products is part of the DBC-system, which registers all relevant (reimbursement) data for the combination of diagnosis and treatment. The NZa report about ‘expensive inpatient drugs’ shows that within the top-25 of inpatient drug expenditures there were two products listed with a paediatric indication: Etanercept (rank 2, € 156 million) and Imatinib (rank 11, € 38 million). However, the report does not make a distinction between the use by children under 18 and the total population.122

The same is applicable for an overview of ‘expensive drugs’ in Medisch Contact that was published this summer (see Table below). Most of these (inpatient) expensive drugs have also a paediatric indication, but more detailed data is lacking.123

Table 5.3 Overview estimated expenditures ‘expensive drugs’ (NL, 2014)

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Expenditures (€)</th>
<th>Remarks - EMA status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab (Humira)</td>
<td>208 million</td>
<td>Agreement on PIP</td>
</tr>
<tr>
<td>Nivolumab (Opdivo)</td>
<td>200 million</td>
<td>Agreement on PIP</td>
</tr>
<tr>
<td>Ipilimumab (Yervoy)</td>
<td>166 million</td>
<td>Agreement on PIP</td>
</tr>
<tr>
<td>Dabrafenib (Tafinlar)</td>
<td></td>
<td>Agreement on PIP</td>
</tr>
<tr>
<td>Vemurafenib (Zelboraf)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Infliximab (Remicade)</td>
<td>144 million</td>
<td>Agreement on PIP, also received a SPC-extension</td>
</tr>
<tr>
<td>Etanercept (Enbrel)</td>
<td>156 million</td>
<td>Agreement on PIP, also received a SPC-extension</td>
</tr>
<tr>
<td>Alglucosidase alfa (Myozyme)</td>
<td>51 million</td>
<td>Orphan drug</td>
</tr>
<tr>
<td>Sofosbuvir (Sovaldi)</td>
<td>44 million</td>
<td>Agreement on PIP</td>
</tr>
<tr>
<td>Palivizumab (Synagis)</td>
<td>15 million</td>
<td>Agreement on PIP</td>
</tr>
<tr>
<td>Dabigatran (Pradaxa)</td>
<td>19 million</td>
<td>Agreement on PIP</td>
</tr>
<tr>
<td>Rivaroxaban (Xareto)</td>
<td></td>
<td>Agreement on PIP</td>
</tr>
<tr>
<td>Abirateron (Zytiga)</td>
<td>9 million</td>
<td>-</td>
</tr>
<tr>
<td>Omalizumab (Xolair)</td>
<td>7 million</td>
<td>Paediatric waiver</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1,019 million</strong></td>
<td></td>
</tr>
</tbody>
</table>


How well does regulation work?

The European context: market authorisations and costs

Since the introduction of the European Regulation on Orphan Medicinal Products in 2000, the European Medicines Agency (EMA) provided more than 1200 orphan designations, while 117 orphan medicines also received a market authorisation. These market authorisations cover a broad range of medical fields, but the majority is covered by oncology and immunology, the digestive system and metabolism.

There are various studies available which have identified the expenditures on orphan drugs for a specific country. The main insights and conclusions from these studies are summarized in Table 5.4 below.

Table 5.4 Overview expenditures in other countries

<table>
<thead>
<tr>
<th>Publication</th>
<th>Main conclusions</th>
</tr>
</thead>
</table>
| Denis et al (2010)  | - In 2008, the budget impact of orphan drug in Belgium was approximately € 66.2 million, which represents approximately 1.9% of the total drug expenditures.  
|                     | - Based on three scenarios, it is expected that the budget impact of orphan drug will increase to €130–204 million in 2013 (depending on the scenario) which cover 4% of the total drug expenditures. |
| Orofino et al (2010) | - In 2007, the percentage of orphan drugs compared to the total drug spending was approximately 1.7% in France, 2.1% in Germany, 1.0% in the UK, 1.5% in Italy and 2.0% in Spain. For the five countries, the average percentage was 1.7% |
| Schey et al (2011)  | - Schey et al present and reflect on existing publications on the (current and future) budget impact of orphan medicines. They observe that there is little published evidence upon which to assess the current or future budget impact of orphan medicines in Europe.  
|                     | - Schey et al conclude that although European orphan drug legislation has led to an increase in the number of approved orphan drugs, the growth in cost, as a proportion of total pharmaceutical expenditure, is likely to plateau over the next decade as orphan growth rates converge on those in the broader pharmaceutical market.  
|                     | - It is expected that in the period 2010-2020 (depending on the scenario) the peak-year orphan drug budget impact ranged between 3% - 6.6% (as percentage of total drug expenditures). |
| Hutchings et al (2014) | - Based on a dynamic forecasting model, the budget impact of orphan drugs in Sweden and France was assessed for the period 2013-2020. It is expected that, due to the growth in the number of orphan drugs, the budget impact will increase in Sweden from 2.7% (2013) to 4.1% (2020) and in France from 3.2% to 4.9%. |

The key message is that over the last 5-8 years the budget impact of orphan drugs ranged from 1.5% to 3% (as percentage of total drug expenditures) but that it is expected to raise in Europe to 4-5% or even more in the coming years.

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125 Nefarma, ‘Weesgeneesmiddelen - Zeldzaam maar niet uitzonderlijk’, September 2014, based on EMA, annual reports.
127 Orofino J, Solo J, Casado MA, Oyagüez I: Global spending on orphan drugs in France, Germany, the UK, Italy and Spain during 2007 Appl Health Econ Health Policy 2010, 8:301–315.
Expenditures on orphan drugs in the Netherlands

A recent study of Kanters (2014) for the Netherlands shows that over the period 2006-2012, the number of reimbursed orphan drugs increased from 11 in 2006 to 43 in 2012. For these orphan drugs a distinction can be made towards outpatient and inpatient drugs. The number of orphan drugs, as well as the number of patients is presented in Table 5.5.

Table 5.5 Number of orphan drugs and number of patients (2006-2012)

<table>
<thead>
<tr>
<th>Year</th>
<th>Outpatient</th>
<th>Inpatient</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>9</td>
<td>2</td>
<td>11</td>
</tr>
<tr>
<td>2007</td>
<td>15</td>
<td>7</td>
<td>22</td>
</tr>
<tr>
<td>2008</td>
<td>18</td>
<td>8</td>
<td>26</td>
</tr>
<tr>
<td>2009</td>
<td>22</td>
<td>9</td>
<td>31</td>
</tr>
<tr>
<td>2010</td>
<td>25</td>
<td>11</td>
<td>36</td>
</tr>
<tr>
<td>2011</td>
<td>30</td>
<td>11</td>
<td>41</td>
</tr>
<tr>
<td>2012</td>
<td>32</td>
<td>11*</td>
<td>43</td>
</tr>
</tbody>
</table>

Number of patients treated with orphan drugs

<table>
<thead>
<tr>
<th>Year</th>
<th>Outpatient</th>
<th>Inpatient</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>2,149</td>
<td>40</td>
<td>2,189</td>
</tr>
<tr>
<td>2007</td>
<td>3,457</td>
<td>146</td>
<td>3,603</td>
</tr>
<tr>
<td>2008</td>
<td>4,410</td>
<td>215</td>
<td>4,625</td>
</tr>
<tr>
<td>2009</td>
<td>6,024</td>
<td>469</td>
<td>6,493</td>
</tr>
<tr>
<td>2010</td>
<td>7,621</td>
<td>531</td>
<td>8,152</td>
</tr>
<tr>
<td>2011</td>
<td>8,250</td>
<td>536</td>
<td>8,786</td>
</tr>
<tr>
<td>2012</td>
<td>9,226</td>
<td>536*</td>
<td>9,762</td>
</tr>
</tbody>
</table>

Kanters estimated that the overall budget impact of orphan drugs increased from € 61 million in 2006 to € 260 million in 2012. The specific expenditures per year are presented in Table 5.6. Compared to the overall expenditures on pharmaceuticals in the Netherlands, the expenditures increased from 1.1% in 2006 to 4.2% in 2012. For 2009/2010, the percentage is more or less in line with the European average of 3.3%.

Table 5.6 Budget impact orphan drugs (€ million, no correction for inflation)

<table>
<thead>
<tr>
<th>Year</th>
<th>Outpatient</th>
<th>Inpatient</th>
<th>Total orphan drug budget</th>
<th>% change (year-to-year)</th>
<th>As % of total drugs budget</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>53</td>
<td>9</td>
<td>61</td>
<td>n/a</td>
<td>1.1%</td>
</tr>
<tr>
<td>2007</td>
<td>69</td>
<td>29</td>
<td>98</td>
<td>60%</td>
<td>~ 1.6%</td>
</tr>
<tr>
<td>2008</td>
<td>98</td>
<td>61</td>
<td>159</td>
<td>62%</td>
<td>~ 2.5%</td>
</tr>
<tr>
<td>2009</td>
<td>118</td>
<td>75</td>
<td>193</td>
<td>22%</td>
<td>~ 3.2%</td>
</tr>
<tr>
<td>2010</td>
<td>142</td>
<td>84</td>
<td>226</td>
<td>17%</td>
<td>~ 3.6%</td>
</tr>
<tr>
<td>2011</td>
<td>156</td>
<td>85</td>
<td>241</td>
<td>7%</td>
<td>~ 3.8%</td>
</tr>
<tr>
<td>2012</td>
<td>175</td>
<td>85</td>
<td>260</td>
<td>8%</td>
<td>4.2%</td>
</tr>
</tbody>
</table>

Outpatient orphan drugs

With regard to the expenditures on outpatient orphan drugs in the Netherlands we received detailed (non-public) data from the SFK for the period 2007-2014 (see Annex A, under A1). The data shows that for the overall Dutch population the outpatient expenditures for this set of orphan drugs increased from € 16 million in 2007 to € 89 million in 2012 and decreased after a shift in the regulatory system again to € 44 million in 2014. This is shown in Figure 5.3.

