

# **The New Paediatric Regulation in the EU – Development, Implications and Comparison with US Experiences in Paediatric Drug Development**

**Wissenschaftliche Prüfungsarbeit**

zur Erlangung des Titels

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vorgelegt von

**Martin Watzl**  
aus Aschaffenburg

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Betreuerin / 1. Referentin: Dr. Rose Schraitle  
2. Referentin: Dr. Christine Mayer-Nicolai

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## List of Abbreviations

AIDS	Acquired Immunodeficiency Syndrome
ANDA	Abbreviated New Drug Application
ADR	Adverse Drug Reaction
AFSSAPS	Agence Française de Sécurité Sanitaire des Produits de Santé (French Medicines Agency)
BPCA	Best Pharmaceuticals for Children Act
BPD	Bronchopulmonary Dysplasia
BLA	Biologic License Application
BMBF	Bundesministerium für Bildung und Forschung (Federal Ministry of Education and Research)
CBER	Center for Drug Evaluation and Research
CDER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulation
CHMP	Committee for Medicinal Products for Human Use (before 20 May 2004: CPMP)
CICP	Paediatric Clinical Investigation Centre
CMD(h)	Coordination Group for Mutual Recognition and Decentralised Procedure – Human
CNS	Central Nervous System
COMP	Committee for Orphan Medicinal Products
CPMP	Committee for Proprietary Medicinal Products (since 20 May 2004: CHMP)
EC	European Commission
EEC	European Economic Community
EFPIA	European Federation of Pharmaceutical Industries Associations
EGA	European Generic Medicines Association
EMA	European Medicines Agency
EU	European Union
FAQ	Frequently Asked Questions

FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
FINPEDMED	Finnish Investigators Network for Paediatric Medicines
FP7	Seventh Framework Programme
GER	Gastrooesophagealreflux
GCP	Good Clinical Practices
HHS	United States Department of Health & Human Services
HIV	Human Immunodeficiency Virus
HMA	Heads of Medicines Agencies
ICH	International Conference on Harmonisation
IND	Investigational New Drug Application
INSERM	Institut National de la Santé et de la Recherche Médicale
IOP	Intraocular Pressure
IPR	Intellectual Property Rights
KKS	Koordinierungszentrum für Klinische Studien (Coordination Centre for Clinical Studies)
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MCRN	Medicines for Children Research Network
MS	Member State
NCA	National Competent Authority
NDA	New Drug Application
NICHD	National Institute of Child Health and Human Development
NIH	National Institutes of Health
OTC	Over The Counter
PAED-Net	Pädiatrisches Netzwerk (Paediatric Network)
PDCO	Paediatric Committee
PEG	Paediatric Working Party
PIP	Paediatric Investigation Plan

PL	Package Leaflet
PPSR	Proposed Pediatric Study Request
PUMA	Paediatric Use Marketing Authorisation
PREA	Paediatric Research Equity Act
Q&A	Questions and Answers
R&D	Research and Development
RMP	Risk Management Plan
SAWG	Scientific Advice Working Group
SME	Small and Medium-Sized Enterprises
SmPC	Summary of Product Characteristics
SPC	Supplementary Protection Certificate
SICA	Specific International Cooperation Actions
UK	United Kingdom
UKCRN	UK Clinical Research Network
US	United States (of America)

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## Explanatory Notes

The names used in this Master Thesis for Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use, amended by Regulation (EC) No 1902/2006, include the following: “Paediatric Regulation”, “new Paediatric Regulation” and “Regulation”.

When reference is made to articles or recitals of Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use, amended by Regulation (EC) No 1902/2006, the Regulation itself is not included in the reference. As far as other legislative texts are concerned the reference always includes the identifier of the Regulation or Directive as well as the respective article.



## **1 INTRODUCTION – OR WHY THERE IS A NEED TO STUDY MEDICINES IN CHILDREN**

Before any medicine is authorised for human use, the product must have undergone extensive testing including pre-clinical tests and clinical trials to ensure that it is safe, of high quality and effective for use in the target population. In contrast, it has been demonstrated that in the European Union (EU) more than 50 percent or more of medicines used in children have never been actually studied in this population and are not authorised for such purpose. Most medicines used in children have been tested only in adults, and, not necessarily in the same indication or the same disease.

In the 27 Member States of the EU, the paediatric population represents more than 100 million people, i.e. about 20 percent of the total population. This is a vulnerable group with developmental, physiological and psychological differences to adults, which makes age and development related research of medicines particularly important.

The use of unlicensed and off-label medicines in children is widespread and it has been an increasing concern over the last years. A doctor prescribing an untested, unlicensed medicinal product for a child in Europe can not be sure that the “off-label” medicine will be truly effective, can not be sure what dose is really appropriate and can not predict exactly what adverse drug reactions (ADRs) the child may suffer, i.e. the risk-benefit assessment for the treatment of children remains unknown.

Additionally, the general lack of information and appropriate pharmaceutical formulations to support the administration of many medicines to children may expose them to unwanted side effects or under dosing without the expected efficacy. The need for more studies to obtain paediatric information for medicines used in children has become a matter of consensus on a global basis.

However, even if there is a clear need for medicines for children, there has been no legal obligation in the EU for a pharmaceutical company to perform studies if it does not intend to develop the medicine particularly for use in the paediatric population.

So far industry has a free choice what medicines to develop, authorise and market. The main drivers of overall return on investment were the size of the target pharmaceutical market and the price achievable within this market. The number of children suffering specific diseases is generally lower than the number of adults and, in terms of research, “children” can not be considered as a single population (please see also section 3.4) so that paediatric studies may be more complex and more expensive. It was clear evidence that market forces alone have proved to be insufficient to stimulate adequate research into and the development and authorisation of medicinal products for children and the industry has thus considered that for many childhood diseases the potential return is insufficient to justify such investment in research and development.

Due to the lack of adequately tested, appropriately formulated and officially licensed medicinal products for paediatric use in the European Community and the lack of sufficient incentives for

the pharmaceutical industry to develop medicinal products for children, the European Parliament and the Council of the European Union issued the Regulation on medicinal products for paediatric use on December 12, 2006, the so-called Paediatric Regulation, which recently came into force, i.e. on January 26, 2007.

The overall objective of this Paediatric Regulation is to improve the health of the children of Europe by:

- Stimulating and facilitating the research and development of medicines for use in children,
- Ensuring that medicines used to treat children are appropriately tested and authorised,
- Ensuring the accessibility of medicinal products for use in the paediatric population,
- Improving the availability of information on the use of medicines in children in the various paediatric populations,
- Ensuring that medicinal products used to treat the paediatric population are subject to ethical research of high quality, i.e. clinical trials should be in full compliance with European Directive 2001/20/EC.

All these objectives should be achieved without conducting unnecessary clinical trials in the paediatric population and without delaying the authorisation of medicinal products for other populations, such as adults.

This is intended to be achieved through the underlying system including combined measures of both obligations and rewards and incentives which is often called the “stick” and the “carrot”. In fact, there are two types of provisions, namely substantive provisions, including core requirements, rewards, incentives, support and facilitating measures that form its core as well as procedural provisions, such as infrastructure, administrative procedures, legal and regulatory context.

All these measures are described and discussed in this Master Thesis after having provided information on the current situation in Europe and the development of the EU paediatric legislative framework. Further a comparison with the US Regulations for paediatric medicines, which have been proven to be extremely successful in stimulating the development of medicinal products for paediatric use, is provided in this Master Thesis.

## 2 CURRENT SITUATION IN EUROPE

It is common knowledge that a substantial proportion of medicines is prescribed to children in the absence of sound scientific evidence concerning the effectiveness of the drug, but the consequences of this are less well-known. The paediatric population represents a little less than one-quarter of the entire European population, but in general consume a considerably smaller proportion of the health care budget than their numbers might suggest. Nonetheless, the social obligations to protect children and their relative small number mean that medicines used by children cost a lot of money and have potentially major health consequences.

In the European Union the 0-18 years old population ranging from neonates to teenagers represents approximately 75 million people. Although this number may appear relatively large, the majority of medicines is still developed and assessed for use in adults only. Pharmaceutical companies have been reluctant to invest in developing specific treatments or adapting existing medicines to meet the needs of the paediatric population, mainly because the market is small and therefore of lower commercial interest and the studies are assessed to be difficult, long and expensive. In addition, developing a suitable formulation which can provide an exact dose, for example a syrup, may be technically difficult and expensive on an industrial scale. This often leaves no alternative to the prescriber than to use off-label and unauthorised products without evidence-based information to guide prescribing and give information about the risk-benefit assessment.

Based on that an unknown but significant percentage of all medicines used in children is unlicensed or prescribed off-label, i.e. outside the terms set in the product license and are prescribed off-label in relation to indication, age, dosage or frequency, route of administration or formulation. Estimates of the extent of this unlicensed and off-label use are highly dependent on location of care (hospital vs. office-based), diagnosis, age of the child and nationality. Studies in various hospital settings showed that many drugs taken by children either are not licensed or are used outside the terms of the product licence [9, 53, 54]. The European Commission estimates that somewhere between 50 and 90 percent of all medicinal products used in children (depending on therapeutic areas) have never been specifically evaluated for use in the paediatric populations [25].

Between 1995 and January 2006 the total number of active substances for which an approval was granted within the European Community was 258. For a considerable percentage thereof the approved adult indication is also relevant for paediatric needs but has not yet been tested in children (44% with a paediatric indication, 32% with a potential paediatric indication) [4].

There is a consensus that off-label use is widespread. There is, however, less of a consensus about the measures to avoid treatment with unlicensed medicines and the potential negative impacts of off-label use in children, e.g. when treatment leads to harm. Reporting of adverse drug reactions (ADRs) in children is neither comprehensive nor unified, but again, there is a common understanding that the incidence of ADRs is higher than would be desired. Although off-label use does not necessarily cause adverse events or leads to more ADRs, the research indicates at least some effects in that direction. [44]

Although there may be ethical concerns about conducting trials in the paediatric population, this has to be balanced by the ethical concerns about giving medicines to a population in which they have not been tested. The new European Union (EU) Directive on clinical trials lays down specific requirements to protect children who take part in clinical trials in the EU.

### **3 EUROPEAN PAEDIATRIC LEGISLATIVE FRAMEWORK**

#### **3.1 DEVELOPMENT**

##### ***What has been done in Europe so far?***

In 1997, the European Commission organised at the EMEA a round table of experts to discuss paediatric medicines. One of the conclusions at that time was that there was a need to strengthen the legislation, in particular by introducing a system of incentives. [22]

In 1998, the Commission supported the need for international discussion on the performance of clinical trials in children in the context of the International Conference on Harmonisation (ICH) - an organisation working on the harmonisation of pharmaceutical regulatory requirements between the EU, Japan and US. An ICH guideline was therefore agreed. The goal was to encourage and facilitate timely paediatric medicinal product development internationally; to provide an outline of critical issues in paediatric drug development and approaches to the safe, efficient, and ethical study of medicinal products in the paediatric population.

Subsequently the ICH guideline (ICH Topic E11 “Clinical Investigation of Medicinal Products in the Paediatric Population”) was transmitted according to the ICH process to the CPMP and released for consultation in October 1999. After the final approval by CPMP in July 2000, the guideline became the European guideline “Note for Guidance on Clinical investigation of medicinal products in the Paediatric Population” (E11) which is in force since January 2001 [12].

Furthermore, the Clinical Trials Directive 2001/20/EC on Good Clinical Practice for Clinical Trials was adopted in April 2001, and came fully into force in May 2004. This Directive takes into account some specific requirements for performing clinical trials in children, and in particular it lays down criteria for their protection in clinical trials.

##### ***How was the legislative process for a paediatric initiative in Europe?***

Following a discussion on a memorandum presented under the French presidency, the European Council of (Health) Ministers adopted a resolution on 14 December 2000 asking the European Commission to draw up a legislative proposal (Regulation) on this topic, which was considered a public health priority.

In November 2001, the European Commission organised a “brainstorming” meeting with representatives of Member States and research-based industry. This was followed by the release of a public consultation paper in February 2002 on “Better Medicines for Children – proposed regulatory actions in paediatric medicinal products”. This paper represented one of the first steps of the Commission to address the problem [35]. A reflection paper followed incorporating the comments received in June 2002. Over sixty sets of comments were received from interested

parties and these were taken into account when drafting the proposal for the Paediatric Regulation.

An ad-hoc working group of the Pharmaceutical Committee was established in 2003 to help develop the proposal and workshops and bilateral meetings were also held.

In March 2004, the European Commission consulted on a draft Regulation on medicinal products for paediatric use. Sixty-nine responses were received (including responses from European and national patient organisations, industry associations, societies of doctors and pharmacists, insurance organisations and ethics groups).

As a result of the Commission's Better Regulation Action Plan the proposed Regulation on medicinal products for paediatric use was subject to an Extended Impact Assessment. This aimed at analysing all economical, social and environmental consequences of any major Regulation and includes details on the public consultation conducted by the Commission. The legislative process could only start after this assessment. [27]

On 29 September 2004, the EU Commission released the first proposal for a Regulation on Medicinal Products for Paediatric Use together with an explanatory memorandum, the Extended Impact Assessment and a “questions and answers” document. Following the plenary vote of the European Parliament on the Commission's proposal on 7 September 2005, the Commission has responded to the parliamentary amendments in the form of a modified proposal. Finally it was adopted by the European Parliament and the Council on 12 December 2006.

The Council of Health Ministers reached political agreement on 9 December 2006. The proposal for a Regulation on Medicinal Products for Paediatric Use went into a second reading in the European Parliament.

On 27 December 2006 the Paediatric Regulation – Regulation (EC) No 1901/2006 as well as the amending Regulation (Regulation (EC) No 1902/2006) – were published in the Official Journal of the European Union. Both entered into force on **26 January 2007**.

### *What are the next steps?*

The implementation of the new Paediatric Regulation is a main priority for the European Medicines Agency (EMA) in its work programme for 2007.

The core of this new piece of legislation is the establishment of a new committee of scientific experts within the EMA – the Paediatric Committee (PDCO) – which should be operational within six months of the date of entry into force of the legislation, i.e. by 26 July 2007 [Article 3 (1)].

The Paediatric Committee's primary responsibilities will be the assessment and agreement of:

- Paediatric Investigation Plans (which set out measures for studying the medicinal product concerned in the paediatric population) (see section 4.1.2)
- Waivers (granted in certain circumstances where paediatric studies are not required or desirable) (see section 4.4.1)
- Deferrals (granted in certain circumstances where the initiation or completion of paediatric studies should be deferred until appropriate studies in adults have been performed) (see section 4.4.2).

The Paediatric Committee will also work with the EU Member States – building on work already performed by the EMEA's Paediatric Working Party (PEG) – to establish an inventory of the specific therapeutic needs of children, so that focus can be placed on the research, development and authorisation of medicines in areas where there are actually unmet medical needs (see sections 4.4.1 and 4.5.3). Paediatric Committee experts will also be advising the EMEA on its development of a European network for clinical trials in children, to be based on existing networks (see section 4.3.4).

An internal action plan for implementing the Paediatric Regulation is currently underway within the EMEA. As part of this, the EMEA and the European Commission published a joint document on their priorities for the implementation in September 2006. The EMEA has also published an FAQ document intended to help companies during the run-up to the entry into force of the new legislation [23, 24]

In order to define priorities for implementation of the Regulation the EMEA and European Commission has drawn up a joint implementation plan for the Regulation in September 2006 providing the implementation tasks to be the main focus of the work during 2006 and 2007 [42]. Based on that plan, a full list of actions to be taken in the future by EMEA, the Paediatric Committee, the European Commission and all Member States is presented in tabular format showing the various implementation tasks with reference to the Articles of the Paediatric Regulation, the lead responsibilities, and timelines (please refer to Table 1).