The SFK-data does not match with the estimated outpatient expenditures in the study of Kanters et al (see Table 5.3). This difference is difficult to explain, but a few observations can be made. First of all, the estimations of Kanters are based on the GIP-database, which includes information about the overall use

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and costs of medicines. Prices were estimated in a top-down manner, and may explain the differences.

Secondly, the prices in the GIP-database includes VAT (6%), the SFK-data does not.

Figure 5.3  Outpatient expenditures for 31 orphan drugs (€ million, 2007-2014, no correction for inflation)

The sharp decrease in expenditures can to some extent be explained by a decrease in the number of ‘Defined Daily Doses’ after 2010 (see Figure 5.4). However the main explanation is related to a change in the regulatory system, which resulted in 2012 in the shift of five products (with total expenditures of € 49 million 2012) from the outpatient expenditures towards the inpatient expenditures.

Figure 5.4  Number of Defined Daily Doses (DDD) for orphan drugs (x million, 2007-2014, outpatient)

In Table 5.7 we present the more detailed product data for the top-15 in 2014. It shows that this top-15 covers approximately 98% of the overall outpatient orphan drug expenditures.

Table 5.7  Expenditures on orphan drugs (outpatient, 2014)

<table>
<thead>
<tr>
<th>Rank</th>
<th>Top-15 in 2014 (INN)</th>
<th>Overall costs (x € 1,000)</th>
<th>DDDs (x 1.000)</th>
<th>Costs/ DDDS (€)</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tobramycine</td>
<td>6,142</td>
<td>163</td>
<td>37,68</td>
<td>14%</td>
</tr>
<tr>
<td>2</td>
<td>Sildenafil</td>
<td>5,731</td>
<td>385</td>
<td>14,89</td>
<td>13%</td>
</tr>
</tbody>
</table>

132 Prices were calculated by dividing drug’s budget impact by the number of DDD multiplied by 365.25 to get the price of treatment per year.

133 This is called the ‘overheveling medisch-specialistische geneesmiddelen’. This is applicable for: Sorafenib, Dasatinib, Nilotinib, Everolimus and Lenalidomide. In total 16 products were shifted.

134 Compared to the data of Kanters (2014) which presents 11 orphan drugs with the highest budget impact, a few observations can be made. First, it becomes clear that a few products where shifted towards the hospital budget (Lenalidomide, Imatinib and Dasatinib). Other products lost their EMA ‘orphan drug’ status (Bosentan, Pegvisomant).
How well does regulation work?

### Top-15 Overall Costs

<table>
<thead>
<tr>
<th>Rank</th>
<th>INN</th>
<th>Overall costs (€ 1,000)</th>
<th>DDDs (x 1,000)</th>
<th>Costs/ DDDs (€)</th>
<th>% of total</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>Deferasirox</td>
<td>4,919</td>
<td>-</td>
<td>-</td>
<td>11%</td>
</tr>
<tr>
<td>4</td>
<td>Sapropterine</td>
<td>4,733</td>
<td>-</td>
<td>-</td>
<td>11%</td>
</tr>
<tr>
<td>5</td>
<td>Ambrisentan</td>
<td>4,309</td>
<td>46</td>
<td>93,50</td>
<td>10%</td>
</tr>
<tr>
<td>6</td>
<td>Hydrocortison</td>
<td>3,417</td>
<td>2,171</td>
<td>1,57</td>
<td>8%</td>
</tr>
<tr>
<td>7</td>
<td>Mercaptopurine</td>
<td>3,200</td>
<td>-</td>
<td>-</td>
<td>7%</td>
</tr>
<tr>
<td>8</td>
<td>Velaglucerase alfa</td>
<td>2,672</td>
<td>2</td>
<td>1,373,57</td>
<td>6%</td>
</tr>
<tr>
<td>9</td>
<td>Ketoconazole</td>
<td>2,224</td>
<td>25,472</td>
<td>0,09</td>
<td>5%</td>
</tr>
<tr>
<td>10</td>
<td>Amifampridine</td>
<td>1,939</td>
<td>24</td>
<td>80,06</td>
<td>4%</td>
</tr>
<tr>
<td>11</td>
<td>Anagrelide</td>
<td>1,182</td>
<td>-</td>
<td>-</td>
<td>3%</td>
</tr>
<tr>
<td>12</td>
<td>Romiplostim</td>
<td>1,140</td>
<td>15</td>
<td>74,67</td>
<td>3%</td>
</tr>
<tr>
<td>13</td>
<td>Hydroxyccarbamide</td>
<td>997</td>
<td>-</td>
<td>-</td>
<td>2%</td>
</tr>
<tr>
<td>14</td>
<td>Ethinylestradiol with drospirenon</td>
<td>852</td>
<td>5,527</td>
<td>0,15</td>
<td>2%</td>
</tr>
<tr>
<td>15</td>
<td>Stiripentol</td>
<td>399</td>
<td>27</td>
<td>14,83</td>
<td>1%</td>
</tr>
</tbody>
</table>

Source: Ecorys. Based on SFK-data. Note: the top-15 is based on the data for 2014.

### Inpatient orphan drugs

With regard to the inpatient expenditures on orphan drugs public data is very scarce. Based on Van der Graaff (2011) and Kanters (2014), an overview of the six most expensive inpatient orphan drugs is presented in Table 5.8 below.

#### Table 5.8 Inpatient orphan drugs (€ million, 2011-2012, no correction for inflation)

<table>
<thead>
<tr>
<th>Rank</th>
<th>INN</th>
<th>Budget 2011</th>
<th>Budget 2012</th>
<th>NZa-tariff (1mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alglucosidase alfa (Myozyme)</td>
<td>15.0</td>
<td>40.3</td>
<td>11.13</td>
</tr>
<tr>
<td>2</td>
<td>Agalactosidase (Fabrazyme)</td>
<td>15.0</td>
<td>16.2</td>
<td>Unknown</td>
</tr>
<tr>
<td>3</td>
<td>Eculizumab (Soliris)</td>
<td>13.3</td>
<td>14.3*</td>
<td>17.23</td>
</tr>
<tr>
<td>4</td>
<td>Galsulfase (Naglazyme)</td>
<td>6.3</td>
<td>6.8*</td>
<td>315.88</td>
</tr>
<tr>
<td>5</td>
<td>Lorandizid (Aldurazyme)</td>
<td>5.8</td>
<td>6.3*</td>
<td>14.84 (unit)</td>
</tr>
<tr>
<td>6</td>
<td>Idursulfase (Elaprase)</td>
<td>4.8</td>
<td>5.2*</td>
<td>555.62</td>
</tr>
</tbody>
</table>

**Total top 6**: 172.8 208.2 -

Source: For 2011 the data is based on a presentation of Martin van der Graaff (ZIN), Weesgeneesmiddelen beoordeling en financiering (intramuraal en extramuraal), 1 oktober 2013. For 2012, the data is based on Kanters et al. 2014. Orphan drugs expenditure in the Netherlands in the period 2006–2012. Orphanet Journal of Rare Diseases 9:154. Notes: the figures marked with a star are estimated figures: we increased the 2011 budget (per medicine) with the overall budget increase for 2012 (4.2%).

#### Expenditures on ATMPs

For the ATMPs, the situation is completely different compared to orphan drugs or paediatrics medicines. Until now only five ATMPs have been licensed by EMA. In Table 5.9 we present an

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overview of these products. Currently, only ChondroCelect is used and reimbursed in the Netherlands.

Table 5.9  Overview licensed ATMPs (spring 2015)

<table>
<thead>
<tr>
<th>ATMP</th>
<th>Licensed</th>
</tr>
</thead>
<tbody>
<tr>
<td>ChondroCelect (tissue engineered product)</td>
<td>Licensed on 4 October 2009</td>
</tr>
<tr>
<td>MACI (tissue engineered product)</td>
<td>Licensed on 27 June 2013, suspended on 17 December 2014</td>
</tr>
<tr>
<td>Provenge (somatic cell therapy product)</td>
<td>Licensed on 6 September 2013</td>
</tr>
<tr>
<td>Glybera (gene therapy product)</td>
<td>Licensed on 25 October 2014</td>
</tr>
<tr>
<td>Holoclar (tissue engineered product)</td>
<td>Licensed on 17 February 2015</td>
</tr>
</tbody>
</table>


Based on interviews, we estimate that in 2014 approximately 90 patients were treated with ChondroCelect. Given an average cost price of about € 21,000 per treatment140, this results in a budget impact of approximately € 1.8 million in 2014. The interviewees indicated that per year 250-300 patients could be treated with this product.141

5.3 Identification of societal costs related to the regulations

Now the expenditures of the orphan drugs, paediatric medicines and the ATMPs are identified, we broaden the scope towards the costs related to the regulations under study. In this section we will focus on the “societal cost” of the regulations which, from the perspective of welfare economics, may be related to for example the costs of monopoly prices or the abuse of the instruments. The incentives included in the regulation are described in Chapter 2.

In this section the emphasis is on the costs related to the main incentives (e.g. market exclusivity), while the other societal costs are not discussed. These other societal costs are for example related to the hospital exemption (also discussed in Chapter 3). The fact that these products do not have a market authorisation implies that the risks for these products are not assessed extensively (like for products with a market authorisation). This results in higher risks in terms of health safety. Another example is the conditional reimbursement. The costs for these products are reimbursed without an extensive assessment. This implies that there is a risk that reimbursements are currently paid, while after future examination it can be decided that the costs will not be reimbursed.

A specific remark can be made in relation to the operational costs of the regulations. The EC indicated that for the period 2007-12, the EU budget contribution to the operation aspects of the paediatric regulation was approximately € 39 million. In addition, MSs contribute specific resources, like for example staff time for the assessment of paediatric investigation plans.142
5.3.1 Societal costs related to market protection

Rationale for market protection

The pharmaceutical market does not only serve an individual (the patient), but also the public (e.g., increasing public health). Medicinal products contribute to the provision of public goods such as public health and well-being. Public goods have two special characteristics that distinguish them from private goods: non-rivaling consumption and non-exclusion. If a product is a public good, the market sometimes does not—or not sufficiently—generate the product. Moreover, people will generally not be willing to pay for a public good if they can ‘free ride’ on the payment by others. To some extent a medicinal product can be characterized as a public good. As soon as a medicinal product is launched, the product components can be traced by the competitors, and they can free-ride on the creativity and large investments of the originator company.

According to economic theory, this public good problem can be solved by production by the government or providing “subsidies” to the providers of public goods. The introduction of “temporary exclusivity rights” (patent protection or market exclusivity) offers a solution for this tension between pursuit of profit and improving public health. The argument is that by generating potential monopoly power—and thus patent monopoly rents—exclusivity provides remuneration for successful innovators. The generated ‘monopoly rents’ function as a reward for (risky) investments and innovation. At the same time, the free-riding on investments by others is restricted for a specific period of time. The fact that the exclusivity right is only temporary and that the information will be publicly available gives the patent holder incentives to invest and innovate further.

Market protection for pharmaceutical products

Medicinal products are protected by patent rights and supplementary protection certificates (SPCs). Currently, a drug developer can obtain a patent either by filing a national application at each respective national patent office of the MSs or by filing a single patent application at the European Patent Office (EPO). In the latter case, which is used by the majority of pharmaceutical companies, a national validation of the ‘European patent’ (granted by the EPO in each MS where the patent owner wishes the patent to exist and to be enforceable) is still necessary. In Europe, patent protection may be obtained for up to 20 years starting from the moment the patent application is filed at the patent office of the territory concerned. However, this patent protection does not mean that also the product information cannot be used during these 20 years. The information protected by the patent will be publicly available, and others can, given certain limitations by the patent right, use this information for improvements and further research. For pharmaceutical products, there is an eight-year period of ‘data exclusivity’ and a two-year period of ‘market protection’. This implies that after eight years a generic application can be filed, and after ten years a generic product can be launched.

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144 European Commission, DG Competition, 2009, Pharmaceutical Sector Inquiry, final report. The criteria EPO uses for granting a patent are based on the European Patent Convention (EPC) of 1973 and later amendments to the EPC. These 20 years is based on WTO-agreements. The Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) determines that patent protection must be available for inventions for at least 20 years. See also: https://www.wto.org/english/thewto_e/whatis_e/tif_e/agrm7_e.htm
145 These 20 years is based on WTO-agreements. The Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) determines that patent protection must be available for inventions for at least 20 years. See also: https://www.wto.org/english/thewto_e/whatis_e/tif_e/agrm7_e.htm
146 European Commission, DG Competition, 2009, Pharmaceutical Sector Inquiry, final report. The Sector Inquiry refers to the fact that this period of 20 years reflects the assessment by the legislator that the end of this period is the point in time where the cost to society of continued patent protection (lack of competition, prices above the marginal costs, extra profits to the patent holder), starts exceeding the benefits (research, investments, etc.).
147 Data exclusivity: period of time during which a company cannot cross-reference to the data in support of another marketing authorisation; See: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/05/WC500143122.pdf
148 Market protection: period of time during which a generic, hybrid or biosimilar cannot be placed on the market, even if the medicinal product has already received a marketing authorisation. In case of a ‘new indication’, the period of market protection will be extended to three years. Available via: http://www.ema.europa.eu/docs/en_GB/document_library/Presentation/2013/05/WC500143122.pdf
Further, in order to protect the originator companies during the period between the filing of a patent application and the authorisation for market launch, the EC (Council regulation 1768/92) created a supplementary protection certificate (SPC) for medicinal products which covers a maximum period of five years. It was determined that the holder of both a patent and a certificate should be able to enjoy an overall maximum of 15 years of exclusivity from the time the medicinal product in question first obtains authorisation to be placed on the market in the Community. The Orphan Regulation and the Paediatric Regulation also contain this type of protection against the ‘normal’ forces of competition.

**Orphan drugs**

Medicines with an orphan designation which have received a marketing authorisation may benefit from a ten year period of ‘market exclusivity’: during this period, no other application for a marketing authorisation will be taken into account by the marketing authority. This market exclusivity is an addition to the regular patent protection. It implies that an application for a similar product can only be filed after ten years instead of eight years. There is one specific exception: the ten-year period of orphan market exclusivity can be extended to twelve years if the requirements for paediatric use are met. This protection is illustrated in Figure 5.5.

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**Figure 5.5 Orphan drug protection**

<table>
<thead>
<tr>
<th>Regular pharmaceutical products</th>
<th>8 years</th>
<th>2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eight years of data exclusivity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Two years of market protection</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Orphan drugs</th>
<th>10 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ten years of market exclusivity</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Orphan drugs with pediatric indication</th>
<th>10 years</th>
<th>2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ten years of market exclusivity</td>
<td></td>
<td>Two additional years of market exclusivity</td>
</tr>
</tbody>
</table>


A producer can apply for an ‘orphan designation’ if the relevant medicine meets a number of criteria (see also Chapter 3). The application is reviewed by the EMA. Producers who receive an orphan designation for their product benefit from certain incentives (as listed in Chapter 2), including market exclusivity once the medicine is on the market. The 10 year period of market exclusivity starts after the positive decision regarding marketing authorisation. The period of market exclusivity is extended by two years if the medicine complies with an agreed paediatric investigation plan (PIP).

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152 The criteria are: (i) it must be intended for the treatment, prevention or diagnosis of a disease that is life-threatening or chronically debilitating; (ii) the prevalence of the condition in the EU must not be more than 5 in 10,000 or it must be unlikely that marketing of the medicine would generate sufficient returns to justify the investment needed for its development; (iii) no satisfactory method of diagnosis, prevention or treatment of the condition concerned can be authorised, or, if such a method exists, the medicine must be of significant benefit to those affected by the condition.
153 For more information about the process, see: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000554.jsp&mid=W0b01ac058061ecbb
Drugs with a paediatric indication

The Paediatric Regulation contains three specific types of protection. The first protection refers to the paediatric-use marketing authorisations (PUMA) which is relevant for already authorised medicines which are no longer protected by the patent or SPC and is to be exclusively developed for use in children. A PUMA will benefit from additional data exclusivity (eight years) and market protection (2 years) for innovation on off-patent drugs. This instrument is exclusively for drugs in use in the paediatric population. The second type of protection refers to the supplementary protection certificate (SPC), which aims to close the ‘protection gap’ between the filing of a patent application and the market authorisation. For regular pharmaceutical products this SPC covers a maximum period of five years. When the requirements of the paediatric regulation are met, the SPC can be extended with six month. This SPC-protection is illustrated in Figure 5.6. The third type of protection refers to the extension of the market exclusivity period for orphan drugs (see above).

Figure 5.6  SPC-protection for drugs with a paediatric indication


The costs of market protection for society

The market protection system is in fact a double-edged sword: it preserves the incentive for R&D on one hand, but on the other, it also creates a negative societal welfare effect due to the creation of a pseudo-monopoly. A crucial regulatory problem is therefore to determine the optimal length of market protection so that drug companies are still willing to take costly risks to develop life-saving drugs, while on the other hand prices are not driven up too high due to excessive monopoly rents. The creation of a pseudo-monopoly also leads to “allocative inefficiencies” due to (i) higher prices as a result of monopoly rents and (ii) the delayed (or even prevented) access of generic medicine providers (with lower prices).

In this section we make an estimation of the actual costs of the identified protection-instruments for orphan drugs and drugs with a paediatric indication. The main assumption for this estimation is that there will be access by generic medicine providers, but that this access is delayed and that the originator company can benefit from monopoly process for a longer period. The outpatient SFK-data will be our main data source for the analysis.

1. Protection costs related to orphan drugs

As indicated above the main protection costs are related to the longer period of market exclusivity. The application for a similar product can only be filed after ten years instead of eight years, what in

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154  Regulation(EC) No 1901/2006 on medicinal products for paediatric use, article 38.
156  Rockett K, 2008, Property rights and invention, discussion paper series no 663, University of Essex; Kelton CML, Rebelein RP, 2005, Social welfare loss in antidepressant and antipsychotic pharmaceutical markets, University of Cincinnati, Vassar College Poughkeepsie.
principle results in a two year delay of generic access and (high) monopoly prices for two additional years.

**Expected price decrease** - In relation to orphan drugs the literature on this specific cost is very limited. In an article about the budget impact of orphan medicines in Europe, Schey (2011) assumes that drug costs will fall in price by 25% from the 10th year after the introduction of the first orphan medicine in a disease area (end of the market exclusivity). This estimation is based on the ‘Pharmaceutical Sector Inquiry Report’ of the EC (DG Competition, 2008) which observed that (i) over the period 2000-2007 the average price reduction after the end of the market protection was 25% and (ii) after two years of market presence the prices of generic medicines, are on average 40% lower than the former price of the medicine of the originator company.

Detailed (public) quantitative data about the development of orphan drugs prices is very scarce. Nevertheless it is possible to make some observation from the SFK-dataset (outpatient drugs). First of all it is important to note that nearly all current top-15 products still have an orphan designation (and a marketing authorisation) and benefit from the market exclusivity. The data shows that for six out of nine products the costs per DDD gradually decrease over time, even if there is still an orphan designation. The price decrease per product varies over the years between +5% and -10%. More detail is provided in Annex A (under A2). Within the SFK-dataset two products can be identified which were present in the top-10 in 2011, for which the orphan designation (and the 10-year market exclusivity status) expired and data on the costs per DDD is available. Bosentan was withdrawn from the Community register of orphan medicinal products in April 2012, Pegvisomant in November 2012. The development of costs per DDD is illustrated in Figure 5.7.

**Figure 5.7 Development of the costs per DDD for Bosentan and Pegvisomant (2007-2014)**

Source: Ecorys. Based on SFK-data. Note: between brackets the month of expiration is shown.

The data shows that in the case of Bosentan the reduction already started after 2010, when the costs (per DDD) dropped from € 117 (2010) to € 80 in 2014. This is a reduction of 31% over the period 2010-2014. For Pegvisomant the price is very stable until the drop of 13% between 2013 and 2014.