Table 1: Implementation Tasks Resulting From the Paediatric Regulation 1901/2006/EC (amended by Regulation 1902/2006/EC)

Topic	EMA	Paediatric Committee	European Commission	Member States
<b>PDCO</b>	<p>Establishment of the Paediatric Committee (PDCO) within the EMA by 26.07.2007 [Art. 3(1)]</p> <p>Appointment of 5 members of CHMP, other members by each MS (not represented through CHMP members), (+ alternates) [Art. 3(1), 4(1a,b)]</p> <p>Publication of the names and qualification of PDCO members [Art. 4(4)]</p>	<p>Drawing up PDCO's rules of procedure (for the implementation of its tasks) (must receive a favourable opinion by EMA and the approval by EC) [Art. 5(2)] and election of its chairman [Art. 4(3)]</p> <p>Publication of PDCO's definitive opinions on PIPs pursuant to articles 25(5) and (7) [Art. 5(1)]</p>	<p>Establishment of the PDCO, i.e. appointment of 3 members representing health care professionals and 3 members representing patient associations (+ alternates) [Art. 4(1c,d)]</p>	
<b>Inventory of Therapeutic Needs</b>	<p>Publication and regular updating of the inventory of therapeutic needs at the earliest by 26.01.2009 and at the latest by 26.01.2010 [Art. 43(1)]</p>	<p>Establishment and regular updating of a specific inventory of therapeutic needs based on data collected by the MSs on all existing uses of medicines in the paediatric population (after consultation of EC, MSs, interested parties) [Art. 6(1)(i), 43(1)]</p> <p>Provide guidance on the content and the format of the available data to be collected by the MSs on all existing uses of medicinal products in the paediatric population by 26.10.2007 [Art. 42]</p>		<p>Collection and communication of available data on all existing uses of medicinal products in the paediatric population to the EMA/PDCO by 26.01.2009 [Art. 42]</p>

Table 1: Implementation Tasks Resulting From the Paediatric Regulation 1901/2006/EC (amended by Regulation 1902/2006/EC) – continued (1)

Topic	EMA	Paediatric Committee	European Commission	Member States
<b>Pre-existing Studies</b>	<p>Publication of clinical trial results (whether or not the study was terminated prematurely) concerning submitted studies which started before and completed after 26.01.2007 (Art. 45), other MAH-sponsored studies which involve the use of the approved drug in the paed. population (Art. 46), and those studies carried out in 3<sup>rd</sup> countries and contained in an agreed PIP (Art. 41(1)) [Art. 41(2)]</p> <p>Coordination of information exchange between MSs regarding pre-existing studies and their implication for any MA concerned (incl. SmPC and PL updates) [Art. 45(1)]</p>		<p>Drawing up guidelines to establish assessment criteria for the significance of studies started before and completed after 26.01.2007 (in consultation with EMA) [Art. 45(4)]<sup>1</sup></p> <p>Drawing up guidelines (following consultation with EMA, MSs, and interested parties) [...] on how clinical trial results should be submitted and how to publish clinical trial results of submitted studies acc. to Articles 45 and 46, and on the EMA's responsibilities and tasks in this regard [Art. 41(3)]<sup>1</sup></p>	<p>Exchange of information regarding the submitted studies (started before and completed after 26.01.2007) and other MAH-sponsored studies which involve the use of the approved drug in the paediatric population as well as their implications for any concerned MA (e.g. SmPC and/or PL update) [Art. 45(1), 46(4)]</p>
<b>Paediatric Symbol</b>		<p>Recommendations for a "paediatric" symbol to the EC [Art. 32(2)]</p>	<p>Selection and publication of a "paediatric" symbol by 26.01.08 (following recommendation by the PDCO) (incl. meaning of the symbol to be included in the PL) [Art. 32(1)(2)]</p>	

<sup>1</sup> Please note that this task has been initiated by a joint working group involving the EMA and CMD(h) (see section 4.3.4).



Table 1: Implementation Tasks Resulting From the Paediatric Regulation 1901/2006/EC (amended by Regulation 1902/2006/EC) – continued (2)

Topic	EMA	Paediatric Committee	European Commission	Member States
<b>EudraCT Database</b>	<p>Publication of parts of the EudraCT database entries concerning paediatric clinical trials [Art. 41(1)(2)]</p> <p>Publication of clinical trial results [...] concerning those studies carried out in 3<sup>rd</sup> countries and contained in an agreed PIP (Art. 41(1)) [Art. 41(2)]</p>		<p>Drawing up guidelines (following consultation with EMA, MSs, and interested parties) on the nature of the information to be published in the EudraCT database entries concerning paediatric clinical trials, [...], and on the EMA's responsibilities and tasks in this regard [Art. 41(3)]<sup>2</sup></p>	<p>Inclusion of clinical trials (acc. to Art. 11 of Dir. 2001/20/EC) including those carried out in third countries and contained in an agreed PIP into the European database EudraCT [Art. 41(1)]</p>
<b>European Network</b>	<p>Development of a European network of existing national and European networks, investigators and centres with specific expertise in the performance of paediatric studies (with the scientific support of the PDCO) [Art. 44(1)]</p> <p>Adoption of an implementation strategy for launching and operation of the European network by 26.01.08 (following consultation with EC, MSs, interested parties) [Art. 44(3)]</p>			

<sup>2</sup> Please note that this task has been initiated by a joint working group involving the EMA and CMD(h) (see section 4.3.4).

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*Table 1: Implementation Tasks Resulting From the Paediatric Regulation 1901/2006/EC (amended by Regulation 1902/2006/EC) – continued (3)*

Topic	EMA	Paediatric Committee	European Commission	Member States
<b>Public Registers/ Public Lists</b>	<p>Maintenance and regular updating (at least annually) and publication of a list of all waivers [Art. 14(1)]</p> <p>Publication of EMA's decisions on PIPs [Art. 25(7)]</p> <p>Coordination and publication of register mentioning deadlines for placing products on the market after paediatric approval for already authorised medicinal products [Art. 33]</p> <p>Publication of MAHs intending to discontinue placing a paediatric medicinal product on the market [Art. 35]</p>		<p>Publication and regular updating of a detailed inventory of all rewards and incentives provided by the Community and MSs to support research into and the development and availability of medicines for paediatric use by 26.07.2008 [Art. 39(3)]</p>	
<b>Funding</b>			<p>Funds for research into off-patent medicinal products for the paediatric population should be provided in the Community budget, i.e. through the Community Framework Programmes [Art. 40]<sup>3</sup></p>	

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<sup>3</sup> Please note that this task has been fulfilled for the year 2007 (see section 4.5.2).

Table 1: Implementation Tasks Resulting From the Paediatric Regulation 1901/2006/EC (amended by Regulation 1902/2006/EC) – continued (4)

Topic	EMA	Paediatric Committee	European Commission	Member States
<b>Guidelines/ Measures to Specify the Regulation</b>	<p>Drawing up a specific procedure for possible consultation between PDCO, CHMP, COMP, their Working Parties and any other scientific advisory group [Art. 3(3)]</p> <p>Drawing up guidelines concerning measures ensuring follow-up of efficacy and possible ADRs to the paediatric use, specific risk management and risk minimisation systems, other pharmacovigilance activities, and annual reports in case of a deferral (Article 34) [Art. 34(5)]</p>		<p>Drawing up detailed arrangements concerning the format and content which applications for agreement or modification of a PIP and validation requirements for requests for waivers or deferrals and concerning the operation of the compliance check referred to in Articles 23 and 28(3) (after consultation with the MSs, EMA, and other interested parties) [Art. 10]<sup>4</sup></p> <p>Adoption of provisions (amendments or supplements of non-essential elements of the Regulation) on the basis of the experience acquired as a result of the operation of the Regulation (Article 20) to define further the grounds for granting a deferral [Art. 20(2)]</p>	

<sup>4</sup> Please note that this task has already been fulfilled. On 31 January 2007 the European Commission published its draft implementing guideline entitled *Commission guideline on the format and content of applications for agreement or modification of a Paediatric Investigation Plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies* for public consultation (Version January 2007). The public consultation period ended on 30 March 2007 and the final guideline is expected soon.

The New Paediatric Regulation in the EU – Development, Implications and Comparison with US Experiences in Paediatric Drug Development

Table 1: Implementation Tasks Resulting From the Paediatric Regulation 1901/2006/EC (amended by Regulation 1902/2006/EC) – continued (5)

Topic	EMA	Paediatric Committee	European Commission	Member States
<b>Reports on Experiences</b>	Preparation of a report about the companies and products that have benefited from any of the rewards and incentives in the Regulation and the companies that have failed to comply with any of the obligations in the Regulation based on the information provided by MSs. Submission of the list to EC [Art. 50(1)]		<p>Publication (at least annually) of a list of the companies and products that have benefited from any of the rewards and incentives in the Regulation and the companies that have failed to comply with any of the obligations (based on EMA's report) [Art. 50(1)]</p> <p>Presentation of a general report on the experience acquired as a result of the application of the Regulation to the European Parliament and the Council by 26.01.2013 including a detailed inventory of all medicinal products authorised for paediatric use since 26.01.2007 [Art. 50(2)]</p> <p>Presentation of a report on the experience acquired as a result of the application of Articles 36, 37 and 38 to the European Parliament and the Council by 26.01.2017, including an analysis of the economic impact of the rewards and incentives, together with an analysis of the estimated consequences for public health with a view to proposing any necessary amendments [Art. 50(3)]</p>	Submission of information on the companies and on the products that have benefited from any of the rewards and incentives in the Regulation and the companies that have failed to comply with any of the obligations in the Regulation to the EMA [Art. 50(1)]

The New Paediatric Regulation in the EU – Development, Implications and Comparison with  
US Experiences in Paediatric Drug Development

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*Table 1: Implementation Tasks Resulting From the Paediatric Regulation 1901/2006/EC (amended by Regulation 1902/2006/EC) – continued (6)*

Topic	EMA	Paediatric Committee	European Commission	Member States
<b>Penalties</b>			<p>Imposition of financial penalties (upon request by EMA) for infringements of the provisions or the implementing measures as far as CP products are concerned [Art. 49(3)]</p> <p>Publication of names of anyone infringing the provisions of the Regulation or of any implementing measures adopted (incl. amount of and reason for the financial penalties imposed) [Art. 49(4)]</p>	<p>Determination and implementation of penalties to be applied for infringement of the provisions and implementing measures of the Regulation as far as MRP and DCP medicinal products are concerned. Information of EC of these provisions by 26.10.2007 and subsequent alterations as soon as possible [Art. 49(1)]</p> <p>Immediate information of EC of any litigation instituted for infringement of the Regulation [Art. 49(2)]</p>
<b>Other Tasks</b>	Provision of free Scientific Advice on paediatric development plans (incl. quality, efficacy, safety in general and pharmacovigilance, RMPs, design and conduct of tests and studies in particular) [Art. 26]			Communication of detailed information of any national measures enacted to support research into and the development and availability of medicines for paediatric use to the EC by 26.01.2008 (including regular updates upon request by EC) [Art. 39(2)]

### 3.2 LEGAL BASIS AND FRAMEWORK

The Paediatric Regulation was drawn up on the experience gained with the existing regulatory framework for medicines in Europe, taking into consideration the requirements and incentives for paediatric medicines in the US and the EU Orphan Regulation. As mentioned above, these have shown that market forces alone cannot deliver the medicines needed to treat childhood diseases and that a balanced package of measures including requirements, rewards and incentives and support measures are required to stimulate the pharmaceutical industry into researching, developing and authorising medicines for children. On the basis of the available evidence it was concluded that it is unlikely that the previous public health issue regarding medicines for children could be resolved in the EU until a specific legislative system is put in place.

The new Paediatric Regulation directly interfaces with five existing Community legislative texts. These are:

- Directive 2001/83/EC (as amended) of the European Parliament and of the Council of 6 November 2001 which sets the framework for the Regulation of medicinal products
- Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 which establishes the EMEA and created the centralised authorisation procedure for medicinal products
- Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 which provides a framework for the Regulation and conduct of clinical trials in the Community (Clinical Trials Directive)
- Regulation (EC) No 141/2000 of the European Parliament and of the Council which establishes a Community system for the designation of medicinal products as orphan medicinal products and incentives to stimulate their development and authorisation, and
- Council Regulation (EEC) No 1768/92 of 18 June 1992 which created the Supplementary Protection Certificate (SPC). [10, 13, 14, 46, 49]

The new Paediatric Regulation utilises the existing Community framework for the Regulation of medicines including the EMEA, committee structures, marketing authorisation procedures, protection of clinical trial subjects, and databases. As will be discussed later, the Regulation includes various key measures that are directly built on the existing regulatory framework. Since a Regulation is binding for all Member States of the Community there is no need for implementing the provisions on a national basis. If such measures were to be adopted in a national and may be uncoordinated manner by the Member States this would create obstacles to intra-Community trade, distort competition and impede the achievement of a single market.

However, Member States will have an important role in the fulfilment of the objectives of the Regulation. The new Regulation invites them to introduce national incentives for research and development of medicinal products for paediatric use and for placing such products on the market, within the framework of their own powers and responsibilities. Member States may wish to consider the training of doctors and other healthcare professionals needed to conduct clinical trials in children, the investment in infrastructure, such as clinical trials centres, needed for clinical trials and funding for clinical trials, particularly where industry is unlikely to invest. Member States may also wish to consider whether the increased supply of robustly tested, authorised medicinal products for children should be complimented by national actions to

encourage the prescription by doctors and use of these medicines in preference to off-label and unlicensed use.

### **3.3 SCOPE**

As laid down in Article 6, the Paediatric Regulation should apply to all medicinal products required for paediatric use and therefore its scope should cover products under development and yet-to-be authorised products covered by intellectual property rights as well as authorised products no longer covered by intellectual property rights.

As detailed in Regulation (EC) No. 1901/2006, recital 11, it is required to present either the results of studies in the paediatric population in accordance with an agreed Paediatric Investigation Plan (PIP) (see section 4.1.2) or to provide the proof of having obtained a waiver or deferral (see sections 4.4.1 and 4.4.2) at the time of filing a marketing authorisation application or an application for a new indication, new pharmaceutical form or new route of administration.

Nevertheless there are some exceptions from the requirements laid down in the Paediatric Regulation:

- Generics or similar biological medicinal products
- Medicinal products authorised through the well-established medicinal use procedure
- Homeopathic medicinal products and
- Traditional herbal medicinal products [Article 9].

### **3.4 AGE CLASSIFICATION OF PAEDIATRIC POPULATION**

Any classification of the paediatric population into age categories is to some extent arbitrary, but a classification such as the one presented in ICH guideline E11, provides a basis for thinking about study design in paediatric patients. Decisions on how to stratify study data by age need to consider developmental biology and pharmacology. Thus, a flexible approach is necessary to ensure that paediatric studies reflect current knowledge of paediatric pharmacology. Furthermore the identification of ages to be studied should be product-specific and justified and thus have to be assessed on a case-by-case basis by applicants and competent authorities.

If the clearance pathways of a medicinal product are well established and well understood, age categories for pharmacokinetic evaluation might be chosen based on any “break point” where clearance is likely to change significantly. Sometimes, it may be more appropriate to collect data over broad age ranges and examine the effect of age as a continuous covariant. For efficacy, different endpoints may be established for paediatric patients of different ages, and the age groups might not correspond to the ICH categories presented below. Dividing the paediatric population into many age groups might needlessly increase the number of patients required. In longer term studies, paediatric patients may move from one age category to another. The study design and statistical plans should prospectively take into account changing numbers of patients within a given age category. [12]

The ICH guideline E11 categorises paediatric age groups as follows. There is, however, considerable overlap in developmental (e.g. physical, cognitive, and psychosocial) issues across those categories (ages are defined in completed days, months, or years).

- Preterm newborn infants (born at < 36 weeks of gestation)
- Term newborn infants (0 to 27 days)
- Infants and toddlers (28 days to 23 months)
- Children (2 to 11 years)
- Adolescents (12 to 16-18 years; dependent on the region)

All of these age categories are described in more detail within the following sections focussing on the homogeneity of each age group, potential differences within each age category and the potential impact on design and conduct of paediatric studies with a focus on specific pharmacological aspects.

### **3.4.1 Preterm Newborn Infants (born at < 36 weeks of gestation)**

The category of preterm newborn infants is not a homogeneous group of patients due to differences in the estimated gestational age (maturity) at birth and birth weight. In case of low birth weight, a further distinction must be made based on whether they are immature or growth retarded.