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159 The status of Ethinylestradiol / Drospirenon is uncertain at EMA.
160 Martin van der Graaff (ZIN), Weesgeneesmiddelen beoordeling en financiering (intramuraal en extramuraal); 1 oktober 2013. See: http://www.slideshare.net/DutchOrphanDrugNetwork/zin-en-onzin-van-een-economische-waardebepaling-van-een-weesgeneesmiddel
Cost assessment – Based on the provided information we are now able to make a (rough) estimation of the costs. The main societal costs are related to the additional two years of market exclusivity (and higher price). Given an average cost of € 16 million per product, two expiring products per year and a price decrease of 25%, the overall costs of protection are € 8 million per year for a period of two years. A more detailed explanation for this estimation is provided in Annex A (under A3).

2. Protection costs related to orphan drugs with a paediatric indication
Also for this product type, the main protection costs are related to the longer period of market exclusivity. Compared to regular pharmaceuticals these products benefit from four additional years of market exclusivity. In 2015, the EC reported that so far only two products ‘received’ the two year extension of their market exclusivity status.\(^{161}\) These two products were Anagrelide (Xagrid) and Tobramycin (Tobi Podhaler). Both products are listed in the top-15 of outpatient drugs expenditures, respectively rank 11 (€ 1.2 million in 2014) and rank 1 (€ 6.1 million in 2014), see also table 5.1. In line with the way of reasoning under point 1 above, the overall costs of protection are € 4 million per year per ‘blockbuster’ for a period of two years.

3. Protection costs related to the paediatric-use marketing authorisations (PUMA)
As indicated before the PUMA is relevant for already authorised medicines which are no longer protected by the patent or SPC (and exclusively developed for use in children). In case a PUMA is granted the product will benefit from additional data exclusivity (eight years) and market protection (2 years). This incentive was mainly created to stimulate research on medicines which were mainly used off-patent for children (only authorisation for adults). To date only two PUMA-applications have been granted, with a few more projects currently in the pipeline.\(^{162}\) The two authorised products are midazolam (Buccolam; authorised in 2011) and propranolol (Hemangiol; authorised in 2014).

Both products are covered by the data received from the SFK. In absolute figures the expenditures on these products are relatively small. Over the period 2007-2014 the expenditures for midazolam varied between € 1,600 and € 3,900. For propranolol the expenditure varied in this period between € 20,000 and € 24,000. Despite these low expenditures, the SFK-data shows that the costs for Midazolam increased sharply after the decision: from € 0.48 per DDD in 2011 to € 1.10 per DDD in 2014 (increase of 130% in three years). For propranolol this development is not visible in the data. This is shown in Figure 5.8.


4. Paediatric drugs - Supplementary protection certificate (SPC)

This type of protection aims to close the ‘gap’ between the filing of a patent application and the market authorisation. A SPC of regular pharmaceutical products covers a maximum period of five years. This can be extended with six months when the requirements of the paediatric regulation are met. Extensions of the SPC are granted by the National Patent Offices at national level. For the period 2010-2014 the Dutch Patent Office granted the 6-month extension to 18 products, while 11 requests were still pending (report 2014). In Annex A (under A4 and A5) we present an overview of products with a SCP-extension.

Expected price decrease – There is no specific literature available regarding the price decrease after the end of the SPC-protection period or extended SPC-protection period. In a position paper about paediatric drug regulation the European Generic Medicines Association refers to the 25% price decrease after patent expiry which DG COMP observed in 2009 (see section on orphan drugs). The detailed SFK-data (see Figure 5.9) shows that for some of the products which benefitted from a SPC-extension, the prices drop sharply after the end of the protection period.

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163 European Generic Medicines Association, ‘EGA contribution to EC public consultation on general Report on experience acquired as a result of the application of the Paediatric Regulation’, November 2012.
Clear examples are **Losartan** (SPC-extension in 2010, price decrease of > 70% in the period 2009-2011; even during the SPC-extension period), **Anastrozol** (SPC-extension in 2010, price decrease of > 80% in the years afterwards) and **Valsartan** (SPC-extension in 2010, price decrease of > 70% in the years afterwards). The price of Nevirapine (2012) reduced less sharply (-15%). For Tiotropium (2012) there is still no generic medicine available, which is reflected in the price (+3%). This also applies to Voriconazol (2014).

**Cost assessment** – Based on the information provided a (rough) estimation of the costs of protection can be made. The main societal costs are related to the additional six month of SPC-protection, which delays the access of generic products and a price decrease. Given an average cost of € 33 million per product, three expiring SPC-extensions per year, a price decrease of 25% and an additional protection period of six month, the overall costs of protection are approximately € 18 million per year. A more detailed explanation for this estimation is provided in Annex A (under A5).
6 Balancing costs and effects – how to move forward?

In this Chapter we reflect on the main topics that were studied for each of the regulations:

- Degree to which unmet medical needs are met;
- Financial impact of the regulations;
- Bottlenecks and possible solutions to improve efficiency in drug spending, while maintaining a balance between access and cost-effectiveness.

As described in this report, the current framework for the pharmaceutical regulation is complex and covers a range of aspects. To identify the bottlenecks and formulate potential solutions to move forward, we will first focus on the results in terms of unmet medical need and the financial impact of each of the regulations.

6.1 Degree in which unmet medical needs are met

In Chapter 3 we elaborated on the definition of “unmet medical need”. An unmet medical need exists when a disease is not effectively addressed by the current/available therapy. There are two types of unmet medical need:

1. when no therapy exists for a certain disease; and
2. when a disease is not adequately addressed by available medicine.

6.1.1 Paediatric Regulation

The Paediatric Regulation has – until now – been modest in addressing unmet medical needs. By the end of 2014, 790 PIPs have been approved, of which about 10% are completed, 2 products have been granted a PUMA and two products have received the orphan reward. Experts in the field notice an increase in scientific studies on paediatric medicines. Although it may still take some more years to judge the effectiveness of the Regulation in terms of its output, they perceive the recent developments as promising. Other stakeholders argue that the Regulation has not reached the goal of bringing more medicines to children but resulted in companies adding paediatric information to medicines developed for adults in lower priority areas.164

6.1.2 Orphan Regulation

Although the Orphan Regulation has been highly successful in terms of number of registered products, there is a debate on whether unmet medical need has been sufficiently met. In 2006 the EC stated “the orphan legislation in the EU has far exceeded initial expectations; more than 450 applications for orphan designation have been submitted in the period between April 2000 and April 2005. Of those, more than 260 have been designated and 22 have gone on to receive a marketing authorisation.” Since then these numbers have steadily increased. Currently, 117 orphan medicines have received marketing authorisation. Furthermore, 1,202 products have currently received an orphan designation. Of these drugs, there are several targeting diseases for which some kind of therapy was available already. For example, Bosentan (Tracleer) is prescribed for pulmonary

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How well does regulation work?

arterial hypertension (PAH), but there are various other drugs prescribed for PAH as well. This contradicts the unmet medical need criterion.

6.1.3 Advanced Therapy Medicinal Products Regulation
Currently, five products have been granted marketing authorisation in the EU. Of these products, only ATMP has granted marketing authorisation in the Netherlands. The number of ATMPs that are applied under the so-called hospital exemption is not known but there are indications that this is not extensively applied in the EU. It is clear that the ATMP that is available in the Netherlands is addressing an unmet medical need (see also Annex B).

6.2 Financial impact of the regulations under study

6.2.1 Paediatric medicines
The available data shows that for the overall Dutch population the outpatient expenditures for 'drugs with a paediatric indication' decreased from € 689 million in 2008 to € 360 million in 2014. The actual expenditures for products for children (under 18) are relatively limited: approximately € 4.4 million in 2014. The expenditures for inpatient drugs are not clear, but may be more than € 700 million per year.

The main societal costs are related to the additional six month of SPC-protection, which delays the access of generic products and a price decrease. We estimate that the overall costs of protection are approximately € 18 million per year. A more detailed explanation for this estimation is provided in Annex A (under A4). Beside that, there exists a PUMA-protection, which grants an additional protection for data exclusivity (eight years) and market protection (2 years). To date only two PUMA-applications have been granted, with relatively low outpatient expenditures (< € 25,000).

6.2.2 Orphan drugs
The available data (Kanters, 2014) estimates that the overall Dutch outpatient expenditures for orphan drugs increased from € 61 million in 2006 to € 260 million in 2012. More detailed SFK-data does not exactly match these figures. In Chapter 5, possible causes for the differences between the SKF-data and the data used by Kanters are identified. Within the top-25 of inpatient drug expenditures (Nza report 2015) there are several orphan drugs listed with a total value of € 177 million: Alglucosidase alfa (rank 6, € 59 million), Lenalidomide (rank 10, € 39 million), Imatinib (rank 11, € 38 million), Everolimus (rank 16, € 21 million), Eculizumab (rank 18, € 20 million).165

The main societal costs of market protection are related to the additional two years of market exclusivity (and higher price). We estimate that the overall costs of protection are € 8 million per year for a period of two years. A more detailed explanation for this estimation is provided in Annex A (under A3). If these orphan drugs also receive a paediatric indication, it benefit from four additional years of market exclusivity. In 2015, the EC reported that so far only two products 'received' the two year extension of their market exclusivity status.166 These two products are Anagrelide (Xagrid) and Tobramycin (Tobi Podhaler), which both are listed in the top-15 of outpatient drugs expenditures. In line with the ‘normal orphan drugs’ the overall costs of protection are € 4 million per year per ‘blockbuster’ for a period of two years.

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6.2.3 ATMPs
Based on interviews, we estimate that in 2014 approximately 90 patients were treated with ChondroCelect in the Netherlands. Given an average cost price of about € 21,000 per treatment, this results in a financial impact of approximately € 1.8 million in 2014. There is potential for growth as estimated by experts in the field.