Because of the unique pathophysiology and responses to therapy in this population, clinical trials in preterm newborn infants are highly challenging. Furthermore, several study design issues make the outcomes difficult to assess, e.g. weight and age stratification, small blood volumes and small numbers of patients at a given centre. The complexity of and ethical considerations involved (see section 3.5) in studying preterm newborn infants require a very careful protocol development with expert input from e.g. neonatologists and neonatal pharmacologists. The likelihood and possibility to extrapolate efficacy results from studies in adults or even in older paediatric patients to the preterm newborn infant is deemed to be very low.

Important features that should be considered for these patients include: (1) gestational age at birth and age after birth; (2) immaturity of renal and hepatic clearance mechanisms; (3) protein binding and displacement issues (particularly bilirubin); (4) penetration of medicinal products into the central nervous system; (5) unique neonatal disease states (e.g., respiratory distress syndrome of the newborn, patent ductus arteriosus, primary pulmonary hypertension); (6) unique susceptibilities of the preterm newborn (e.g., necrotizing enterocolitis, intraventricular haemorrhage, retinopathy of prematurity); (7) rapid and variable maturation of all physiologic and pharmacologic processes leading to different dosing regimens with chronic exposure; and (8) transdermal absorption of medicinal products and other chemicals. [12]

### **3.4.2 Term Newborn Infants (0 to 27 days)**

While term newborn infants are developmentally more mature than preterm newborn infants, many of the physiologic and pharmacologic principles described above, including an increased sensitivity to pharmacological agents, also apply to term newborn infants. The newborn have a different body composition (e.g. more water, limited energy stores), have poorly developed



regulatory mechanisms and are at greater risk of respiratory depression. Distribution characteristics of medicinal products may be different from those in older paediatric patients because of different body water and fat content and a very high body surface area to weight ratio. Other potential hazards include enhanced drug penetration to the brain since the blood-brain barrier is still not fully mature and rapid variation with age of protein binding. Further, oral absorption of medicinal products may be less predictable than in older paediatric patients. Hepatic and renal clearance mechanisms are immature and rapidly changing so that doses may need to be adjusted during therapy over the first weeks of life. [11, 12]

### **3.4.3 Infants and Toddlers (28 days to 23 months)**

This is a period of rapid CNS maturation, immune system development and total body growth. Oral absorption becomes more reliable. Hepatic and renal clearance pathways continue to mature rapidly. Between one and two years of age, clearance of many drugs on a mg/kg basis may exceed adult values. The developmental pattern of maturation is dependent on specific pathways of clearance. There is often considerable inter-individual variability in maturation. [12]

### **3.4.4 Children (2 to 11 years)**

Within this ICH age group several important milestones of psychomotor development, which could be adversely affected by CNS active drugs, are passed. Most pathways of drug clearance (hepatic and renal) are mature, with clearance often exceeding adult values. Within this category a number of factors should be used to determine the effects of the medical product, such as skeletal growth, weight gain, school attendance and school performance including cognitive and motor skills. In addition to those factors with a great developmental inter-individual variability, there are further important pharmacokinetic differences in this age group which have to be additionally considered when planning clinical studies.

Before starting clinical trials in that age group, it should be ensured that the entire age range is adequately represented, as it is important to ensure a sufficient number of younger patients for evaluation. Even though stratification by age within this category is often unnecessary, it may be appropriate to stratify patients based on pharmacokinetic and/or efficacy endpoints.

The onset of puberty is highly variable and occurs earlier in girls. Since puberty can affect the activity of drug-metabolising enzymes, and dose requirements for some medicinal products on a mg/kg basis may decrease dramatically (e.g., theophylline), it may be advisable to specifically assess the effect of puberty on a medicinal product by studying pre- and post-pubertal paediatric patients in some cases. [11, 12]

### **3.4.5 Adolescents (12 to 16-18 years, dependent on region)**

This is a period of rapid growth, sexual maturation and continued neurocognitive development. Medicinal products may interfere with the actions of sex hormones and impede development. Many diseases are also influenced by the hormonal changes around puberty (e.g., insulin resistance increases in diabetes mellitus, seizures may recur around menarche, frequency and severity of migraine and asthma may change). Hormonal changes may thus influence the results of clinical studies. In certain studies, pregnancy testing and review of sexual activity and contraceptive use may be appropriate. Medicinal products and illnesses that delay or accelerate

the onset of puberty can have a profound effect on the pubertal growth. Evolving cognitive and emotional changes could potentially influence the outcome of clinical studies.

Within this age group, adolescents are assuming responsibility for their own health and medication. Non-compliance may become a special problem, particularly when medicinal products, e.g. steroids, affect appearance.

The upper age limit of that age category is different dependent on region. Nonetheless it may be possible to include older adolescents in adult studies, although issues of compliance may present problems. In general, it may be appropriate to consider studying adolescent patients (whether they are to be included in adult or separate protocols) in centres knowledgeable and skilled in the care of this special population. [11, 12]

### **3.4.6 Conclusions**

As a matter of fact children respond to medicinal products differently depending on their physiology and anatomical stage of development, i.e. the paediatric population and the possible sub-populations are not a homogeneous group. In any case, children are not miniature versions of adults. There is a wide variation between individuals in terms of weight, surface area and stage of development for a given age (e.g. maturity in the preterm infant or stage of puberty in children and/or the adolescent).

Due to age-related differences in drug handling or drug effects which may lead to different dose requirements to achieve efficacy or to avoid ADRs, specific clinical trials in all paediatric populations are normally required. In addition, there may be practical problems of administration e.g. difficulties in swallowing tablets if e.g. a liquid oral formulation is not available or, more significantly, serious calculation errors when using adult formulations which may lead to inadequate paediatric dosages. [12]

However, classification of children by age group is useful for the evaluation of medicinal products, as age is almost always accurately known, and in case an adequate subset is defined by age for a given population it is likely to be representative for extrapolation of the results of the trial to prescribing information for that population [11].

## **3.5 CONDUCT OF CLINICAL TRIALS IN CHILDREN**

Although especially parents may have concerns about conducting trials in children, these concerns have to be balanced by the ethical issues related to giving medicines to a population in which they have not been tested and therefore their effects, positive or negative, are unknown. In order to address the concerns about trials in the paediatric population it has to be stressed that the Clinical Trials Directive 2001/20/EC lays down specific requirements to protect children who take part in EU clinical trials.

Furthermore, there is evidence that individuals treated in clinical trials have a positive benefit compared with individuals treated outside a trial [5, 43]. In terms of both public health and ethics, it is clearly preferable to test medicines in children in a safe and controlled clinical trial environment, where the individual child is protected and the studies generate data and

information for the benefit of the rest of the children of the EU, than to continue with the daily “experiments on children” that occur today because such medicines for children have never been designed and evaluated for this particular paediatric use and purpose.

In general there is a necessity to carry out specific trials in each paediatric age group in order to improve the treatment available to them. Paediatric trials should only be performed by trained investigators with paediatric experience. In addition, there are various ethical aspects which need to be considered when investigating medicinal products for paediatric use:

- As the child (minor) is unable to provide legally binding consent, the Clinical Trials Directive requires the informed consent of the parent(s) or legal representative before starting treatment. Article 4 of the Clinical Trials Directive states a clinical trial in children should only be performed if:
  - the informed consent of the parents (in some MS only one parent) or legal representative has been obtained (consent must represent the child’s presumed will and may be revoked at any time, without detriment to the child)
  - the child has received information according to its capacity of understanding from staff experienced with minors, regarding the trial, the risks and the benefits
  - the explicit wish of a child capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is considered by the investigator or where appropriate the principle investigator.

Involving children in discussions and decision-making process respects their emerging maturity. The Clinical Trials Directive only requires that the minor’s will be “considered”, however, although not a legal requirement, it is recommended that the investigator obtains assent (according to age groups, including cognition and ability to provide assent) in addition to informed consent of the legal representative. [13]

In Article 4(h) of the Clinical Trials Directive the need for appropriate expertise in the Ethics Committee when providing opinion on a clinical trial to be performed in children of any age group is described. The neonate represents the most vulnerable of all paediatric age groups and requires even more careful review. The experts should be involved when the initial protocol is submitted for review and during the period of amendments to the clinical trial in progress. Experts may involve physicians with paediatric qualification, paediatric ethicists, qualified paediatric nurses or psychologists with experience in paediatric care.

- The clinical trial design highly depends on the objective(s) of the trial and the scientific question(s) to be answered and may have to be specifically adapted according to the requirements and needs in the different paediatric age groups which may include the following:
  - Use of placebo in children is more restricted than in adults, because children cannot consent. Placebo should not be used when it means withholding effective treatment, particularly for serious and life-threatening conditions. Placebo use is not equivalent to absence of treatment, for example placebo should be used on top of standard care.

In all cases, exposure should be minimised and irreversible harms avoided, especially in serious or rapidly evolving diseases

- Equivalence and non-inferiority trials, and in particular the choice of equivalence or non-inferiority margins, may raise issues as any decrease in quality of the trial performance blurs the difference between treatments, increasing the probability of concluding that products are equivalent when this is not the case. Therefore superiority designs might be more appropriate for paediatric trials
- As many medicines used in children have not been fully tested and are not authorised, the choice of active control products should be discussed thoroughly. Unlicensed products and medicines used off-label may be considered suitable as controls if they represent evidence-based standard of care.
- Pain should be prevented as much as possible, and effectively treated when unavoidable. This requires that pain intensity is assessed and regularly monitored within the trial. Patient-controlled analgesia may be used where appropriate, i.e., in children of sufficient understanding.
- Fear, distress and parental separation should be prevented if possible, or if not, minimised. The need of the child for comfort and reassurance should always be kept in mind.
- When they exist, age-appropriate formulations should be used to avoid the risk of adverse reactions, the risk of dosing errors or inaccuracy. [1]

In summary, the ethical and research needs of children are very different from that of adults and thus paediatric clinical trials need to be tailored to the individual patient group as well as the disease or condition intended to be treated. Children are not small adults and respond very differently to medicines at various ages and stages of development. When designing and planning paediatric studies it should always be kept in mind that children are much more vulnerable than others and may not have capacity to assent for themselves.

#### 4 KEY PROVISIONS INCLUDED IN THE REGULATION

In order to understand the nature of the Paediatric Regulation and its implications on the various stakeholders (pharmaceutical industry, regulatory authorities, health care professionals, pharmacists, health insurers and government, clinical researchers, and children) the details of the Regulation are described and explained in the following subsections. Since the Regulation includes a variety of different provisions and key measures, these may be divided into two types of provisions, namely substantive provisions (the requirements, rewards, incentives and support measures that form its core) and procedural provisions (infrastructure, administrative procedures, legal and regulatory context). In the provided assessment, the primary focus is made on the substantive provisions.

The following five groups of provisions are reflected in the Paediatric Regulation and are the basis of the present Master Thesis:

- ***Core requirements***  
The requirement to include the results from studies performed in accordance with an agreed Paediatric Investigation Plan (PIP) forms the core of the new Regulation.
- ***Rewards and incentives***  
In exchange for the costs and efforts necessary to meet the core requirements the industry or manufacturers are given a form of intellectual property right protection, such as an extension of the Supplementary Protection Certificate (SPC) for patented medicinal products, an extension of the marketing exclusivity period for orphan medicinal products and for non-patented medicines a new form of marketing authorisation, the so-called Paediatric Use Marketing Authorisation (PUMA), was introduced associated with a 10-year period of data protection.
- ***Additional requirements***  
Those requirements are aimed to guide the effects of the core requirements in the right direction. For example, for products already on the market for which a paediatric indication is granted, the MAH must market the product within 24 months after approval, so that the paediatric tested product becomes available.
- ***Facilitating measures***  
The two main facilitating measures are waivers and deferrals. Waivers will be granted to avoid unnecessary testing in children. Deferrals govern the period of transition and should ensure that the requirements for paediatric data do not delay a product being made available for adults. In addition, paediatric medicines are eligible for using the centralised procedure.
- ***Support measures***  
In order to encourage the development and increase of the knowledge about paediatric medicines the Regulation provides different support measures, e.g. free scientific advice and study funds. [44]

## 4.1 CORE REQUIREMENTS

### 4.1.1 Marketing Authorisation Requirements

Starting from 26.07.2008 all new applications for marketing authorisations (according to Art. 6 of Directive 2001/83/EC) for products not yet authorised within the Community shall be regarded as valid only if the application includes (1) the results of all studies performed and details of all information collected in compliance with an agreed Paediatric Investigation Plan, (2) a decision of the EMEA granting a product-specific or class waiver or (3) a decision of the EMEA granting a deferral [Article 7].

These provisions also apply to already authorised medicinal products which are protected either by a supplementary protection certificate (according to Regulation (EEC) No 1768/92) or by a patent which qualifies for the granting of the SPC, in case of applications for new indications (including paediatric indications), new pharmaceutical forms and new routes of administration. Since the scope of the requirements for patent-protected products will include both the new and existing indications, pharmaceutical forms and routes of administration the obligations will be effective not until 26.01.2009. [Article 8]

However, there are some exceptions from the requirements laid down in Articles 7 and 8. Referring to Article 9 of the Regulation, the requirements will not apply to:

- generics or similar biological medicinal products
- medicinal products authorised through the well-established medicinal use procedure
- homeopathic medicinal products and
- traditional herbal medicinal products (please refer also to section 3.3).

The Paediatric Investigation Plan (PIP) is defined as research and development programme which should provide all necessary data to determine the conditions under which a medicinal product may be approved to treat the paediatric population. Thus it will be ensured that the development of medicinal products intended for use in children becomes an integral part of the development of medicinal products for adults. All documents intended to be submitted to fulfil the paediatric requirements must cumulatively cover all subsets of the paediatric population, in case of both, submissions of a PIP and requests for a waiver or deferral. The Paediatric Committee responsible for assessing such plans has to consider two global principles: first, that studies should only be conducted in case there is a potential benefit for children, i.e. an unmet medical need will be addressed (including avoiding of duplicate studies) and secondly, that the requirements for paediatric studies should not delay the authorisation of medicines for other populations, such as adults.

The timing of studies will be of particular importance as a core measure and is a new requirement for all studies performed in accordance with an agreed PIP. The PIP itself has been included as a core requirement to ensure that medicines are developed for children based on their therapeutic needs rather than just on the basis of when the paediatric market may be profitable or incentives might be financially attractive.

#### **4.1.2 The Paediatric Investigation Plan (PIP)**

The Paediatric Investigation Plan (PIP) is the document upon which the development and authorisation of medicinal products for the paediatric population should be based and which itself will be the basis upon which compliance with the new requirement is judged. The Paediatric Investigation Plan should include details of the timing and the measures proposed to demonstrate the quality, safety and efficacy of the medicinal product in the paediatric population. Since the paediatric population is in fact composed of a number of population subgroups (see section 3.4), the PIP should specify which population subsets need to be studied, by what means and by when, [Articles 7(2), 15]

In addition, it shall describe any measures to adapt the formulation of the medicinal product in order to make its use more acceptable, easier, safer or more effective for different subsets of the paediatric population [Article 15].

As detailed above, the introduction of the Paediatric Investigation Plan in the legal framework aims at ensuring that the development of medicinal products that are intended to be used for the paediatric population becomes an integral part of the development of medicinal products, i.e. integrated into the development programme for adults. Thus, PIPs should be submitted early during product development, in time to allow the conduct of studies in the paediatric population before an application for marketing is submitted, where appropriate. Regulation (EC) No. 1901/2006, Articles 16(1) and 20(1), respectively, specify that the PIP or the application for a waiver (see 4.4.1) or deferral (see 4.4.2) shall be submitted with a request for agreement not later than human pharmacokinetic studies in adults (phase I) are completed. Even though the objective of this requirement is to ensure that an opinion on use in the paediatric population of the medicinal product concerned can be given at the time of the assessment of the application for marketing authorisation, it remains questionable whether it is always reasonable and feasible to plan and perform clinical trials in children at a relatively early stage of product development, i.e. already at the pre-phase II stage.

With regard to the submission of a PIP, it can be concluded that it is up to the applicant to determine when would be the best time to submit a request for a Paediatric Investigation Plan. However, such a request can only be submitted to the European Medicines Agency once the Paediatric Committee (PDCO) is established within the EMEA (please refer also to section 3.2).

Nonetheless, it seems to be appropriate for a pharmaceutical company to set a deadline for the submission of a Paediatric Investigation Plan in order to ensure early dialogue between the sponsor and the Paediatric Committee. Furthermore, early submission of a PIP, combined with the submission of a deferral request as described in section 4.4.2, will avoid delaying the authorisation for other populations.

After having submitted a Paediatric Investigation Plan to the EMEA [Article 15(1)], the EMEA will verify the validity of the request and prepare a summary report for the Paediatric Committee within 30 days [Article 16(2)]. Subsequently the Paediatric Committee will appoint a Rapporteur and issue an opinion within 60 days as to whether the proposed studies will ensure the generation of adequate data and conditions enabling the treatment of the paediatric population or subsets

thereof, as to whether or not the expected therapeutic benefits justify the proposed studies and will consider whether an appropriate formulation of the medicinal product will be used. Both time periods mentioned above may be suspended in order to allow the applicant to provide further information (orally or in writing) requested by the EMEA, to revise the PIP and/or to allow the PDCO another 60 days for assessing PIP modifications [Article 17].

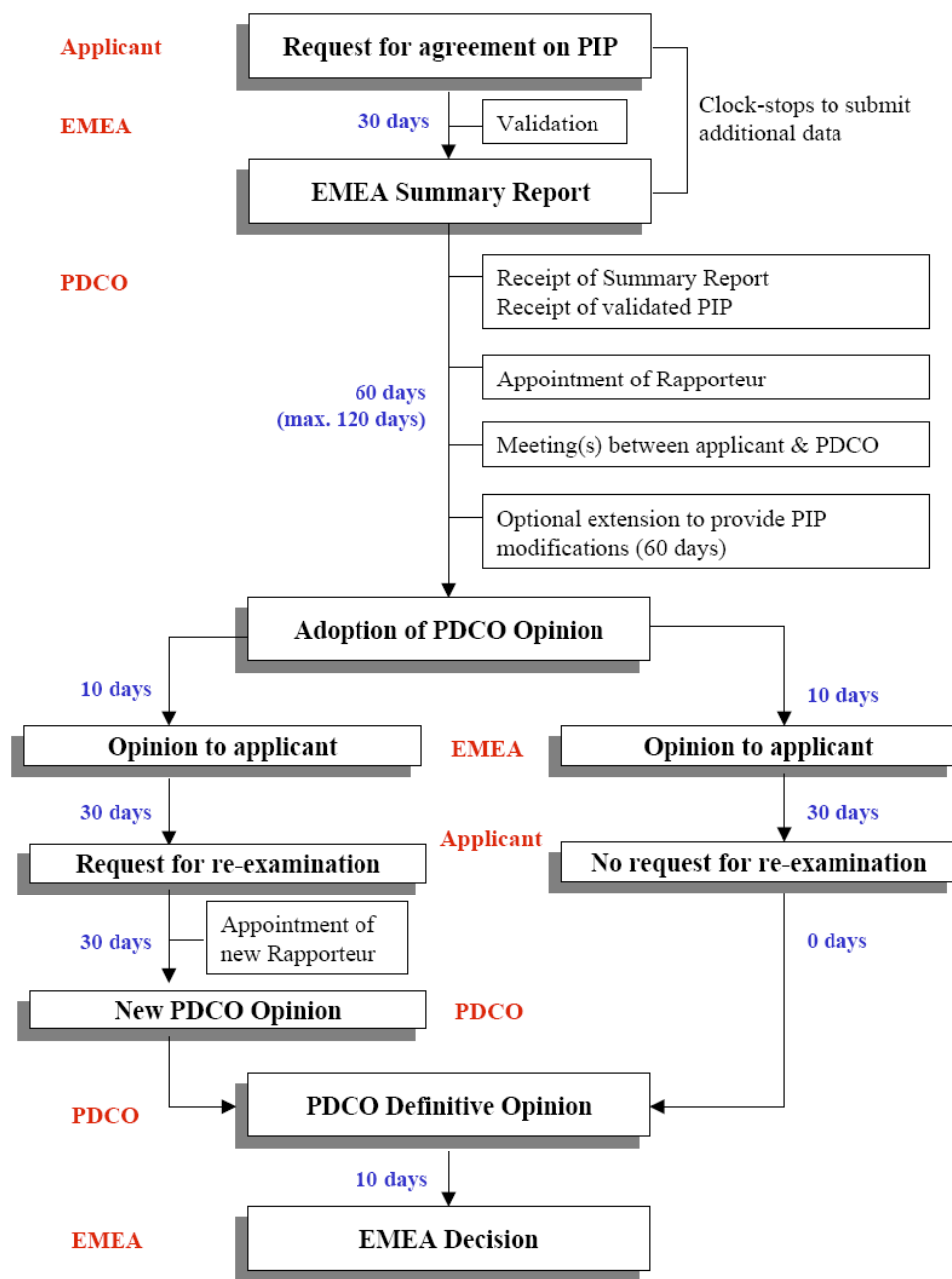
The PDCO's opinion should be forwarded to the applicant within 10 days by the EMEA. In well-justified cases, the applicant has the opportunity to request a re-examination of the opinion. The request must be submitted within 30 days following receipt of the opinion. In case a re-assessment is requested the PDCO will appoint another Rapporteur and will issue a new opinion confirming or revising the previous. This step may take up to another 30 days and should include a mutual dialogue between the applicant and Rapporteur. The opinion should be duly reasoned and a statement of reasons for the conclusion reached shall be appended to the new opinion, which is intended to become definitive. If, within the 30-day period referred to above, the applicant does not request re-examination, the opinion of the Paediatric Committee shall become definitive after 30 days, too. The EMEA will then adopt a decision within a period not exceeding 10 days following receipt of the Paediatric Committee's definitive opinion. In the Regulation it is further foreseen to publish all EMEA decisions after deletion of any information of a commercially confidential nature. Overall, the duration of the complete procedure will approximately be between 140 and 200 days (excluding possible appeal) [Article 25]. A detailed flow-chart of the procedure is presented in Figure 1. It is important to note, that, for the first time, the EMEA is empowered to make a decision. Usually binding decisions are limited to the power of the European Commission.

Since it is easily imaginable that applicants may become difficulties with the implementation of the PIP resulting from the fact that the development of medicinal products is a dynamic process which is highly depending on the results and timing of ongoing studies, the Paediatric Regulation includes provisions for modifying an agreed plan where necessary. Such PIP modifications, which may include additional requests for waivers or deferrals, should be refused or accepted by the PDCO within a 60-day evaluation period [Article 22]. The PDCO's opinion will be followed by the procedure described in Article 25 of the Regulation (see previous paragraph). It is further important to note that any changes related to the clinical trial protocol (including timelines), which must be reflected by the appropriate protocol amendments, have also to be implemented into a PIP resulting in PIP modifications which again need to be agreed by the Paediatric Committee [4].

In the light of Article 10 of the Regulation, the Commission has published a draft guidance in January 2007 detailing the arrangements to be followed concerning the format and content of applications for agreement or modification of a PIP and requests for waivers or deferrals. The guideline also provides advice on the operation of the compliance check with the PIP which needs to be performed by the competent authorities assessing the applications [Articles 10, 23, 24], the latter will not be further discussed in this Thesis.



Figure 1: Procedure for Requesting and Agreeing on PIPs (incl. Deferrals) and Waivers



### **The Paediatric Committee (PDCO)**

As laid down in the Paediatric Regulation a Paediatric Committee should be established by 26 July 2007, with expertise and competence in the development and assessment of all aspects of medicinal products to treat paediatric populations. However, it is not yet decided whether requests for PIPs can be submitted earlier to the EMEA so that the Agency may start to validate the submissions before the PDCO has been established. In fact, this opportunity could help marketing authorisation holders and applicants to reach consensus on their paediatric development program at an earlier stage but may also contribute to a reduced workload for the PDCO assumed the PIP submissions are spread more evenly within the first months of the committee's operational activity.

The rules on scientific committees of the EMEA, as laid down in Regulation (EC) No 726/2004, should also apply to the Paediatric Committee. Members of the PDCO should therefore not have financial or other interests in the pharmaceutical industry which could affect their impartiality, should undertake to act in the public interest and in an independent manner and should make an annual declaration of their financial interests [Article 3]. The Paediatric Committee should primarily be responsible for the scientific assessment and agreement of Paediatric Investigation Plans and for the system of waivers and deferrals thereof. In its work, the PDCO should consider the potential significant therapeutic benefits for the paediatric patients involved in the studies or the paediatric population at large including the need to avoid unnecessary or duplicate studies.

Furthermore it should follow existing Community requirements, including the Clinical Trials Directive 2001/20/EC, as well as ICH guideline E11 on the development of medicinal products for the paediatric population and should avoid any delay in the authorisation of medicinal products for other populations, such as adults, deriving from the requirements for studies in the paediatric population.

The Paediatric Committee will be composed of:

- 5 members (with their alternates) of the Committee for Medicinal Products for Human Use (CHMP), to be appointed by the CHMP itself
- 1 member (and an alternate) appointed by each of the 22 Member States whose national competent authority is not represented through the Paediatric Committee members appointed by the CHMP
- 3 members (and their alternates) representing health professionals, to be appointed by the European Commission
- 3 members (and their alternates) representing patient associations, to be appointed by the European Commission.

The PDCO will be operational with 27 members, even before finalisation of the appointment by the European Commission of the further 6 members representing health care professionals and patient associations. The PDCO chairman as well as each committee member will be appointed for a renewable period of three years. [Articles 3-6] [2]

When preparing its opinions, the committee should use its best endeavours to reach consensus on a scientific basis and should consider whether or not any proposed studies can be expected to be of significant therapeutic benefit to and/or fulfil a therapeutic need of the paediatric population.

The committee's main tasks are summarised in Article 6 of the Regulation. The most important assignments include the following:

- Evaluation of Paediatric Investigation Plans
- Assessment of requests for waivers and deferrals
- Compliance check of applications for marketing authorisations including agreed PIPs (at the request of CHMP, NCAs, or applicants)
- Assessment of any data generated in accordance with an agreed PIP
- Support and advice for all parties involved including scientific assistance for paediatric research and paediatric needs
- Establishment of a specific inventory of paediatric medicinal product including updates on a regular basis.

The very first meeting, which is intended to serve as a training meeting for the assigned members, is scheduled to occur on 4 July 2007. Within the first regular monthly PDCO meeting (20 July 2007) the Committee will start with the evaluation of the first PIPs. Referring to a recently published press release by the EMEA, the Agency expects to receive significantly more applications than was originally forecasted for Paediatric Investigation Plans and waivers between 20 June 2007, when applications can be submitted for the first time, and the beginning of 2008. The workload could be some 50% to 70% over the initial forecast, and demonstrates the impact this new piece of legislation will have on the EMEA [21]. More precisely, the EMEA expects around 50 applications in the first round and approximately 60 new applications in each following month. The first Paediatric Investigation Plans have already been received by the EMEA, but have been considered not to be in compliance with the required EMEA template. The EMEA template will be set up on the basis of template as proposed by the "*Commission guideline on the format and content of applications for agreement or modification of a Paediatric Investigation Plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies*" for public consultation but will not be available until end of June 2007 [50].

#### **4.2 REWARDS AND INCENTIVES**

During the development phase of the proposal for a new Paediatric Regulation, there was a great discussion about striking the right balance between requirements to be fulfilled by the industry and the question whether any requirements should be rewarded and if rewarded by how much.

Before the Regulation came into force, industry had a free choice which medicines to develop for children, and if successful, authorise and market. As pharmaceutical companies (with the exception of the generic industry) primarily base their choice on potential revenue from sales balanced against the costs of research and development, manufacturing and marketing, the main drivers of overall return on investment are usually the size of the pharmaceutical market and the price achievable within that market. Since the number of children suffering from specific diseases is normally lower than the number of adults and, in terms of research, the paediatric

population cannot be considered a single population such studies are usually more complex and financially less attractive to be performed.

Since market forces alone have demonstrated to be insufficient to stimulate adequate research and development of paediatric medicines, the Paediatric Regulation includes combined measures of incentives, rewards and obligations.

However, for new medicines as well as for patent-protected, authorised ones a requirement without rewards would have placed the entire burden of this public health issue on industry and could negatively influence innovation for adults. Another possibility, which was discussed during the developmental phase of the Paediatric Regulation, had been a system of reimbursement to industry for the costs of developing, authorising and marketing medicines for children. But, such a system would not be feasible to administer, for example, it would be necessary to know in advance the costs for research and development and it would be difficult if not even impossible to calculate the reimbursement and to separate the sales for the paediatric population from the sales for adult use of the product.

There was also a debate on including incentives in the form of intellectual property rights (IPRs) without requirements. Even though some companies would feel encouraged and do the necessary research and development, the main driver for research would remain market forces i.e. the potential for industry to profit from the research conducted and the IPRs awarded. This would mean that some therapeutic needs of children would come second or even be disregarded in favour of more valuable markets. As important public health needs would remain unmet, the objective of improving the health of the children of Europe would have only been partially met. [2]

#### **4.2.1 SPC Extension**

Where an application includes the results of all studies conducted in compliance with an agreed Paediatric Investigation Plan (see section 4.1.2), the holder of the patent or supplementary protection certificate (SPC) shall be entitled to a six-month extension of the SPC referred to in Articles 13(1) and 13(2) of Regulation (EEC) No 1768/92, i.e. this will result in effect in an extension of patent protection. Obviously, this incentive does not apply for off-patent medicines, but also not for medicinal products designated as orphan medicinal products (see section 4.2.3). [10]

For products protected by a patent or SPC, the six-month extension will only be granted:

- if all the measures agreed within the Paediatric Investigation Plan are complied with,
- if the product is authorised in all Member States of the Community and
- if all relevant information derived from the paediatric studies conducted are included in the patient information.

Because the reward is for conducting studies in children and not for demonstrating that a product is effective and safe in the new population, the reward will also be granted where completion of the agreed Paediatric Investigation Plan failed to lead to the approval of a paediatric indication, but the results of the studies conducted are reflected in the SmPC (Summary of Product

Characteristics) and, if appropriate, in the package leaflet of the medicinal product concerned. The reason to require an EU-wide marketing authorisation is based on the need to prevent a community-wide reward without community-wide benefits to the paediatric population in all Member States.

In order to enable the patent offices to awarding the SPC extension, a statement that the PIP measures have been fully met will be included in the marketing authorisation, if applicable. Referring to Article 7(4) of Regulation (EEC) 1768/92 (which was amended by Article 52 of the Paediatric Regulation), an application for an extension of the duration of a SPC already granted shall usually be lodged not later than two years before the expiry of the certificate. Irrespective from that provision within five years following the entry into force of the Paediatric Regulation (i.e. by 26 January 2012), the application for an SPC extension is allowed to be applied for not later than six months before the SPC expiry date [10].

By extending the patent life of a product, generic competition will be delayed for the entire product range based on the active substance. Since the SPC extension will occur when the market sales of the concerned product are on peak level, this will result in increased returns from the market for the innovator company and may compensate the costs incurred as a result of the new requirements. But, this is highly depending on the success of the product in the market. For successful products this may become true whereas for others, less successful medicines, the SPC extension may not fully outweigh the costs. Overall it is likely that for the majority of products industry will be adequately compensated. In this way the SPC extension can be viewed as a mixed reward and incentive. [2]

#### **4.2.2 The Paediatric Use Marketing Authorisation (PUMA)**

In order to stimulate research and development also for off-patent medicines, a new type of marketing authorisation, the Paediatric Use Marketing Authorisation (PUMA), has been introduced as a vehicle for providing incentives. A PUMA utilises existing marketing authorisation procedures but covers exclusively therapeutic indications which are relevant for use in the paediatric population and must be accompanied by the particulars and documents necessary to establish quality, safety and efficacy in the paediatric population, including any specific data needed to support an appropriate strength, pharmaceutical form or route of administration, in accordance with an agreed Paediatric Investigation Plan. The PUMA application must also include the decision of the EMEA agreeing on the Paediatric Investigation Plan concerned [Article 30(2)].