6.3 Bottlenecks and possible solutions
We identified several bottlenecks for each of the three regulations, which are summarized below, and for which we formulate possible solutions.

6.3.1 General observation
Each of the three regulations could benefit from more specific definitions with regard to “significant clinical benefit” and “unmet medical need”. For example, clinical benefit is defined as “a clinically relevant advantage or a major contribution to patient care.” Addressing the issue of definitions is not new, but could be improved. In June 2012, EMA organised a workshop on the criterion ‘significant benefit’ in the Orphan Regulation, which is also planned for December 2015. One of the conclusions of the workshop in 2012 was that “work should be done to have a better definition of the scientific justifications for significant benefit.” It is not clear if and how this was taken forward. Based on this study we conclude that at present, the terms “significant clinical benefit” and “unmet medical need” are still interpreted rather widely. It is expected that the regulations could provide both more clarity and direction when the definitions are more specific. Especially in the area of orphan drugs, a more specific and stringent interpretation of these terms could steer the attention of developers to areas for which no or limited therapy exists in order to obtain the orphan status.

6.3.2 Paediatric Regulation
According to experts in the area of paediatric medicines (including researchers and representatives of governmental agencies), the incentives of the current Regulation are very restricted. It is estimated that the costs for research and development are excessively high and that the incentive of six months additional market protection does not cover these costs. The RAND-study (2004), however, indicates that the value of a six-month extension of the SPC clearly outweighs the costs of the additional testing which is required under the Paediatric Regulation. It is estimated that the pharmaceutical industry is able to recover the costs for these additional tests and still makes a profit on the SPC extension between € 63 million and € 205 million (profits minus discounted costs of testing over a ten-year period). These findings show that more clarity is needed to establish whether the incentives are sufficiently strong to stimulate the development of new paediatric medicines. In addition, our case study indicates that the procedure for obtaining additional market protection could benefit from more coordination and cooperation between developers and researchers.

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167  http://www.medicijnkosten.nl
The number of applications for waivers and deferrals is growing, which indicates that research on paediatric medicines is growing. Still, to increase the number of paediatric medicines that meet an unmet medical need, further improvements need to be made.

An important improvement could be realized if the effectiveness of current (off-label) medicines used by children was closely monitored and used in the registration procedure. Many drugs have been prescribed to children off-label for a long period and a lot of information is available to build upon. According to the Regulation this is not sufficient, but patients must be included in a formal study at an average cost of €10.000 per patient. Changing this practice would greatly contribute to the registration of paediatric medicines.

Finally, a license for market entry is granted at a certain point in time. The question which then remains is whether and how the drug will fulfil its promise. If not, there should be a mechanism for price negotiations. However, this mechanism is not present in the regulations as this is the mandate of MSs.

6.3.3 Orphan Regulation

Although the Orphan Regulation is widely considered a success in stimulating the development of new drugs, it also faces some pitfalls.

An important characteristic of the Regulation is the fact that only the first applicant working on a specific molecule can receive market exclusivity. This hampers the further development of a number 2 and 3, while it would be important to develop alternatives to the initial medicine. Legislators hoped this element would stimulate cooperation instead of competition between researchers. Since this cooperation has not taken place, it may be time to evaluate this part of the Regulation.

An important issue is the fact that once a drug has been registered, little further research is done in this area. The drug developed for cystic fibrosis, for example, focuses on only 8 to 9 possible mutations of the protein involved. Patients with other mutations still will get this medicine off-label prescribed by their physician. As a result, there is no incentive left for the pharmaceutical company to research the effectiveness of the drug on other mutations. By incorporating requirements for future research on other applications in the actual approval document, this issue may be dealt with.

The Orphan Regulation is sometimes used by registering low-cost magistral formulae in order to increase the price (and profits). Perhaps this strategic use of the Orphan Regulation could be considered as a price we must be willing to pay, but should be evaluated. Well intended regulations may turn into perverse incentives. Although it could be valuable to establish scientific evidence for former magistral formulae, there should be mechanisms in place to allow for price controls in order to prevent perceived price explosions.

The element of high prices paid for orphan drugs touches the very core of the Regulation itself: The regulation was introduced for companies which under normal market conditions were unable to develop medicines without a coherent set of incentives. Given the high prices of sometimes €200K-€400K per year, it is doubtful if these ‘normal market conditions’ still exist. Even without incentives, a company should be able to invest in research given the profits made, even for ultra rare diseases.

In addition to high prices, the increased use of orphan drugs is increasing health care costs. This can be explained by situations in which medicines first intended to be used in a late stage of treatment are increasingly being used in an early stage of treatment. The solution is a system in
which the price of the orphan drug is mandatorily diminished as soon as the threshold of the incidence/prevalence for the orphan indication is exceeded.

The success of the Regulation combined with the relatively high prices for orphan drugs pose a threat to affordability and the sustainability of health care. Although some countries are rather successful in negotiating agreements with pharmaceutical companies, better results might be achieved at a European level. Currently however, this role is not rendered to the EU and still the responsibility of the MSs.

6.3.4 Advanced Therapy Medicinal Products Regulation

The impact of the Regulation differs per type of developer. For a publicly owned firm, for example, market protection as a financial stimulus is more important than for a researcher working in a clinical setting. For this latter group, communication with EMA, e.g. as part of free scientific advice, is considered as very important during the registration process of an ATMP.

At present, the CAT consists of members from every MS. These members may change frequently and not every member is an expert from the field of ATMP, with the result that decisions may sometimes be influenced by personal opinions of non-experts. Decision-making should be based on expert knowledge rather than one vote for every MS. In addition, expert panels could be organized for specific registration-related issues. For example, a panel in the area of research methodology could be beneficial. Research methods differ in terms of applicability, but the members of the CAT seem unaware of this. An expert panel could help solve this issue. In addition, diminishing the administrative burden and shortening procedures could help to facilitate to registration process. European legislators could scrutinize existing procedures in Asia to identify potentials for improvement.

Hospital exemptions can be considered as a pragmatic instrument to prevent the high costs that are incurred for registration by EMA. In Germany, hospital exemptions are widely used. One hospital obtains a hospital exemption for an ATMP. Through contracts and by establishing legal entities with other hospitals, these ATMPs are made available to other hospitals as well.

In addition to the growing use of hospital exemptions in some countries, researchers are increasingly facing a dilemma in response to the stringent application of complex and demanding rules. In Asia regulators focus primarily on safety of the new ATMP: when minimal safety norms are met, the product can be used for further research. This is also related to the orientation towards science in this region, as well as cultural aspects (everything that can be done, should be stimulated). In western countries we are more focused on must everything that can be done also be stimulated? As a result, the gap between Europe and Asia is growing. The costs of conducting trials are extremely high, leading to high prices for these products. Physicians in turn are hesitant to apply these ATMPs in their treatment and health insurers are reluctant to pay the costs. This all leads to a vicious circle which is hampering instead of stimulating the development of ATMPs. Action is needed to turn this tide and reverse the vicious circle. This is also supported in the case study on ATMPs (see Annex B).

6.4 The most prominent issues to address in the near future

It is obvious that the three regulations under study differ in terms of balancing costs and effects:

- The Paediatric Regulation has not yet fully obtained its full potential as it has been modest in addressing unmet medical needs and its overall (budget) impact is not yet fully known. In
addition, more research is needed to determine whether the incentives are sufficiently strong to stimulate the development of new paediatric medicines;

- The Orphan Regulation has been highly successful in terms of number of registered products, but there is a debate on whether unmet medical need has been sufficiently met. In addition, the Regulation results in relatively high prices for orphan drugs and subsequent a relatively high budget impact;

- The Regulation on ATMPs is definitely addressing high unmet medical needs but the development of ATMPs is hampered. ATMPs are frequently innovative, complex products which typically have a limited knowledge base regarding the manufacturing processes, quality attributes, and preclinical/clinical study experience on which to base product-related decisions. Therefore, these barriers exist primarily for developers, and secondarily regulators. Ongoing research on these products and ongoing communications between developers and regulators are helpful to minimizing these barriers.

The issues could be (partly) addressed at MS level but as the regulations affect the EU, some and better results might be achieved at EU level.

EU level
Examples of the most prominent issues which might be addressed at European level include:

- Provide more clarity and direction with regard to the definitions/terms “significant clinical benefit” and “unmet medical need”.

- In the area of paediatric medicines, better monitoring of the effectiveness of current (off-label) medicines used by children (also at MS level) and subsequently use the outcome in the registration procedure.

- In the area of orphan drugs:
  - Consider revising the current legislation. At present, only the first applicant working on a specific molecule can receive market exclusivity, thereby hampering the development of additional drugs for the same condition. If such revision is difficult, it may be linked to the following issue.
  - The Orphan Regulation includes the stipulation that when a drug renders sufficient financial benefits, market exclusivity can be limited from 10 to 6 years. At present, EMA is responsible for providing the evidence that this is the case. The responsibility for providing such evidence could be shifted towards the pharmaceutical companies by letting them prove that the costs for developing medicines still outweigh the financial revenues.
  - The Orphan Regulation was once introduced for pharmaceutical companies which under normal market conditions were unable to develop medicines without a coherent set of incentives. Given the current situation, with relatively high prices of certain orphan drugs (e.g. €200K-€400K per year), it can be questioned whether ‘normal market conditions’ still exist. It would be beneficial to have a discussion on what is perceived as ‘normal market conditions’, which may include a price cap that could help prevent perceived price explosions for this type of drugs.

- For ATMPs, the CAT may benefit from the inclusion of more experts in the field of ATMPs. This may result in more effective norms and rules for research, thereby bridging the gap between research practices in Europe and Asia.