Where a PUMA is granted via the Centralised Procedure (according to Regulation 726/2004/EC), the Mutual Recognition or Decentralised Procedure (according to Directive 2001/83/EC, as amended), the European data protection periods shall apply, i.e. a 10-year period of data protection, in other words a generic medicinal product is not allowed to be placed on the market until ten years have elapsed from the initial authorisation of the reference product but is allowed to refer to the non-clinical and clinical data of the originator after the first 8 years of the protection period. The 10-year period can be extended to a maximum of 11 years if, during the first eight years of those ten years, the Marketing Authorisation Holder (MAH) of the reference

product obtains an authorisation for one or more new therapeutic indications which are held to bring a significant clinical benefit in comparison to existing therapies. [14]

As stated elsewhere, a PUMA covers only a medicinal product which is not protected by a supplementary protection certificate or by a patent which qualifies for granting a SPC. The system for a PUMA is independent from the patent system, but will delay generic competition and hence may stimulate innovation too. However, data protection is weaker than patent protection as a competitor can conduct its own research and development on the same active substance. Therefore, data protection does not guarantee market exclusivity.

It is worthwhile to note that the Paediatric Regulation has thereby extended the scope of medicinal products qualifying for being authorised by the community, i.e. via the centralised procedure in accordance with Regulation (EC) No. 726/2004. As described in Article 31 of the Paediatric Regulation, an application for a PUMA may be submitted to the EMEA and conducted as a centralised procedure. This option will be applicable from 26.07.2007.

In addition, the existing brand name of the corresponding product authorised for adults can be utilised for such medicines granted a PUMA [Article 30(4)]. Furthermore, where a product is granted a marketing authorisation for a paediatric indication, the product's label will include a symbol to aid recognition and prescribing. This symbol is not yet defined but is supposed to be selected by the Commission following a recommendation of the Paediatric Committee by 26 January 2008 [Article 32].

An additional incentive applied to the PUMA that may prove particularly powerful at attracting small and medium-sized enterprises (SMEs), including generic industry, to develop off-patent medicines for the paediatric population is an amendment to the data requirements to be submitted for PUMA applications. An application for a PUMA will require data justifying that the product is effective, safe and of high quality, specifically in children. These data might be derived from new studies in children or from the published literature. However, an application for a PUMA may refer to data contained in the dossier of a medicinal product which is or has been authorised in the Community (whether centralised or decentralised). For the first time, therefore, it will be possible to submit new data in an otherwise generic-type application. [Article 30(3)] [2]

### **4.2.3 Extended Market Exclusivity for Orphan Medicinal Products<sup>5</sup>**

Where an application for an orphan medicinal product (pursuant to Regulation (EC) No 141/2000) is submitted and that application includes the results of all studies conducted in compliance with an agreed Paediatric Investigation Plan, the ten-year period of marketing exclusivity (referred to in Article 8(1) of Regulation (EC) No 141/2000) which is granted for an

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<sup>5</sup> **Designation criteria for orphan medicinal products:** 1.) Regulation (EC) No 141/2000, Art. 3 (1a): A medicinal product intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than 5 in 10,000 persons in the Community when the application is made, **or** that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment **and** 2.) Regulation (EC) No 141/2000, Art. 3 (1b): no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community exist, **or**, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

authorised orphan medicinal product shall be extended to twelve years. Similar to the measures for patent-protected medicinal products (see section 4.2.1), this should also apply where completion of the agreed Paediatric Investigation Plan fails to lead to the authorisation of a paediatric indication, but the results of the studies conducted are reflected in the SmPC and/or PL of the product. [46]

During the public consultation phase of the proposal for the Regulation concerns have been raised, that, if SPC extension would be the only reward offered for compliance with the requirement, the requirement would not be rewarded for a significant proportion of orphan medicinal products as many of those medicines are not patent-protected at the time of authorisation. Others were concerned that, for orphan medicines covered by a patent, a double incentive would be granted (SPC extension from the Paediatric Regulation and ten-year market exclusivity from the Orphan Regulation). To meet these concerns, the Paediatric Regulation excludes orphan medicines from the SPC extension and, instead, rewards them for compliance with the above mentioned additional two years of the market exclusivity. Two years have been chosen rather than six-months as the market exclusivity only covers the medicinal product in the orphan indication. In contrast, the SPC extension covers the active substance and therefore relates to all products of the MAH containing it. [2]

In case the assessment of an application for marketing authorisation by a competent authority concludes that the studies are not in conformity with the contents and timelines of an agreed Paediatric Investigation Plan, the product shall not be eligible for the rewards and incentives provided in the Regulation [Article 24].

### **4.3 ADDITIONAL REQUIREMENTS**

#### **4.3.1 Placing a Medicinal Product on the Market**

Where medicinal products are authorised for a paediatric indication and those products have already been marketed with other indications, the marketing authorisation holder shall place the product on the market taking into account the paediatric indication, within two years following the date of approval of the paediatric indication [Article 33].

This requirement is only related to products already authorised and therefore does not apply to medicines authorised via a PUMA. But, since a PUMA is linked to an incentive that only becomes apparent in case the product is launched, such a deadline to market a product is not needed here. [2]

In the interests of public health it is necessary to ensure the continuous availability of safe and effective medicinal products authorised for paediatric indications. If a marketing authorisation holder intends to withdraw such a medicinal product from the market then arrangements should be in place so that the paediatric population can continue to have access to the medicinal product in question. Therefore the following measure has been included in the Regulation: If a medicinal product has been authorised for a paediatric indication and the MAH has benefited from rewards or incentives (as described in section 4.2), and these periods of protection have expired, and if the marketing authorisation holder intends to discontinue placing the medicinal product on the

market, the MAH shall transfer the marketing authorisation or allow a third party, which has declared its intention to continue to place the medicinal product in question on the market, to use the pharmaceutical, pre-clinical and clinical documentation contained in the file of the medicinal product. The marketing authorisation holder shall inform the EMEA of its intention to discontinue the placing on the market of the product no less than six months before the discontinuation. [Article 35]

Overall, these measures will increase access of the Community population to new medicinal products tested and adapted for paediatric needs, and will minimise the chance of granting community-wide rewards without a benefit for the paediatric population from the availability of newly and appropriately authorised medicines.

#### **4.3.2 Post-Marketing Obligations**

In order to meet the necessity of collecting robust safety data in children, and in order to take action to minimise risks from those medicines and maximise benefits for the paediatric population it is essential to ensure that pharmacovigilance mechanisms are adapted by the MAHs. Therefore, an additional requirement has been implemented in the Paediatric Regulation (in addition to the already existing requirements for post-marketing monitoring):

The application for a marketing authorisation must describe the proposed measures to ensure the long-term follow-up of efficacy and of possible adverse drug reactions to the specific use of the medicinal product in the paediatric population. As laid down in Article 34 of the new Regulation, this applies for:

- applications for a marketing authorisation that includes a paediatric indication
- applications intended to add a paediatric indication to an existing marketing authorisation (Line Extensions)
- applications for a paediatric use marketing authorisation (PUMA).

Additionally, where there is particular cause of concern, the applicant may be required to submit and implement a risk management system (or to adapt the existing system) and/or perform specific post-marketing studies as a post-marketing condition. The risk management system should comprise a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products, including the assessment of the effectiveness of those safety measures [Article 34 (2)].

In case of a deferral was granted for paediatric testing (see section 4.4.2), the MAH is obliged to submit to the EMEA an annual report on the progress of paediatric studies in accordance with the agreed Paediatric Investigation Plan [Article 34 (4)].

It is proposed that the EMEA will issue a detailed guidance relating to paediatric pharmacovigilance issues to support these important public health measures [Article 34 (5)].

#### **4.3.3 Labelling**

For all medicines authorised for a paediatric indication the label will include a symbol to aid recognition and prescribing. Additionally the package leaflet shall contain an explanation of the meaning of the symbol. The symbol will have to be selected by 26 January 2008 by the



Commission after consultation with the Paediatric Committee. This measure aims to increase the visibility of medicines which have been tested and approved for the paediatric population in comparison to others and will retrospectively apply for all medicinal products authorised before the entry into force of the new Regulation if they are authorised for paediatric indications. In the latter case, the symbol and the explanation should be included in the labelling and package leaflet respectively not later than two years after the symbol has been made public [Article 32].

#### 4.3.4 Pre-existing Studies

Since one of the key objectives of the new Paediatric Regulation is to increase the availability of information for the appropriate use of medicinal products in the paediatric population, the industry is requested to submit all information on completed clinical trials, which have been terminated by the date of entry into force of the Regulation (26.01.2007), for assessment to the competent authorities by 26.01.2008 at the latest [Article 45(1)].

Furthermore, any other MAH-sponsored study which involves the use of an already-approved product in the paediatric population, whether or not conducted in compliance with an agreed PIP and whether or not the MAH intends to apply for a marketing authorisation of a paediatric indication, should be submitted to the competent authority within six months of completion of the studies concerned [Articles 46(1)(2)].

As further described in Article 45 and 46 respectively, the competent authorities may update the SmPC and package leaflet and may vary the marketing authorisation based on the provided data. Moreover competent authorities should exchange information regarding the studies submitted and, as appropriate, their implications for any marketing authorisation concerned.

All existing paediatric studies and all paediatric studies initiated prior to the entry into force of the Regulation shall be eligible to be included in a Paediatric Investigation Plan and shall be taken into consideration by the Paediatric Committee when assessing applications for PIPs, waivers and deferrals and by competent authorities when assessing applications including paediatric indications [Article 45(2)]. Even though existing studies are allowed to be included into the PIP, only for those applications containing significant studies the rewards and incentives as described in section 4.2 may be granted, provided that the studies are part of an agreed PIP and are completed after 26 January 2007 [Article 45(3)]. A study will be regarded as completed when the last visit of the last patient has occurred (according to the current study protocol submitted to the competent authority) [8].

As foreseen in the Regulation the Commission has published a draft guideline to establish assessment criteria for the significance of studies [8].

The draft guideline provides the following examples as a guide to assess the significance of studies. The following study types will normally be considered as significant:

- Comparative efficacy studies (randomised / active control or placebo)
- Dose-finding studies
- Prospective clinical safety studies, if the results are expected to make a major contribution to the safe use of the medicinal product in the paediatric population

- Studies to obtain a new age-appropriate formulation, if the formulation is expected to be of clinical relevance for the safe and effective use of the medicinal product in the paediatric population.

However, the EMEA or competent authorities will assess the significance of each study proposed in a PIP on a case-by-case basis. In order to be considered as significant, the studies should normally cover all paediatric subsets affected by the condition where sufficient data are not available. However, exceptionally, studies conducted in a single subset of the paediatric population will be considered as significant if carried out in a subset considered particularly difficult to study, for example neonates. Studies will not be considered as significant where sufficient data for one or more of the paediatric subsets are already available [8].

In general, it is the quality rather than the quantity of the studies, as well as the clinical relevance of data for the paediatric indication, which will determine whether a study is significant or not. In exceptional cases, a set of non-significant studies might be considered as significant too if the results taken together are expected to provide important and clinically meaningful information [8].

In case the studies included in the PIP (which were initiated prior to and were completed after 26 January 2007) are considered to be significant in the meaning of Article 45(3) of the Paediatric Regulation, the EMEA or competent authority will include a statement of compliance indicating whether the paediatric trials performed are significant or not [Article 28(3)]

Overall, these measures have been introduced to improve the safe and effective use of medicines in children and thus promoting public health in general. In addition, these measures will help to prevent duplication of testing and the conduction of unnecessary paediatric studies and will increase the availability of appropriate paediatric information.

This will be realised through the existing Community database for clinical trials, EudraCT, in which information is entered by Member States in whose territory the clinical trial takes place [13]. The Paediatric Regulation foresees to build onto this database an information resource of all ongoing and completed paediatric studies.

In addition to the clinical trials required to be included in accordance with the Clinical Trials Directive, any paediatric clinical trial, carried out both in the community and in third countries, which is contained in an agreed PIP will have to be entered into the database.

Deferring from Article 11 of Clinical Trials Directive 2001/20/EC the database should not only be made accessible to the competent authorities of the Member States, the EMEA and the Commission, but also to the public with regard to specific information on paediatric clinical trials.

Since the implementation of these provisions is not detailed in the Regulation the Commission is obliged to draw up guidelines on the nature of the information to be published in the EudraCT database entries concerning paediatric clinical trials, on how clinical trial results should be

submitted and how and to what extent clinical trial results of submitted studies in accordance with Articles 45 and 46 of the Regulation should be published, and on the EMEA's responsibilities and tasks in this regard, following consultation with the EMEA, the Member States, and interested parties [Article 41(3)].

In order to implement the above mentioned provisions, the CMD(h) and the EMEA have agreed on principles for the submission of paediatric studies according to Articles 45 and 46 in form of a draft Q&A document published in May 2007 (deadline for comments elapsed on 14 June 2007). This document explains how MAHs should comply with the requirements, which data are to be submitted, which format should be used and what else should be submitted by the MAH.

The main topics of the guidance documents are summarised in the following:

- Already submitted paediatric studies (to EMEA and National Competent Authorities, as part of the EU Work sharing procedure for the assessment of paediatric data), do not need to be resubmitted
- A line listing should be provided for already submitted paediatric studies by 26.01.2007 identifying the studies, the National Competent Authorities where the studies were submitted and the respective outcome, including changes to the Product Information and using the provided template
- A line listing should be provided for not yet submitted studies identifying potential regulatory consequences, e.g. proposals to amend the product information, if appropriate (using the provided template)
- All studies not yet submitted should be submitted if they are of paediatric relevance and may include: non-clinical studies as well as phase I to IV clinical trials, whether completed or discontinued, whether published or not, whether positive or negative and regardless of the region where they have been performed
- A short critical expert overview should be added, clarifying the context of the data, including any FDA outcome and the relevance for EU situation
- A listing of wording concerning paediatric use in national SmPCs, where relevant, should be submitted
- MAHs do not need to resubmit safety data (as opposed to studies), provided that they have been submitted as part of a Periodic Safety Update Reports (PSURs)
- In addition a table listing should be submitted of all authorised medicinal products with either an indication in children (0 to 17 years inclusive) in SmPC section 4.1, or dosing information in children in SmPC section 4.2, identifying the Member States where the product is authorised.

In order to assess those data attempts have been made on European level. The so-called *EU work sharing procedure in the assessment of paediatric data*, as agreed by Heads of Medicines Agencies (HMA) and published in the *Best Practice Guide on the EU Work sharing procedure in the assessment of paediatric data* foresees that the National Competent Authorities are working together in the assessment of the paediatric data submitted with the intention to agree on the same information and to share the workload. The main principle of that initiative is that two Member States assess the data and prepare an assessment report for the other Member States. In

an agreed timeframe other Member States can comment on the assessment reports. The conclusions from the assessment will be included in the relevant Product Information and the assessment reports will be published to make more information available for health care professionals. Although the newly submitted data are most of the time not sufficient to approve an indication for use in children, the available data can provide useful and important information for health care professionals who have to decide which medicines can be used to treat children. [7]

#### **4.4 FACILITATING MEASURES**

The two main facilitating measures concern waivers and deferrals. Waivers will be granted to avoid unnecessary testing, deferrals will ensure that the requirements laid down in the new Regulation will not delay the authorisation or availability of a product for adults, e.g. in case it is more appropriate (particularly in terms of safety) to study the use of the product in adults before children. In addition, the possibility to initiate a Community referral procedure for existing marketing authorisations has been introduced.

Furthermore it is foreseen that there will be a direct path to the centralised procedure as laid down in Articles 5 to 15 of Regulation (EC) No 726/2004. New applications may be submitted in accordance with the centralised procedure for a marketing authorisation which includes one or more paediatric indications on the basis of studies conducted in compliance with an agreed Paediatric Investigation Plan [Article 28(1)]. Without prejudice to the conditions defined for products classifying to be applied for in the centralised procedure [Article 3(2) of Regulation (EC) No 726/2004], an application for a paediatric use marketing authorisation may also be made in accordance with the centralised procedure [Article 31]. [49]

The three main facilitating measures are detailed in the following subsections.

##### **4.4.1 Waivers**

It is evident that not all medicines which are developed for adults will be suitable for children too or will be needed to treat paediatric patients. In order to deal with such situations a system of waivers has been introduced in the Paediatric Regulation, more precisely in Articles 11 to 14. It is the responsibility of the Paediatric Committee to determine whether a PIP receives a favourable opinion or whether a waiver is granted. Based on the Committee's opinion, waivers may be granted by the EMEA.

The grounds for a waiver are defined in Article 11. Waivers are granted if there is evidence showing the following:

- that the specific medicinal product or class of medicinal product is likely to be ineffective or unsafe in the paediatric population (or part of the paediatric population) [Article 11(1a)]

*A request for a waiver based on lack of efficacy in the paediatric population(s) should consider the seriousness of the condition or disease and the availability of alternative treatments or methods. All available data should be submitted to support the lack of*

*efficacy accompanied by a well grounded justification which may be based on pharmacological properties of the product or class of product, results from non-clinical studies, clinical trials or post-marketing data and on the existing experience with the product, when available. At an early stage of development, the absence of any available data on the safety or efficacy in the paediatric population will not be accepted as the sole justification for a waiver [8].*

- that the disease or condition for which the medicinal product is intended occurs only in adult populations [Article 11(1b)]

*A justification for such a waiver should be based on detailed information on the incidence or prevalence of the disease in different populations in form of a comparison between the adult and the paediatric population or between different paediatric subsets (when a waiver for specific subsets is requested). For waivers covering the totality of the paediatric population the grounds should particularly focus on the earliest age of onset of the condition or disease. The discussion on similarities and differences of the condition or disease should focus on the seriousness of the disease, aetiology, clinical manifestations and prognosis and variability in terms of genetic background in the paediatric subsets. This may be based on published references, or standard textbooks [8].*

- that the specific medicinal product does not represent a significant therapeutic benefit over existing treatments for paediatric patients [Article 11(1c)]

*Waivers may also be granted on the basis of a lack of significant therapeutic benefit. The Paediatric Committee will assess whether the conduct of paediatric clinical trials is expected to be of significant therapeutic benefit to children, whether a therapeutic need in children is met or an added value can be expected in comparison to existing therapies. This benefit might also be based on extrapolations from non-clinical or adult clinical data, if available, or on well-justified and plausible assumptions, provided that they are based on reasonable arguments and relevant literature. The latter cases may become more relevant at an early stage of product development when the experience with the use of the medicine is usually limited.*

*To enable the Paediatric Committee to make its evaluation the applicant should provide a comparison of the medicinal product in question with the current standard of care for the treatment, diagnosis or prevention of the disease or condition. The applicant should consider in the request for a waiver all established treatment methods including non-pharmacological treatment methods, medical devices, prevention methods and non-approved methods if there is sufficient scientific evidence and consensus as to the value of such methods.*

*Significant therapeutic benefit might also be present because existing treatments are not satisfactory and alternative methods with an improved expected benefit risk balance are needed.*

*On this basis, significant therapeutic benefit could be based on:*

- a) Expected improved efficacy in a paediatric population compared to the current standard of care for the treatment, diagnosis or prevention of the condition concerned*
- b) Expected substantial improvement in safety in relation to either adverse events or potential medication errors*
- c) Improved dosing scheme or method of administration (number of doses per day, oral compared to intravenous administration, reduced treatment duration) leading to improved safety, efficacy or compliance*
- d) Availability of a new clinically relevant age-appropriate formulation*
- e) Availability of clinically relevant and new therapeutic knowledge for the use of the medicinal product in the paediatric population leading to improved efficacy or safety of the medicinal product in the paediatric population*
- f) Different mechanism of action with potential advantage for the paediatric population(s) in terms of improved efficacy or safety [8].*

*If significant therapeutic benefit cannot be fully justified at that early stage of product development, the Paediatric Committee may consider deferral as appropriate instead of a waiver (see section 4.4.2).*

In general, a product-specific waiver may be issued with reference either to one or more specified subsets of the paediatric population, or to one or more specified therapeutic indications, or to a combination thereof [Article 11(2)]. Requests for product-specific waivers should therefore clearly define their scope in terms of paediatric subset and indication and should follow a simple procedure as defined in Article 13 of the Regulation (60-day procedure; excluding potential clock-stops, which may be needed in case the applicant is requested to submit supplementary information). The procedure will work hand in hand with the procedure for agreeing Paediatric Investigation Plans since a waiver (and a deferral; see section 4.4.2) can be viewed as an integral part of the PIP.

In order to increase the knowledge about the use of medicines in children, Article 42 of the Paediatric Regulation determines that all Member States should collect available data on all existing uses of medicinal products in the paediatric population and should communicate these data to the EMEA by 26 January 2009. On the basis of this information (and after consulting the Commission, the Member States and interested parties) the Paediatric Committee is supposed to establish an **inventory of therapeutic needs**, with the focus on identifying research priorities for the pharmaceutical industry. The EMEA will make the inventory public between 26 January 2009 and 26 January 2010. As knowledge on science and medicine evolves over time it is likely that the need for medicines in children will change and, as a result, the inventory has to be updated on a regular basis.

If the therapeutic need is included in the inventory of therapeutic needs the applicant should refer to the inventory when submitting a Paediatric Investigation Plan. Where the applicant considers its proposed paediatric development could meet a therapeutic need and this therapeutic need is not yet included in the inventory as established by the Paediatric Committee, sufficient information to explain this assumption must be provided.

In order to simplify the system for agreeing Paediatric Investigation Plans and issuing product-specific waivers the Paediatric Committee will create **lists of waivers** of medicinal products, classes of medicinal products and parts of classes of medicinal products, as soon as the Committee is established. Those lists of waivers are intended to be published and updated (at least annually) by the EMEA so that applicants will know in advance for which products the requirements for paediatric studies will be waived and for which there is no need to conduct paediatric studies [Article 14(1)].

In case a product is covered by such a class waiver, no product-specific waiver is needed to satisfy the requirements of the Paediatric Regulation. If the scope of a class waiver is not precisely enough and thus the concerned product is only partially covered, the class waiver(s) should be referenced when specifying the scope of the product-specific waiver [8].

As it applies for the inventory of therapeutic paediatric needs, the published list of waivers is also a dynamic feature as it reflects the current state of knowledge on clinical and medical science and the experience in the use of medicinal products. But this will not complicate the requirements for studies in the paediatric population at the time of marketing authorisation application as, if a waiver is removed from the published list, the requirement will not apply for 36 months. This period allows time to submit and agree on a PIP and to initiate studies in children prior to the application for marketing authorisation [Article 14(3)].

#### **4.4.2 Deferrals**

Sometimes studies in children will be more appropriate when there is some initial experience on use of a product in adults.

Therefore the Paediatric Regulation allows for deferral of the initiation or completion of the measures included in a Paediatric Investigation Plan. Any request for deferrals of the initiation or completion of some or all of the measures should be based on indication, route of administration and pharmaceutical form and should be further specified by age group. As a general rule, all requests for deferrals should be justified on scientific and technical grounds or on grounds related to public health [Article 20(1)].

Justifications for deferrals might include the following:

- It is considered appropriate to conduct studies in adults prior to initiating studies in the paediatric population
- When studies in the paediatric population will take longer to conduct than studies in adults
- Additional non-clinical data are considered necessary
- Major quality problems prevent development of the appropriate paediatric formulation(s) [8].

Article 20(1) further specifies that a deferral must be granted when it is appropriate to conduct studies in adults prior to initiating studies in the paediatric population (e.g. when a study in children is judged to be safer if delayed after first data become available from adult studies) or

when studies in the paediatric population will take longer to perform than studies in adults. In all other events, granting of deferrals will be judged on a case-by-case basis.

Deferrals from the requirement will allow a medicine to be authorised for adults and the results of studies in children to be presented at a later date. It is thus required that, once a marketing authorisation has been granted, companies will have to submit annual reports to the EMEA providing an update on the progress of the deferred studies and to continuously demonstrate compliance with the agreed Paediatric Investigation Plan [Article 33(4)].

Overall, this measure will ensure that studies in children only occur when they are assessed to be safe and that the requirements of the Paediatric Regulation do not delay the authorisation of medicines for adults [2].

#### **4.4.3 Community Referral for Existing Marketing Authorisations**

In order to allow the straightforward and rapid introduction of information relevant to the use of a medicinal product in the paediatric population into the national product information (SmPC and package leaflet), it is possible that an applicant may use the existing procedure set out in Articles 32, 33 and 34 of Directive 2001/83/EC, as amended. This so-called referral or arbitration procedure has been established to make it possible to obtain a single community-wide opinion for a nationally authorised product when data on the paediatric population (in accordance with an agreed PIP) form part of the marketing authorisation application. The opinion of the CHMP will be made by majority vote within 90 days from the start of the arbitration resulting in a subsequent binding decision by the European Commission. It is important to note that this option may only be used for products already approved through a Decentralised or Mutual Recognition Procedure and for which a new indication, including the extension of an authorisation for use in the paediatric population, a new pharmaceutical form or a new route of administration is applied for [Article 29].

As the procedure should be limited to the assessment of the specific sections of the summary of product characteristics to be varied this measure will allow the adoption of a community-wide, harmonised decision on the paediatric use of the medicinal product concerned and will permit the inclusion of all relevant paediatric information in all national product information [Article 29].

### **4.5 SUPPORT MEASURES**

#### **4.5.1 Free Scientific Advice**

The provision of the Paediatric Regulation relating to free scientific advice provided by the EMEA is applicable from the date of the Regulation's entry into force, i.e. as of 26 January 2007 [Article 26].

The fee exemption for scientific advice covers any part, i.e. quality, safety and/or efficacy of a request, but is limited to aspects of paediatric development and should focus on questions related to 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. If the request covers



both adult and paediatric development, the appropriate fee level will be determined by the questions concerning adult development.

On the other hand requesting scientific advice is not mandatory and the advice given is not binding on the Paediatric Committee. Scientific advice may be requested from the EMEA at any stage in the development of a product. Therefore, applicants may choose to request scientific advice first, to help in the preparation of a Paediatric Investigation Plan, or to submit a Paediatric Investigation Plan directly and follow it up with a request for scientific advice on, for example, combined adult and paediatric development in light of the Paediatric Investigation Plan requirements.

#### **4.5.2 Funding of Studies into Off-patent Products**

An additional tool for promoting high quality, ethical research that may lead to the development and authorisation of adequate medicines for the paediatric population should be the provision for research into paediatric use, including clinical trials, of medicines not covered by a patent or a supplementary protection certificate to be financed by community research programmes [Recital 12 of Regulation (EC) No 1901/2006]. Funding is considered necessary as the return from investment for off-patent medicines is more limited than for patent-protected medicines and the data protection associated with the PUMA, although this represents a valuable IPR, does not guarantee market exclusivity. This provision is described in Article 40 of the Paediatric Regulation: *“1) Funds for research into medicinal products for the paediatric population shall be provided for in the Community budget in order to support studies relating to medicinal products or active substances not covered by a patent or a supplementary protection certificate. 2) The Community funding referred to in paragraph 1 shall be delivered through the Community Framework Programmes for Research, Technological Development and Demonstration Activities or any other Community initiatives for the funding of research.”*

As the measures contained in the Paediatric Regulation are not directly dependent on the funding of paediatric study programmes, the children of Europe will gain most through the speedy introduction of the established measures in the existing Regulation. The value of the community paediatric funding program, the Seventh Research Framework Programme (FP7), is intended to be added later. Furthermore, a number of the measures included in the Regulation, including the inventory of therapeutic needs of children (by identifying research priorities) and the creation of a network for the performance of clinical trials (to facilitate the conduct of studies) will lay the foundation for funding.

FP7 is the short name for the Seventh Framework Programme for Research and Technological Development. This is the EU’s main instrument for funding research in Europe. FP7, which applies to the years 2007-2013, is the natural successor to the Sixth Framework Programme (FP6), and is the result of years of consultation with the scientific community, research and policy making institutions and other interested parties. Since their launch in 1984, the Framework Programmes have played a lead role in multidisciplinary research and cooperative activities in Europe and beyond. FP7 continues that task, and is both larger and more comprehensive than earlier Framework Programmes. Running from 2007 to 2013, the programme has a budget of

53.2 billion euros over its seven-year period, the largest funding allocation yet for such programmes. [34]

The core of FP7 and its largest component, the Cooperation programme, fosters collaborative research across Europe and other partner countries and includes amongst various other themes also health. The objective of the Cooperation Programme 2007 for Health is to advance the understanding on how to more efficiently promote good health, to prevent and treat major diseases and to deliver health care by supporting world-class collaborative research with specific attention to translational research. [26, 28]

The work programme describes the research topics in which project proposals can be submitted in response to the first two calls for proposals, FP7-HEALTH-2007-A and FP7-HEALTH-2007-B. The first call (deadline in April 2007) will commit the 2007 budget. The second call (deadline on 18 September 2007) is still provisional because it will require approval of the 2008 budget. The budget of the Call FP7-HEALTH-2007-A has been increased by € million up to €637 million. [26, 50]

Child health has been identified as one of the overarching issues of strategic importance of the work programme. Support will be given in particular to specific clinical studies to provide evidence for the appropriate use of off-patent products currently used off-label in paediatric populations (HEALTH-2007-4.2-1). In addition, specific topics will address research issues related to child health and paediatric diseases (see Table 2).

Further implications for child health and paediatric diseases should be taken into account whenever appropriate.

Participation in the Seventh Framework Programme is open to a wide range of organisations and individuals, such as universities, research centres, multinational corporations, SMEs, public administrations, even individuals, from anywhere in the world. If interested in participating in the EU funding programmes an application and project proposal has to be submitted to the European Commission, according to the call for proposal deadlines and dedicated work programme. Project proposals should also take into account the priority list of off-patent medicinal products of the PEG (see following paragraphs). The European Commission guarantees proper evaluation of the submission by 3-7 independent evaluators, who are experts in that field. The Commission will notify the applicant of the evaluation results. If they are positive, contract negotiations will begin and the funded project may be initiated. [26]

Table 2: FP7 Cooperation Work Programme: Child Health Topics

<b>Topic</b>	<b>Identifier</b>	<b>Funding scheme</b>
Innovative approaches for the development of vaccines for young children	HEALTH-2007-1.4-2	Collaborative project (small or medium scale focused research project)
Childhood and adolescent mental disorders	HEALTH-2007-2.2.1-10	Collaborative project (small or medium scale focused research project)
Paediatric formulations of drugs against HIV/AIDS, malaria and tuberculosis	HEALTH-2007-2.3.2-5	Coordination and support action (Coordination or support action)
Combined forms of diabetes in children	HEALTH-2007-2.4.3-2	Collaborative project (small or medium scale focused research project)
Promoting healthy behaviour in children and adolescents	HEALTH-2007-3.3-1	Collaborative project (small or medium scale focused research project)
Addressing knowledge gaps in pregnancy malaria	HEALTH-2007-2.3.2-4	Collaborative project (small or medium scale focused research project)
Health care intervention research – improving pre-natal and maternal care	HEALTH-2007-3.5-4	SICA: Collaborative project (small or medium scale focused research project)

As explained before the CHMP's existing Paediatric Working Party (PEG) has finalised a list of paediatric priorities for off-patent medicines. The first list was drafted in 2003. In 2006, the PEG revised the list in terms of combining the off-patent priority list with the list of paediatric needs, which had already been identified by the PEG in different therapeutic areas and performed a systematic search and review of newly available literature. This current final list, adopted by the Paediatric Committee on 27 April 2007, contains 89 active substances or substance classes (to treat 25 different conditions/diseases) and specifies for each condition and product the specific paediatric needs and the paediatric sub-population or age group for which the currently available knowledge and/or data is considered insufficient. The list thus provides a measure of the scale of research that needs priority funding and the scope of products to be targeted [19, 20].

The main priorities identified in terms of unmet medical paediatric needs are the following:

- 1) Migraine (prevention of recurrence), e.g. beta blockers, Topiramate
- 2) Seizures/epilepsy (generalised and partial seizures), e.g. Clobazam, Cisplatin, Methotrexate
- 3) Gastrooesophagealreflux (GER), oesophagitis, peptic ulcers, e.g. proton pump inhibitors, H<sub>2</sub>-receptor antagonists
- 4) Atopic dermatitis, e.g. topical steroids
- 5) Bronchopulmonary dysplasia (BPD), e.g. steroids, diuretics
- 6) Obstructive lung disease, e.g. inhaled steroids
- 7) Asthma, e.g. inhaled and oral steroids
- 8) Tubulopathies, e.g. Indomethacin, Hydrochlorothiazide
- 9) Sedation, e.g. Clonidine, Midazolam, Propofol
- 10) Pain (acute and chronic), e.g. Clonidine, Diclofenac, Fentanyl, Ibuprofen, Morphine, Tramadol.