Member State level
At the level of individual MSs, we recommend focusing on the following issues:

- Price negotiations - this may include a pay-for-performance element to prevent paying high prices for drugs without a significant clinical benefit. Also, bilateral cooperation (between 2-3 MSs) might be beneficial when it concerns e.g. low volume medicines. To limit high societal costs for orphan drugs, price negotiations may focus on realizing a discount based on volumes.
• Strategic use of the Orphan Regulation (in terms of registering low-cost magistral formulae in order to increase the price) should be evaluated and mechanisms developed that allow for price controls in order to prevent perceived price explosions.
• Individual MSs may consider the use of hospital exemptions for ATMPs to stimulate the availability of these treatments while limiting the costs involved. It would be recommended to monitor the use of hospital exception in order to determine the evidence base.
Annex A  Additional information on Chapter 5

A0. Information about the SFK-dataset

Ecorys received from the SFK a detailed dataset with information about the outpatient use and expenditures of orphan drugs and drugs with a paediatric indication. SFK receives and registers information from public pharmacists and covers approximately 95% of the overall turnover of pharmacists. The missing 5% refers to General Practitioners with a pharmacy license. The SFK-database includes information about the reimbursement of the pharmacist to the health insurers who pay for the drugs included in the national health insurance (‘basispakket’). Information about corrections and mistakes in the data are not registered. The dataset received included the following information:

- Information about the annual overall expenditures which are reimbursed by the health insurers (‘gedeclareerde materiaalkosten’), which exclude the (relatively small) handling fee for the pharmacist;
- Information about the annual number of ‘Defined Daily Doses’ (DDD);
- Based on this information, also the expenditures per DDD were provided.

Orphan drugs - Ecorys provided the SFK / the Ministry of Health with a list of 78 orphan drugs which received a market authorisation by EMA. Most of these authorised orphan drugs are also reimbursed in the Netherlands via the national health insurance (outpatient) or via the hospital budget (inpatient). For the period 2007-2014 Ecorys received data about 31 different products (overall expenditures, DDDs). For some of these 31 products specific observations were missing (information not registered).

Drugs with a paediatric indication - Ecorys provided the SFK / the Ministry of Health with a list of 55 products which received a compliance statement under the Paediatric Regulation (period 2007-2014). Ecorys received data concerning 41 different products (overall expenditures, DDDs). For some of these 41 products specific observations were missing (not registered), for example for Palivizumab. Within this dataset it was possible to make a distinction between the use by children under 18 years old (U18) and the total population.

A1. Top-11 orphan drugs in 2011

Kanters estimated that the overall budget impact of orphan drugs increased from € 61 million in 2006 to € 260 million in 2012. Within the total group of orphan drugs, the eleven drugs with the largest expenditures covered approximately 72% of the overall expenditures on orphan drugs in 2011 (2012: 80%). A more detailed overview is provided below.

<table>
<thead>
<tr>
<th>Rank</th>
<th>INN (trade name)</th>
<th>Setting</th>
<th>Budget 2011</th>
<th>Budget 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Imatinib (Glivec)</td>
<td>Outpatient**</td>
<td>37.3</td>
<td>36.4</td>
</tr>
<tr>
<td>2</td>
<td>Lenalidomide (Revlimid)</td>
<td>Outpatient**</td>
<td>30.7</td>
<td>36.2</td>
</tr>
<tr>
<td>3</td>
<td>Bosentan (Tracleer)</td>
<td>Outpatient</td>
<td>22.8</td>
<td>23.0</td>
</tr>
<tr>
<td>4</td>
<td>Alglucosidase alfa (Myozyme)</td>
<td>Inpatient</td>
<td>15.0</td>
<td>40.3</td>
</tr>
<tr>
<td>5</td>
<td>Agalactosidase (Fabrazyme)</td>
<td>Inpatient</td>
<td>15.0</td>
<td>16.2</td>
</tr>
<tr>
<td>6</td>
<td>Eculizumab (Soliris)</td>
<td>Inpatient</td>
<td>13.3</td>
<td>14.3*</td>
</tr>
<tr>
<td>7</td>
<td>Pegvisomant (Somavert)</td>
<td>Outpatient</td>
<td>13.2</td>
<td>14.3</td>
</tr>
</tbody>
</table>
How well does regulation work?

<table>
<thead>
<tr>
<th>Rank</th>
<th>INN (trade name)</th>
<th>Setting</th>
<th>Budget 2011</th>
<th>Budget 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Dasatinib (Sprycel)</td>
<td>Outpatient**</td>
<td>8.6</td>
<td>9.3*</td>
</tr>
<tr>
<td>9</td>
<td>Galsulfase (Naglazyme)</td>
<td>Inpatient</td>
<td>6.3</td>
<td>6.8*</td>
</tr>
<tr>
<td>10</td>
<td>Laronidase (Aldurazyme)</td>
<td>Inpatient</td>
<td>5.8</td>
<td>6.3*</td>
</tr>
<tr>
<td>11</td>
<td>Idursulfase (Elaprase)</td>
<td>Inpatient</td>
<td>4.8</td>
<td>5.2*</td>
</tr>
<tr>
<td></td>
<td><strong>Total top 11</strong></td>
<td></td>
<td><strong>172.8</strong></td>
<td><strong>208.2</strong></td>
</tr>
</tbody>
</table>

Source: For 2011 the data is based on Martin van der Graaff (ZIN), Weesgeneesmiddelen beoordeling en financiering (intramuraal en extramuraal); 1 oktober 2013. For 2012, the data is based on Kanters et al. 2014. Orphan drugs expenditure in the Netherlands in the period 2006–2012. Orphanet Journal of Rare Diseases 9:154. Notes: the figures marked with a star are estimated figures: we increased the 2011 budget (per medicine) with the overall budget increase for 2012 (4.2%). INN = International Non-proprietary Names; *weighted average of infantile patients (€706,666/patient) and adult patients (€422,314/patient).

Some of these top-11 orphan drugs also rank relatively high in terms of the number of users, for example nr. 1 Glivec (1,485 patients, ranking number 1 in terms of number of patients), nr. 2 Revlimid (1,089 patients, rank 2) and nr. 3 Tracleer (900 patients, rank 5).

A2. Development of orphan drug prices

In the table below we present a detailed overview of the price development of the top-15 products for which SFK-data is available. The table shows that for most products the costs per DDD gradually decrease over time, even if there is still an orphan designation.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tobramycine</td>
<td>42.14</td>
<td>41.20</td>
<td>39.29</td>
<td>37.13</td>
<td>37.41</td>
<td>39.27</td>
<td>39.03</td>
<td>37.68</td>
</tr>
<tr>
<td>2</td>
<td>Sildenafil</td>
<td>15.73</td>
<td>15.79</td>
<td>15.69</td>
<td>16.02</td>
<td>15.44</td>
<td>15.12</td>
<td>14.84</td>
<td>14.89</td>
</tr>
<tr>
<td>5</td>
<td>Ambrisentan</td>
<td>109.76</td>
<td>109.36</td>
<td>104.49</td>
<td>102.97</td>
<td>100.17</td>
<td>98.95</td>
<td>93.50</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Hydrocortison</td>
<td>0.31</td>
<td>0.35</td>
<td>0.38</td>
<td>0.46</td>
<td>0.49</td>
<td>0.54</td>
<td>0.64</td>
<td>1.57</td>
</tr>
<tr>
<td>8</td>
<td>Velaglucerase alfa</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1409.34</td>
<td>1409.34</td>
<td>1409.29</td>
<td>1409.32</td>
</tr>
<tr>
<td>9</td>
<td>Ketoconazol</td>
<td>0.14</td>
<td>0.14</td>
<td>0.13</td>
<td>0.12</td>
<td>0.10</td>
<td>0.08</td>
<td>0.09</td>
<td>0.09</td>
</tr>
<tr>
<td>10</td>
<td>Amifampridine</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>83.07</td>
<td>80.80</td>
<td>79.98</td>
<td>80.06</td>
</tr>
<tr>
<td>12</td>
<td>Romiplostim</td>
<td>71.94</td>
<td>72.17</td>
<td>72.93</td>
<td>74.70</td>
<td>74.60</td>
<td>74.67</td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Stiripentol</td>
<td>15.75</td>
<td>15.67</td>
<td>15.16</td>
<td>14.88</td>
<td>14.73</td>
<td>14.83</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Ecorys. Based on SFK-data. Note: For certain products the cost per DDD is missing in the source data or contain only one or two observations; these are not presented. All of these products still have an orphan designation; between brackets the year of the designation is indicated. The top-15 is based on the data for 2014.

The data shows that for most products the costs vary over the years between +5% and -10%. Ketoconazol is an exception, but has a very low absolute value (9 cents in 2014). This is visualized in the next figure. Also, Hydrocortison shows a different pattern: over the period 2007-2014 the costs multiply by five (not shown).
A3. Cost assessment orphan drugs protection

In relation to the assessment of the protection costs for orphan drugs the following assumptions / steps have been made.

**Overall expenditures** – Kanters (2014) estimated the total expenditures for orphan drugs to be €260 million in 2012, including inpatient (€ 85 million) and outpatient drugs (€ 175 million). This division is outdated due to the fact that in 2012 a number of expensive drugs were shifted from the national health budget to the hospital budget. There is no other (more recent) estimation available. If we assume that the expenditures on orphan drugs increase 8% per year (which was the case in 2011 and 2012), the expenditures in 2014 were approximately €303 million. This estimation is in line with the estimation from the NZa (€ 177 million for the top-5 inpatient orphan drugs) and the data from the SFK (€ 44 million for the top-15 outpatient drugs).

The article of Kanters (2014) indicated that in 2011-2012 the top-11 orphan drugs covered approximately 70-80% of the overall expenditures on orphan drugs. Most likely this estimation of 70% is still applicable for 2014: € 177 million for the top-5 inpatient drugs (NZa-data) and € 26 million for the top-5 outpatient drugs (SFK-data). We assume that the top-15 covers 80% of the overall expenditures (€ 240 million) and that the average cost for a top-15 product is € 16 million.

**Expiration of orphan drug designations** – Since the introduction of the orphan drug regulation approximately 120 medicines received a market authorisation and benefit from the 10 year market exclusivity. Every year approximately 10-15 products lose their market exclusivity (differs per year). A more detailed check of the most expensive orphan drugs shows that every year one or two ‘blockbusters’ lose their market exclusivity, e.g. Bosentan in April 2012, Pegvisomant in November 2012 and Laronidase in June 2013. We assume that every year two top-15 products will lose their market exclusivity status.