Additionally the updated list includes acute and chronic hypertension, heart failure, cardiac arrhythmia, hypercholesterolaemia, infection, fungal infection, meningitis, tuberculosis, herpes virus and HIV infections, psychosis and glaucoma-IOP. [19, 20]

Since its creation, the Paediatric Working Party has been working on therapeutic areas and products which may be considered as paediatric needs for drug development and/or needs for data from appropriate trials in children. One important step in this process is to base the choice of products on available evidence and on unmet therapeutic needs. As stated in the introductory preface to that priority list, the list has been prepared from a public health perspective and the outcome is supported as much as possible by evidenced based medicine. Several Member States attempted similar work, which have been considered by the group when establishing the methodology (e.g. France, UK, Germany), although most of them related to defining priorities for products to be studied rather than needs. The methodology used is based originally on the work carried out at the French Medicines Agency (AFSSAPS). The AFSSAPS drew up lists of substances of current and potential use, the legal status (authorised for adult use or not), available paediatric information and appropriate formulations, if any. [18]

In detail the methodology used to set up the list included two steps:

- In the first step, priority points were assigned to illnesses based on the severity of the disease, the paediatric age groups affected (with special regard to the neonatal population), the non-availability of treatment alternatives and the prevalence of the disease in the paediatric population.
- In a second step, for each condition, published therapeutic reviews were analysed to identify off-label products of therapeutic interest. Priority points were assigned to these products according to the level of evidence available and known or suspected efficacy or safety issues. The final selection was based on the sum of the priority points for the condition and the product [19, 20].

In order to put the list into a European perspective, the PEG carries out extensive consultation of experts in the relevant areas, contact points at national authorities and European Learned Societies relevant to the therapeutic areas. [18]

Overall, it should be emphasised that the measures set out in the Regulation, including the agreement of Paediatric Investigation Plans, should not preclude obtaining any other community incentives or rewards to support research, such as the funding of research projects under the Community Framework Programmes for Research, Technological Development and Demonstration Activities [Recital 30 of Regulation (EC) No 1902/2006]. [48]

#### **4.5.3 Inventory of Therapeutic Needs**

The Paediatric Regulation offers the opportunity to identify where children's needs are currently not being met, and where efforts should be directed to address these needs. As already mentioned in section 4.4.1 the Paediatric Regulation determines that all Member States should collect available data on all existing uses of medicinal products in the paediatric population and should communicate these data to the EMEA by 26 January 2009. On the basis of this information and after having consulted the Commission, the Member States and interested parties the Paediatric Committee will establish an inventory of therapeutic needs, with the focus on identifying research priorities for the pharmaceutical industry. As specified in Article 43(2) of the Regulation the Paediatric Committee should consider the prevalence of the conditions in the paediatric population, the seriousness of the conditions, the availability and suitability of alternative treatments, including the efficacy and the adverse reaction profile of those treatments, as well as any unique paediatric safety issues and any data resulting from studies in third countries when establishing the inventory of therapeutic needs.

The inventory will be published between 26 January 2009 and 26 January 2010 and will be updated on a regular basis as the need for medicines in children is likely to change over time.

This measure focuses on identifying which medicines there are, which are used off-label, and where there are therapeutic gaps that need to be closed. The inventory may help in focusing the attention of policy makers, pharmaceutical industry and health researchers.

#### 4.5.4 Community Network for the Performance of Clinical Trials

Clinical trials in children may require specific expertise, specific methodology and in some cases, specific facilities. One of the challenges of creating a system which will effectively increase the number of clinical trials performed to develop or adapt medicines for use in children is the need to ensure that these studies are carried out in suitably adapted facilities by appropriately trained investigators and paediatricians. Some Member States, anticipating the increased amount of research which the Regulation will stimulate, have already taken steps to create national networks for paediatric clinical trials, for paediatricians and for providing a health service infrastructure to support clinical paediatric research and remove barriers to its conduct, but there has been little attempt at cross border collaboration so far. [25]

Member States to be particularly mentioned in this context are Finland, France, Germany and the UK:

- The Finnish Investigators Network for Paediatric Medicines (FINPEDMED), founded in the beginning of 2007, will be developed in joint collaboration with the five Finnish university hospitals. According to the EU Paediatric Regulation the national network will be linked to the European paediatric trials network [37].
- The PAED-Net (Pädiatrisches Netzwerk – Paediatric Network) in Germany, founded in 2002, is a network of experts with an appropriate infrastructure to professionally plan and perform multicentre paediatric studies supported by the Federal Ministry of Education and Research (BMBF). It consists of six paediatric units as part of the German Centres for Coordination of Clinical Studies – KKS (Cologne, Freiburg, Heidelberg, Leipzig, Mainz and Muenster). It is administrated by a central coordinating unit located in Mainz [39].
- In France, the 2002 founded network of Paediatric Clinical Investigation Centres (CICPs) consists of eight research centres integrated into teaching hospitals. They collaborate with medical and surgical departments, medicotechnical departments, INSERM (Institut National de la Santé et de la Recherche Médicale) research units and university research units. The aims of the network are to conduct paediatric clinical trials and basic scientific research (primarily related to growth and neurosciences) and contribute to technical innovations. The CICIP facilities are specifically designed for the conduct of research in children [41]
- In the UK the Medicines for Children Research Network (MCRN) was formally launched only recently in December 2006. It will be part of the UK Clinical Research Network (UKCRN). A consortium from the University of Liverpool, Royal Liverpool Children's Hospital, Imperial College London, the National Perinatal Epidemiology Unit (University of Oxford), Liverpool Women's Hospital and the National Children's Bureau has established the Coordinating Centre for the MCRN. The MCRN will provide a world-class health service infrastructure to support clinical paediatric research and remove barriers to its conduct [38].

As detailed in section 3.5 clinical trials in the paediatric population are usually more complex than adult trials and hence may require specific expertise, specific methodology and in some cases specific facilities and should be carried out by appropriately trained investigators in appropriately experienced centres. Thus the EMEA will develop, with the scientific support of

the Paediatric Committee, a European network of existing national and European networks, investigators and centres with specific expertise in the performance of studies in the paediatric population [Article 44(1)].

The network aims to link existing national networks and clinical trial centres in order to build up the necessary competences at a European level and to ensure and facilitate the conduct of high-quality, safe and ethical clinical studies, to increase and ensure cooperation and communication, to stimulate harmonisation of procedures and quality standards, to coordinate paediatric studies and avoid duplication of clinical trials [Article 44(2)] [15]. The EMEA is in charge to adopt an implementing strategy for the launching and operating of this network by 26 January 2008. This will contribute to the work of strengthening the foundations of the European Research Area in the context of the Community Framework Programmes for research, technological development and demonstration activities and should benefit the paediatric population and provide a source of information and expertise for industry [Article 44(3)]. [2]

#### **4.5.5 Community Funding**

Since the objective of the Paediatric Regulation, namely improving the availability of medicinal products tested for paediatric use, cannot be sufficiently achieved by the Member States alone but more easily at European level, Community funding should be provided to cover all aspects of the work of the Paediatric Committee and of the EMEA resulting from the implementation of the Regulation, such as the assessment of PIPs, fee waivers foreseen for scientific advice and information and transparency measures, including the database of paediatric studies and the network. [Recital 35] [2]

## 5 IMPACT ASSESSMENT

In October 2003 the European Commission asked RAND Europe to conduct a study to assess the impact of the proposed Paediatric Regulation. The RAND Corporation (the name was derived from a contraction of the terms *research and development*) is a non-profit institution that helps to improve policy and decision making through research and analysis and is specified in objective analysis and effective solutions that address the challenges facing the nation as well as the world [40].

The study describes the economic, social, environmental and sustainable impacts of the proposed Paediatric Regulation. The assessment indicates that the proposed Regulation will achieve its objectives, although the effects will vary. But, since the analysis by RAND was based on a draft version of the Regulation (dated November 2003) and further revisions have been implemented to obtain the final version of the Paediatric Regulation, RAND's Extended Impact Assessment may no longer apply to all provisions laid down in the final Regulation.

The paper draws the conclusion that the EU's new Regulation on medicinal products for paediatric use will cost money to industry, government and consumers but will overall improve the health of children and, on balance, the gains will outweigh the losses.

### 5.1 STAKEHOLDERS

The new Paediatric Regulation will have implications on a wide range of different stakeholders. In order to understand these implications, it is important to know the key stakeholders which will be affected. The following stakeholders have been considered by RAND Europe to be relevant in terms of impacts related to the new Paediatric Regulation:

- ***Pharmaceutical Industry***

The pharmaceutical industry must be divided into the originator and generic industry: The innovative industry undertakes its own research and development including manufacture of medicinal products whereas the generic industry manufactures products whose patents (and data exclusivity periods) have expired. The industry activities are closely linked with the research community and governmental agencies and their investments are influenced by both of them. Once a medical product is approved companies are highly involved in the marketing phase and in the survey to ensure post-marketing safety and effectiveness, involving private and public health care providers and purchasers, regulatory bodies, health care professionals and consumers.

Generic industry and wholesalers will play an important role in the continued use and promotion of the drug in the off-patent-period. Generic companies may exert influence on the development and testing of existing paediatric therapies that are currently used off-label and will induce a decrease in prices for paediatric medicines once the protection periods foreseen in the Regulation have expired as it is already currently the case for existing generic products.



- ***Regulatory Authorities***

The main task of the regulatory authorities is to oversee the appropriate design and safe performance of clinical trials and the approval of those clinical trial applications within the Community and to assess the outcomes of such research activities intended to establish the efficacy and safety of medicinal products together with the evaluation of quality of medicinal products when applications for marketing authorisation are submitted by the pharmaceutical industry. Furthermore, regulatory authorities, i.e. the EMA and national competent authorities, are responsible for authorisation of medicinal products and pharmacovigilance. In particular they bear an important role in the innovation phase and during product development (incl. paediatric drug development) since they offer scientific advice to industry (incl. assessment of Paediatric Investigation Plans).

- ***Health Care Professionals***

Health care professionals comprise paediatricians, general practitioners, pharmacists and nurses. Doctors are those who prescribe medicinal products which are approved for human use and thus may play a role in guiding pharmaceutical companies with respect to the need for development of paediatric drugs, products and/or appropriate formulations. The doctor's prescription behaviour itself may be influenced by different national and insurance company formularies as well as by their individual treatment experiences in the use of medicinal products. They usually become deeper involved at a later stage of drug development. When pharmaceutical companies come towards the end of the pivotal trials period they often closely liaise with doctors towards phase IV for marketing purposes, when the potential impact of the drug on the current market is intended to be established.

The crucial role health care professionals play in terms of on- and off-patent products lies with their preference in delivering health care using high-quality products. In the absence of licensed medicines that are specifically tested and approved for children, doctors can prescribe drugs that are not licensed for paediatric purposes as their decision is based upon clinical judgement [33]. Therefore the legal responsibility for prescribing falls to the doctor who signs the prescription. Nonetheless, these professionals are normally legally liable for negative effects developed by their patients due to treatment.

- ***General Public Including Children in Particular***

Both children and their health are the reasons for the new legislative framework and thus represent the ultimate stakeholders (and beneficiaries) of the provisions. In addition to children the group includes their parents and guardians. Their main interest is to receive high-quality, safe and effective drugs, which are convenient to take. As it applies for health care professionals, the general public triggers also the need for paediatric medicines. In phase IV the public has a role in evaluating the product in terms of use, effectiveness and safety.

- ***Health Insurers and Governments***

Health insurers and governments will have to pay for the medical costs of the insured if the insured becomes sick. The insurer may be a private organisation or a government agency depending on the national health care system and how the Member States have regulated reimbursement of prescribed drugs. Their interest is in value for money.

- ***Researchers***

Research organisations are usually independently-based companies sub-contracted by the pharmaceutical industry to conduct for instance clinical trials and may be affected by the Paediatric Regulation. [44]

## **5.2 THE NATURE OF IMPACTS**

It is not easy to predict how the different stakeholders will respond to the provisions of the Paediatric Regulation. Some implications may be predicted more precisely than others since they derive from absolute requirements laid down in the Regulation. But the majority of impacts depends on the way the various measures are implemented and how they are handled in practise.

The RAND analysis has provided some examples of open questions related to the choice and implementation which clearly indicates that the assessment of impacts can only be made upon the basis of the current expectations and likelihood of the behaviour of the numerous stakeholders towards the different provisions:

- *How will pharmaceutical companies choose to respond to the rewards and incentives in the Regulation? Are they sufficiently attractive?*
- *How will companies organise their paediatric investigations and where will the clinical trials take place?*
- *How will companies deal with the costs of paediatric testing? Will paediatric testing go at the expense of testing for use in adults?*
- *How will insurers, hospitals, general practitioners and households respond to the choice between tested and untested medicinal products for paediatric use with different prices?*
- *How much money will be allocated to the study fund?*
- *What will be the nature and quality of the scientific advice?*

Overall, the effects of different provisions and the effectiveness of the Regulation depend on the nature of the individual provisions. Based on that, three types of provisions have been taken into consideration by RAND Europe: requirements, rewards and incentives and support measures. Each type provokes a different response and thus has a different impact. The link between the type of provision, the identity of the stakeholder, and the nature of the impact is a key element to assess the effects and effectiveness of the Paediatric Regulation.

- **Requirements**

Benefits: The main requirement of the Regulation, the obligation to provide study results carried out in accordance with an agreed PIP (incl. potential waivers and/or deferrals) as an integral part of the application for marketing authorisation, is mandatory and hence has to be followed strictly. Based on that paediatric testing will be performed in future with higher and more homogeneous quality throughout Europe and the availability of appropriately tested and authorised medicinal products for use in children will increase, resulting in better and safer treatment.

Costs: The fulfilment of requirements will cause the majority of costs related to the new Regulation. Examples of the costs for compliance for the industry are costs for designing and conducting clinical trials in children and for developing Paediatric Investigation Plans, costs for implementing label changes, for complying with post-marketing requirements, for launching a product within two years following the date of approval of the paediatric indication (PUMA) or for approving the product throughout the entire European Union (which is required for patented products to obtain the 6 months SPC-extension). Since administrative costs will also increase for pharmaceutical industry, the question may be raised whether the requirements are equally burdensome for large and medium-sized companies, for companies specialised in a single product or companies that produce a wide range of different medicinal products.

Further costs are related to the monitoring and enforcement. These costs will occur on the agencies side (including the establishment and managing of the PDCCO) since they are responsible for checking whether the requirements are met and in case they are if they are met adequately. A centralised monitoring is possible for the main requirement (submitting the results from studies carried out in accordance with an agreed PIP when applying for an authorisation), whereas other requirements (such as placing a product on the market, implementation of paediatric pharmacovigilance) may be more difficult to monitor.

- **Rewards and Incentives**

Benefits: A reward is normally granted automatically when the requirements are complied with and is intended to compensate the costs related to fulfil the requirements. On the other hand incentives represent rewards for a specific behaviour. Rewards have been designed to encourage that behaviour and are solely realised in form of a benefit when the desired behaviour is met.

Costs: In order to make the system work, the relevant regulatory and governmental bodies have to create the appropriate infrastructures to dispense the incentives and rewards, which represent costs of administration. In order to meet the requirements financial costs will also occur for the pharmaceutical industry. But it remains questionable whether the 6 months SPC-extension for patented products, the data protection periods granted for a PUMA or the 2 years added to the market exclusivity period for orphan medicinal products will be sufficiently attractive.

- ***Support Measures***

Benefits: All support measures (including free scientific advice, study and Community funding, network on paediatric clinical trials) are made available without any charge, e.g. funds are not counterbalanced by revenues. Here, the clear benefit is on the side of pharmaceutical industry – most notably SMEs and research organisations – and the public society.