**Price decrease after expiration** – The sector enquiry of DG COMP observed a price decrease of 25% (of the original product) after the end of the patent and the entry of a generic medicine provider and even 40% after two years. The detailed SFK-data for a limited number of products suggests
that, despite the fact that products still benefit from their market exclusivity status, the costs per DDD gradually decrease with 0-10% per year. The price decrease after expiration of the market exclusivity for the two ‘blockbusters’ Pegvisomant (-13%) and Bosentan (-30% over a longer period) is more or less in line with the estimation of DG COMP. We assume that the price decrease after the expiration of the market exclusivity is 25% per year, while the number of DDDs stays stable.

**Cost assessment** – The main societal costs are related to the additional two years of market exclusivity (and higher price). Given an average cost of €16 million per product, two expiring products per year and a price decrease of 25%, the overall costs of protection are €8 million per year for a period of two years.

Every year the market exclusivity expires for two products (total expenditures are two times 16 million = €32 million). Without the market exclusivity-delay the expenditures of these products would decrease in one year with 25% (reduction of €8 million, from €32 million to €24 million). With the extended market exclusivity this decrease in expenditures is delayed with two years, which results in a cost of protection of €8 million per year for a period of two years.

**A4. Overview of products with a SPC-extension (for the Netherlands)**

In the table below we present an overview of the products which received a SPC-extension, including the year of the decision by the Dutch Patent Office. Also, decisions which are pending are shown.

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Year of decision</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SPC-extensions 2010</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caspofungin – Cancidas</td>
<td>Granted 2010</td>
<td></td>
</tr>
<tr>
<td>Losartan – Cozaar</td>
<td>Granted 2010</td>
<td></td>
</tr>
<tr>
<td>Anastrozole – Arimidex</td>
<td>Granted 2010</td>
<td></td>
</tr>
<tr>
<td>Valsartan – Diovan</td>
<td>Granted 2010</td>
<td></td>
</tr>
<tr>
<td>Abatacept – Orencia</td>
<td>Granted 2010</td>
<td></td>
</tr>
<tr>
<td>Zoledronic acid - Zometa</td>
<td>Granted 2010</td>
<td></td>
</tr>
<tr>
<td><strong>Atorvastatin – Sortis</strong></td>
<td>Pending 2010</td>
<td></td>
</tr>
<tr>
<td><strong>SPC-extensions 2011</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Latanoprost – Xalatan</td>
<td>Granted 2011</td>
<td></td>
</tr>
<tr>
<td>Montelukast – Singular</td>
<td>Granted 2011</td>
<td></td>
</tr>
<tr>
<td><strong>Clopipogrel – Plavix</strong></td>
<td>Pending 2011</td>
<td></td>
</tr>
<tr>
<td><strong>SPC-extensions 2012</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etaanercept – Entrel</td>
<td>Granted 2012</td>
<td></td>
</tr>
<tr>
<td>Infliximab – Remicade</td>
<td>Granted 2012</td>
<td></td>
</tr>
<tr>
<td>Nevirapine – Viramune</td>
<td>Granted 2012</td>
<td></td>
</tr>
<tr>
<td>Rizatriptan – Maxalt</td>
<td>Granted 2012</td>
<td></td>
</tr>
<tr>
<td><strong>Aripiprazole – Abilify</strong></td>
<td>Pending 2012</td>
<td></td>
</tr>
<tr>
<td><strong>Clopipogrel – Plavix</strong></td>
<td>Pending 2012</td>
<td>Also pending in 2011</td>
</tr>
<tr>
<td><strong>SPC-extensions 2013</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tiotropium bromide – Spiriva</td>
<td>Granted 2013</td>
<td>Is reported twice as ‘granted’ (2013 and 2014)</td>
</tr>
<tr>
<td>Tolvaptan – Samsca</td>
<td>Granted 2013</td>
<td></td>
</tr>
<tr>
<td><strong>SPC-extensions 2014</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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How well does regulation work?

### Product Name (INN – Invented name)

<table>
<thead>
<tr>
<th>Product Name</th>
<th>Year of decision</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Imatinib – Glivec</td>
<td>Granted 2014</td>
<td>Is reported twice as ‘granted’ (2013 and 2014)</td>
</tr>
<tr>
<td>Tiotropium bromide – Spiriva</td>
<td>Granted 2014</td>
<td></td>
</tr>
<tr>
<td>Voriconazole – Vfend</td>
<td>Granted 2014</td>
<td></td>
</tr>
<tr>
<td>Rupatadine – Rupafin</td>
<td>Granted 2014</td>
<td></td>
</tr>
<tr>
<td>Aripiprazole – Abilify</td>
<td>Pending 2014</td>
<td>Also pending in 2014</td>
</tr>
<tr>
<td>Colesevelam – Cholestagel</td>
<td>Pending 2014</td>
<td></td>
</tr>
<tr>
<td>Tolvaptan – Samsca</td>
<td>Pending 2014</td>
<td>This seems to be a mistake, already granted in 2013</td>
</tr>
<tr>
<td>Bosentan – Tracleer</td>
<td>Pending 2014</td>
<td></td>
</tr>
<tr>
<td>Valganciclovir – Valcyte</td>
<td>Pending 2014</td>
<td></td>
</tr>
<tr>
<td>Entecavir – Baraclude</td>
<td>Pending 2014</td>
<td></td>
</tr>
<tr>
<td>Vaccine against human papillomavirus - Gardasil</td>
<td>Pending 2014</td>
<td></td>
</tr>
</tbody>
</table>

Source: Annual Reports (2007-2014) to the European Commission on ‘companies and products that have benefited from any of the rewards and incentives in the Paediatric Regulation and on the companies that have failed to comply with any of the obligations in this Regulation’. Note: for the years 2007-2009 no information was provided.

### A5. Cost assessment drugs with a paediatric indication and SPC-extension

**Overall expenditures** – Based on the list of SPC-extensions (granted or pending, see A4) and the data availability in the SFK-database we selected the top-15 products with the highest outpatient expenditures in 2014. This is presented in the next table. In 2014, the overall outpatient expenditures for this top-15 were approximately € 161 million.

**Expenditures on drugs with paediatric indication and SPC extension (outpatient 2014)**

<table>
<thead>
<tr>
<th>Rank</th>
<th>Top-15 in 2014 (INN)</th>
<th>Overall costs (x € 1,000)</th>
<th>DDDs (x 1,000)</th>
<th>Costs/ DDDs (€)</th>
<th>% of total</th>
<th>EGA (x € 1,000)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Tiotropium (2013)</td>
<td>87,027</td>
<td>63,225</td>
<td>1.38</td>
<td>53.9%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Aripiprazol *</td>
<td>19,729</td>
<td>3,964</td>
<td>4.98</td>
<td>12.2%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Atorvastatin *</td>
<td>10,784</td>
<td>182,616</td>
<td>0.06</td>
<td>6.7%</td>
<td>347,700</td>
</tr>
<tr>
<td>4</td>
<td>Nevirapine (2012)</td>
<td>9,378</td>
<td>1,324</td>
<td>7.08</td>
<td>5.8%</td>
<td>29,900</td>
</tr>
<tr>
<td>5</td>
<td>Entecavir *</td>
<td>6,691</td>
<td>496</td>
<td>13.49</td>
<td>4.1%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Voriconazol (2014)</td>
<td>5,578</td>
<td>82</td>
<td>68.18</td>
<td>3.5%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Valganciclovir *</td>
<td>4,882</td>
<td>103</td>
<td>47.45</td>
<td>3.0%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Valsartan (2010)</td>
<td>4,112</td>
<td>81,272</td>
<td>0.05</td>
<td>2.5%</td>
<td>85,300</td>
</tr>
<tr>
<td>9</td>
<td>Rizatriptan (2012)</td>
<td>3,419</td>
<td>2,417</td>
<td>1.41</td>
<td>2.1%</td>
<td>29,300</td>
</tr>
<tr>
<td>10</td>
<td>Losartan (2010)</td>
<td>3,341</td>
<td>98,220</td>
<td>0.03</td>
<td>2.1%</td>
<td>126,900</td>
</tr>
<tr>
<td>11</td>
<td>Clopidogrel *</td>
<td>2,572</td>
<td>33,852</td>
<td>0.08</td>
<td>1.6%</td>
<td>111,700</td>
</tr>
<tr>
<td>12</td>
<td>Zoledronic (2010)</td>
<td>2,096</td>
<td>13</td>
<td>156.45</td>
<td>1.3%</td>
<td>17,600</td>
</tr>
<tr>
<td>13</td>
<td>Colesevelam *</td>
<td>812</td>
<td>228</td>
<td>3.55</td>
<td>0.5%</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Anastrozol (2010)</td>
<td>539</td>
<td>4,614</td>
<td>0.12</td>
<td>0.3%</td>
<td>48,800</td>
</tr>
<tr>
<td>15</td>
<td>Rupatadine (2014)</td>
<td>221</td>
<td>813</td>
<td>0.27</td>
<td>0.1%</td>
<td></td>
</tr>
</tbody>
</table>

**Top-15** 161,179 99.9% 797,300

Source: Ecorys. Based on SFK-data. Note: The column '% of total' refers to the percentage of the overall costs for products with a SPC-extension (€ 161 million in 2014). The * refers to products for which the SPC-extension was still pending in 2014. The year (for example 2012) is reflecting the decision year of the SPC-extension.
As indicated in the main report (Chapter 5) the overall expenditures (inpatient and outpatient) on drugs with a paediatric indication and a SPC extension are not clear. For this specific group of products, the EGA provided for eight products estimated 2012 annual sales data (inpatient and outpatient), which is shown in the last column.\textsuperscript{173}

Given the uncertainty of the overall inpatient costs, we assume that the overall expenditures for the top-15 are approximately € 700 million per year. This gives an average expenditure of € 47 million per product per year.

**Expiration of the SPC-extension** - For the period 2010-2014 the Dutch Patent Office granted to 18 products the 6-month extension, which implies that on average three SPC-extensions expire per year. This is more or less in line with the overview of top-15 products above (four products in 2010, two products in 2012, one product in 2013, and two products in 2014). We assume that on average every year three of the top-15 products will lose their SPC-extension.

**Price decrease after expiration** – As shown in the main report the detailed SFK data shows that for some products the prices drop significantly after the expiration of the SPC-extension, even up to 70-80% after a few years. The sector enquiry of DG COMP provides a more robust estimation for regular pharmaceuticals, with an observed price decrease of 25% (of the original product) after the end of the patent and even 40% after two years. We assume that the price decrease after the expiration of the SPC-extension is 25% per year, while the use of the product stays stable.

**Cost assessment** – The main societal costs are related to the additional six month of SPC-protection, which delays the access of generic products and a price decrease. Given an average cost of € 33 million per product, three expiring SPC-extensions per year, a price decrease of 25% and an additional protection period of six month, the overall costs of protection are approximately € 18 million per year.

\textsuperscript{173} European Generic Medicines Association, ‘EGA contribution to EC public consultation on general Report on experience acquired as a result of the Application of the Paediatric Regulation’, November 2012. Please note that this paper seems to suggest (table p. 8) that in 2012 eleven products ‘lost’ their SPC-extension, which is not in line with the overview of the decisions of the Dutch Patent Office (see under A4).
Annex B  Case studies

Registration of an orthopaedic ATMP

Input derived from an expert in the area of ATMPs

Orthopaedic surgery or orthopaedics (sometimes spelled orthopaedic surgery and orthopaedics) is the branch of surgery concerned with conditions involving the musculoskeletal system. The knee clinic of the Mobility in UMC Utrecht works on patient-oriented progressive treatment methods against joint damage. In particular, the focus lies on cell therapy for cartilage defects. The first two ATMPs that were registered in Europe entail cartilage therapy solutions by autologous chondrocyte transplantation (ChondroCelect and MACI). The scientific basis for this therapy was provided by multidisciplinary studies conducted in several European centres with the UMC Utrecht (Saris) as lead author. Based on more than 10 years of experience the team concluded that there is a strong need for a solution in which cell therapy is applied. This application can take place in a patient-oriented setting with clear improvement and cost reduction as a result. In conjunction with colleagues of regenerative medicine, the fundamental researchers from the department of orthopaedics, the cell therapy facility and patients, the team of Saris decided to work on the development of IMPACT.

The mechanism of ATMP including the "need met"

IMPACT is a cell therapy solution for cartilage defects which can be used in an operation. Cartilage can not repair itself when trauma or disease causes damage to the joint surface. The current treatment consists of two operations. First an arthroscopy whereby cartilage is taken from the joint and subsequently grown for three months at an external biotech company and placed back in in the joint as part of an open procedure. Next, the rehabilitation begins and can take between 12 and 18 months.

IMPACT is designed in a way in which the patient's own cartilage is recycled and can be combined with stem cells from the donor bank. In an operation, the damaged cartilage defect is cleaned, and the tissue that is released in this process is used to obtain chondrons. These are cells with a small piece of cartilage matrix which contains the extra cellular communication. As the cell number is far too low for the recovery of such symptomatic defects, it is mixed with MSCs donor cells from the stem cell bank. Our hypothesis is that the stem cells around the joint feel calmed and emit appropriate growth signals by which recycled cartilage cells from the patient themselves have the ability to properly recover, resulting in a treatment that provides cell therapy for cartilage damage of large defects in an operation and is unique in the world.

Selected route

In order to achieve this goal, the IMPACT-project was carefully designed consisting of several phases. Initially, scientific recycling of own cartilage was tested. Some animal experiments were then done to establish proof of concept. In parallel, the health technology assessment department at the University of Twente was consulted for a cost effectiveness analysis. The objective was to examine what the feasible cost of the new therapy might be to fit within the care system and help achieve a relevant cost reduction. These studies showed it would be feasible for a quarter of the cost impact as an innovative therapeutic treatment. We felt that impact as ATMP had to be realized in practice and as a result chose not to use the hospital exemption. In an early stage, we had a preliminary discussion with the CCMO. The unique nature and the use of allogeneic stem cell genes were discussed, allowing us to use the advice of CCMO and other experts in our project.
As a result, we came up with an effective way to design a clinical study with an ATMP cartilage cell therapy with humans. A subsidy from ZonMw was obtained and a translational adult stem cell funding allowed us to complete the impact trial within two years. Through social media, the national media, peer referral etc., patients quickly found out about this therapy and requested to participate in the study.

**Observations regarding the registration process**

With this project, we managed to move from a hypothesis through basic research and proof of concept studies for a first-in-man clinical trial in a period of just three and a half year. Although the benefits included patient-focused innovation, cost savings and better quality, we had to overcome a number of obstacles.

The ATMP legislation in Europe is severely restrictive and subject to changes. The resulting complexity and burden in terms of time and costs are too high for an academic institution, especially considering that no biotech firm is involved and no government subsidies are available for such projects.

An example of the excessive nature of the ATMP rules is the fact that while earlier it was sufficient to prove that tissue engineering products resulted in structural repair, now we need to prove that the tissue is really recovered. This implies that all patients should receive a second operation with a biopsy of the tissue. Of course, there is much resistance as: a) fine tissue repair does not always mean absence of complaints and b) there are fortunately many patients who experience a better quality of life after the treatment and who are very satisfied, while under the microscope not 100% normal tissue has grown.

In addition, the committee requires not one RCT, but two. From a scientific point of view, this is not necessary and it also doubles the already high costs for one RCT.

Despite the fact that the treatment has proven to be safe and feasible, current law and regulations may still prevent it from being used among patients. Although it is undesirable to return to the old situation with inadequate safety regulations, the current structure leaves no other conclusion than that it inhibits innovation and limits care. In fact, it is only possible for publicly listed companies with massive budgets and projects.

**Bottlenecks**

European ATMP registration is subject to change and unfeasible rigorous and complex to physicians and researchers. As a result, there is no level playing field compared to the device industry and associated regulations.

It may take years between registration of a therapy or product and termination of the Phase III study. During that period no suitable therapy would be available to patients.

Insurers in the Netherlands often consider new innovative treatments as ‘experimental’ or ‘unproven’ allowing them not to take responsibility for new innovations in healthcare. New treatments are often considered only from a financial point of view. Despite the fact that the treatment saves costs over time, no insurer has contracted it yet.

**Suggestions for improvement**

At present, the CAT consists of members from every MS. These may change frequently and not every member is an expert from the field of ATMP. This sometimes results in decisions that are
influenced by personal opinions of non-experts. Decision-making should be based on expert knowledge rather than on votes for every MS.

Expert panels could be organized for specific registration-related issues, for example, in the area of research methodology. Research methods differ in terms of applicability, but the members of the CAT seem unaware of this. An expert panel could help solve this issue. In addition, diminishing the administrative burden and shortening procedures could help to facilitate to registration process.
Developing an orphan and paediatric medicine

Input derived from an expert in the area of orphan drug with a paediatric application

Our expert is involved with the development of Khondrion KH176. This is an orphan drug with a paediatric application for a Mitochondrial Disease (for more information, see box below). His work includes an analysis of norms set to obtain marketing authorisation. Already it is evident that meeting these norms requires a huge investment, although certain norms should be applied to prevent accidents from happening.

In general, Dr. Spaans perceives the registration process as a part of the job although to amount of requirements radiate distrust. The quality system itself has become excessive focusing on traceability although this does not automatically guarantee better drugs.

Big pharmaceutical companies are doing a good job in meeting the requirements while start-up companies simply lack the capacity to do so. As some standards are being developed in conjunction with quality departments of big pharmaceutical companies, it will become increasingly difficult for small companies.

Being a developer himself, he considers the regulations for orphan drugs and paediatric medicines as a single set of rules. Although in theory it might be more effective to conduct paediatric research in the US, no decision was made to actually do so. Working according to the paediatric investigation plan is extremely elaborate and costly.

Mitochondrial Disease

Within all cells of the human body, mitochondria act as a powerhouse – collectively producing energy that is essential for life. When these mitochondria are defective, the result can take the form of a wide range of serious and debilitating illnesses. Signs and symptoms of mitochondrial diseases can include: fatigue, intolerance to exercise, muscle weakness and loss of muscle coordination, heart failure, diabetes, deafness, blindness, stunted growth, and learning disabilities (see figure below for details). Leigh Disease, MELAS, LHON and Friedreich Ataxia belong to the ever-expanding group of mitochondrial diseases. Mitochondrial failure is usually the result of genetic defects in either the mitochondrial DNA or the nuclear DNA, but can also be caused by environmental factors, including adverse reactions to certain drugs. While it is possible to alleviate several clinical problems, including diabetes, there is still no cure for mitochondrial disease. That's why at Khondrion, we strive to contribute all we can to finding a cure for mitochondrial diseases.

Source: http://www.khondrion.com/

Paediatrics

The applicability of the paediatric investigation plan could be enhanced by making some adaptations. There is a strong need for developing drugs based on existing therapies, while the regulations focus primarily on the development of new therapies.

Some companies decide not to communicate with EMA as based on the information shared EMA can decide for which indication one should develop a therapy. They may even require a developer to conduct research for another indication. This is difficult to deal with as it may have a big impact on scientific agendas.
For example, CD6/9 inhibitors can be used for various indications (e.g. in the area of oncology or immune diseases). Registration was based on just a single indication while six competing paediatric investigation plans have been filed as well. Clearly, more coordination and cooperation would be beneficial. This could include a fund to finance research on paediatric therapies.

**Orphan drugs**

The number of scientific advisors with experience in the area of drug development is limited. As a result, their rules and procedures do not fit well with current research processes applied throughout the industry.
Sound analysis, inspiring ideas