Costs: In order to establish funds and exchange information and knowledge expenditures are needed to set up and manage an appropriate infrastructure. [44]

### 5.3 FOUR TYPES OF IMPACT

The RAND analysis defined the following four types of impact:

- ***Economic impacts, including:***
  - Direct costs related to the implementation of the provisions of the Regulation
  - Indirect costs such as price for patients/consumers
  - Effects on the competitiveness of the pharmaceutical industry
- ***Social impacts, including:***
  - Distributional issues by social group, region, company size and industrial sector
  - Quality of life of children and their parents
  - Equal treatment of patients, manufacturers and other parties
- ***Environmental impacts, including:***
  - Use of resources in the pharmaceutical industry
- ***Sustainability impacts, including:***
  - The ability of future generations to attain the same quality of life, i.e. in this case health and health care as the current generation [44]

## 5.4 ASSESSMENT OF EACH INDIVIDUAL PROVISION OF THE REGULATION

The Extended Impact Assessment conducted by the RAND Corporation was based on a structured analysis including the following six key questions.

1. *Who is affected out of the four main groups of stakeholders (pharmaceutical industry, government, health care professionals and children and their parents and guardians)?*
2. *What are the consequences that each individual provision of the Regulation may theoretically have? This will include operationalisation, short-term effects, long-term effects, risks and uncertainties and will differentiate between four types of impact.*
3. *Where will the costs accumulate and benefits occur?*
4. *Which stakeholders will win and which lose?*
5. *Which stakeholders, industrial sectors, regions, social groups or policy areas will benefit and who will have to pay?*
6. *Will patients in countries with different systems of health care and health insurances benefit to the same extent?*

The structured analysis describes the extent of the implications from the quality point of view for each stakeholder, provides quantitative estimates of selected indicators, such as numbers of patients treated, number of deaths avoided, number of patent applications, number of companies involved and finally assesses the monetary valuation of the quantitative impacts, distinguishing costs and benefits. These three approaches have been combined into an integral assessment of the costs and benefits of each element of the Paediatric Regulation which is summarised in the following subsections. [44]

### 5.4.1 Impact of Core Requirements

As detailed in section 4.1 the core requirements of the Paediatric Regulation are the Paediatric Investigation Plan and the marketing authorisation requirements for new products and for authorised medicinal products.

#### ***Operationalisation***

Pharmaceutical companies have to integrate into their clinical product outlines the development of paediatric formulations, where appropriate, and will have to perform clinical studies in the paediatric population based on an agreed Paediatric Investigation Plan for every new medicinal product and for every new indication, new pharmaceutical form and new route of administration of already authorised medicinal products in order to provide data on the adequate use of medicinal products in children, unless there is a product-specific or class waiver.

The Paediatric Committee has to evaluate PIPs and compliance with PIPs while the EMEA and national competent authorities have to evaluate the submitted dossiers and decide whether or not a marketing authorisation can be issued. Health care professionals and the research community

may advice on scientific questions related to the needs and development of paediatric medicines. The research organisations will have to perform and monitor the paediatric studies. The paediatric population will be enrolled in the clinical trials and parents (or guardians) need to give their consent.

### *Short-term effects*

The demand for specialists in the paediatric field will increase dramatically for both clinicians in the pharmaceutical industry or paediatric research and experts in regulatory agencies and thus will induce higher expenses. Adequate paediatric expertise is especially needed for the Paediatric Committee, but also for the national competent authorities. On the other hand the workload of EMEA will rise considerably which may result in longer assessment periods. Since the field of paediatric pharmacology and pharmacokinetics is rather small the evaluation of paediatric studies and PIPs may become a bottleneck for the Agency and the industry. Referring to a recent press release, the EMEA's management board adopted a proposal from the Executive Director to request an increase in staff to cope with the heavy workload expected to arise from the implementation of the new EU paediatric legislation [21]. As far as the regulatory agencies are concerned the time will tell if the particular expertise required for paediatric investigation will either be manageable by the increased number of experts involved or lengthen the approval process.

The RAND analysis estimates that the EMEA's budget would have to increase to between €130 and €195 million only to scope with the expected increase in marketing authorisation applications (presumed worst-case scenario). In either case the augmented workload will necessitate an expansion of the numbers of EMEA staff (e.g. scientific administrators and managers) and associated experts in the network (e.g. pharmacists and paediatricians).

The requirement to submit study results in accordance with an agreed Paediatric Investigation Plan may raise a new market for specialist services and the employment of experts in developing and advising on PIPs. The plan itself, the performance of the agreed clinical trials in children as well as the administrative work resulting thereof will definitely cause costs for the industry. RAND Europe estimates these costs between €1 and €7 million per drug for phase III clinical trials in children. The total annual costs of additional paediatric testing are approximated at €60 million in the first year the Regulation is in place falling to between €160 and €360 million in the subsequent years.

The overall impact of paediatric testing on the costs of drug development is estimated by RAND Europe to be increased for phase III studies of 25% in the first year and between 7% and 16% in the following years when paediatric testing is added. As the investments needed for phase III clinical trials usually represent not more than 15% of total drug development costs, the estimated increase in total European expenditure on drug development will be 1% to 2.5% after the first year. The costs of paediatric testing are relatively modest (probably between €1 and €4 million per drug) but will result in an increase in the revenues of companies and experts involved in paediatric R&D activities.

Obviously the number of clinical trials in paediatric populations will necessarily increase. In addition, they may lengthen the entire drug development process. In case of new products, it is advisable for pharmaceutical companies to start with the paediatric development as soon as possible and in parallel with the adult development, provided that it is reasonable, feasible and safe to perform clinical trials in children at an early stage (e.g. pre-phase II). Indeed the Regulation foresees that the proposals for paediatric development strategies should be submitted not later than human pharmacokinetic studies in adults (phase I) are completed in order to ensure that an opinion on use in the paediatric population of the medicinal product concerned can be given at the time of the assessment of the application for marketing authorisation. But normally the time to market should not be affected by this provision since there is the option of deferrals (see 4.4.2).

In general, paediatric investigations can be difficult. Some of the barriers to paediatric testing include administrative burdens, the requirement to differentiate between different age groups, more complex recruitment and/or lower recruitment rates which both may be associated with the need for parental consent (especially when both parents have to give their consent; see also section 3.5) and the general lower number of children compared to the adult population. Overall these barriers will result in higher costs and more tightened timeframes.

Smaller companies may find it more difficult to compete in product development and may thus be forced to charge higher prices for their products in a competitive market.

Last but not least, households will be faced with higher drug costs and higher insurance premiums (depending on the national reimbursement systems) since the additional costs for paediatric testing will most probably be passed on to consumers. RAND estimates that the costs of paediatric testing will add 0.1% to 0.3% to consumer expenditure and 0.2% to 0.7% to industrial costs.

### ***Long-term effects***

One of the most important long-term impacts of the Regulation is the fact that paediatric testing will be performed in future with higher and more homogeneous quality throughout Europe. On the basis of the requirement to submit paediatric clinical study results according to an agreed PIP it may safely be assumed that there will be an increase of standardised methods and procedures for paediatric testing. The safety of clinical trials in children will be controlled and certified by the Paediatric Committee.

The expected increase in the supply of licensed paediatric medicines will allow doctors to provide better treatment, to select out of a wider range of new and existing products tested for use in children, to reduce the incidence of ADRs, to reduce the number of prescriptions of off-label and unlicensed products and thus lower the chance of liability suits and increase the quality of life of the entire paediatric population. But at the end it will depend on the doctors who prescribe paediatric medicines and the question remains open whether they are willing to switch to tested medicinal products.

There are also social effects related to the estimated decrease in off-label use and unlicensed prescriptions. RAND Europe concluded that social savings could be achieved between €10 to €36 million and €140 to €252 million (depending on assumptions<sup>6</sup>) in case of a complete eradication of off-label and unlicensed prescriptions as a result of the new Regulation.

Since it is only an assumption that health care professionals will favour tested and authorised products over untested off-label products, there will be a challenge to policy makers in the health care domain to enforce and ensure that unlicensed and off-label medicines will not be prescribed anymore for children. If the Regulation is successful, an increasing proportion of the available medicinal products will be tested and prescribing practices will automatically shift in the desired direction. However, if the incentives are insufficient or the Regulation is incomplete, the basic problem may persist.

### ***Risks and Uncertainties***

As laid down in the Paediatric Regulation the PDCO should be established by 26 July 2007, with expertise and competence in the development and assessment of all aspects of medicinal products to treat paediatric populations. However, it is not yet clear whether the excessive workload of the Committee, which will most likely occur within the first months of the Committee's operational activity, can be managed in an adequate and timely manner. Even though there are legal limits to the assessment process and its duration, in practise the workload may delay the authorisation and marketing of medicinal products.

If the industry responds favourable to the incentives of the Regulation and complies fully and rapidly with the requirements, the first period of entry into force of the provisions may result in a severe backlog of applications and assessments. The EMEA and the Paediatric Committee may not be capable to execute or handle the workload efficiently. As the development of medicinal products is a dynamic process which is highly dependent on the results and timing of ongoing studies, an agreed PIP is necessary to be modified throughout the entire product development process. Since PIP modifications require the evaluation and approval by the PDCO (usually within a 60-day period) and may comprise subsequent scientific advice procedures, the Agency's capacities are likely to be exceeded soon.

In addition, SMEs may not have adequate infrastructure and resources to successfully apply whereas other companies will develop their own centres of paediatric expertise.

Another issue which remains open is the question to what extent the prices for paediatric medicines will increase. For most products it is assumed that the costs for paediatric testing will be manageable. The pharmaceutical industry may, however, translate not only the costs involved in paediatric testing but also the risks of phase II trials in children, including medical risks to the test subjects as well as financial risks of potential failure, and raise the price of its medicines

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<sup>6</sup> There are two cost scenarios for the effects of off-label and unlicensed prescription on health care costs: (1) Most likely scenario: The total costs for the EU of an additional two-day stay in hospital due to adverse events would amount to between €10-36 million. (2) Scenario of more frequent adverse events: In case children have to stay in hospital for an additional three days and more children are hospitalised annually the costs would rise to between €140-252 million.



more than warranted by the real costs. As stated above RAND estimates that the costs of paediatric testing will add 0.1% to 0.3% to consumer expenditure in the vent that only the additional costs for paediatric testing will be passed on to consumers. If the industry will decide to also consider the potential risks related to the costs of paediatric medicines, the increase on costs for consumers will then lead to a price rise of 0.1% to 0.4%. Due to that marginally increase it seems to be unlikely that the affordability of medicines for children would reduce. But, since industry is usually free in terms of pricing, it is not possible to precisely assume the impact on consumer prices, which may further differ for specific individual drugs.

Concerning research there might be a risk that the requirements may lead to more research in the most profitable areas rather than into development of drugs that are most needed for the paediatric population. Although an inventory of therapeutic needs will be established and a priority list for studies into off-patent paediatric medicinal products exists this might not lead to the desired research priorities.

RAND Europe further anticipates a risk that companies will become reluctant to develop new indications, new pharmaceutical forms and new routes of administration (so-called line extensions) in small markets and for products with small sales. However, the costs of paediatric development are manageable and in addition these efforts will be sufficiently compensated by the 6-months extension of the SPC for patented medicinal products.

Since an MAH for a patented product is only obliged to perform paediatric testing when he applies for a new indication, new pharmaceutical form or a new route of administration, the authorised adult version of the product may still be used to treat children off-label. If this adult version of the tested drug is in addition less expensive than the tested paediatric formulation of an alternative product, health care professionals may still prefer the cheaper adult medicine for use in children. On the other hand line extensions in e.g. adult indications are not allowed unless a PIP has been agreed with the Paediatric Committee and all PIP studies have been completed and submitted together with the application for that line extension. In this context it is also important to understand that costs of developing a line extension are usually lower than the costs of developing a new drug, but the reward is the same. This may result in a developmental focus on existing patented products and in a delay in the development of new medicinal products.

Overall, the full success of the provisions laid down in the Regulation depends not only on the behavioural changes of the different stakeholders involved, especially pharmaceutical industry and health care professionals but also on those responsible for the delivery of health care in Europe and for the inclusion of appropriately tested and authorised medical products for use in children on national formularies and reimbursement lists [52]. [44]

### **5.4.2 Impact of Rewards and Incentives**

As described in section 4.2 rewards are granted for companies when they comply with the core requirements of the Regulation, namely the six-months SPC-extension for patented products, 10 years of data protection for products with a PUMA and 2 years added to the marketing exclusivity period for orphan medicinal products.

#### ***Operationalisation***

Manufacturers of off-patent medicinal products may voluntarily apply for a PUMA for drugs solely designated for use in the paediatric population or a subset thereof. The respective application has to include the results in compliance with a previously agreed PIP. At time of application the Paediatric Committee will have assessed the PIP and the EMEA or the competent national authorities will start the evaluation of the results of these plans, in consultation with the Committee, if necessary.

For on-patent medicinal products the 6-months extension of the SPC may only be granted if all the measures agreed within the Paediatric Investigation Plan are complied with, if the product is authorised in all Member States of the Community and if relevant information out of the paediatric studies conducted is included in the product information (SmPC and package leaflet).

#### ***Short-term effects***

The most valuable and attractive reward is the 6-months extension of the SPC for patented medicinal products for which results of a Paediatric Investigation Plan are submitted. This may attract a lot of interest amongst the originator drug companies. But, since paediatric testing is a requirement, industry does not really have a choice. Furthermore it is important to note that the extension of the certificate does not apply for medicinal products no longer covered by a Supplementary Protection Certificate or patent. This must be considered carefully during paediatric drug development (including the Paediatric Investigation Plans), particularly in terms of timing paediatric testing.

The Commission hopes that the PUMA and its incentives will also be attractive for the development of off-patent medicines for paediatric use. But, the PUMA will only be accessible to products with a therapeutic benefit for children.

#### ***Long-term effects***

By extending the patent life of a product, generic competition will be delayed for the entire product range based on the active substance. Since the SPC extension will occur when the market sales of the concerned product are on peak level, this will result in increased returns from the market for the innovator company and may compensate the costs incurred for paediatric testing. For successful products this may become true whereas for others, less successful medicines or niche products, the SPC extension may not fully outweigh the costs. Overall it is likely that for the majority of products industry will be adequately compensated.

For off-patent products, the PUMA provides the opportunity to buy market access and enter an exclusive part of the paediatric market. A PUMA is expected to be more attractive for SMEs

rather than for big players in the pharmaceutical sector. The incentive will most likely be less valuable than the SPC extension.

The incentive for off-patent products and the rewards for patented medicines are fundamentally different. Data protection extends only to paediatric use whereas patent protection is applicable for the entire spectrum and uses of the product, including e.g. adult indications. Furthermore data protection does not involve market exclusivity and competitors can consequently compete for the same market niche. In case paediatric studies fail to reach their objectives and thus no PUMA is granted, no incentive can be given to industry. In case the paediatric studies for a patented product do not yield in positive results, the reward for originators is granted for all uses in form of the SPC extension. The number of line extensions awarded may probably exceed the number of drugs newly licensed for children.

The value of the 6-months extension of the SPC has been assessed by the RAND Corporation to be easily capable to balance the costs of paediatric testing. Under current conditions the pharmaceutical industry will be able to recover the costs of testing and make a profit on the SPC extension of between €3 million and €205 million. This is based on the assumption that industry will test paediatric uses ten years before patent expiry. If they manage to successfully complete testing five years before the patent expire an additional benefit will result. The profits per drug associated with the SPC extension are estimated to vary between €0.8-9.1 million whereas the costs of phase III trials in children amount to an estimated €1-4 million. However, it has to be stressed again that companies will have to invest in paediatric testing long before the financial benefits of the SPC extension will become effective.

There will also be impacts on the revenues, profits and market share of generic industry. RAND assumes that every year 5% of all patented products become available for off-patent production with an annual turnover value of €3.42 billion (at original prices). Due to the Regulation this proportion of medicines will not be available for an additional period of six months. Even though many products will be excluded from the reward associated with the requirement as a result of a waiver, the maximum potential six-month loss of revenues can be estimated at between €6 million and €42 million and the six-month loss of profit can be estimated at between €4 million and €1 million which represents the costs to adjust to new market conditions. These potential losses represent maximum values and will only occur as a one-time cost. After the transitional period generic manufacturers will simply continue with business as usual even though they will have lost part of their market share.

In fact the originator industry will have more time to economically exploit a patent and thus be able to strengthen their relative competitiveness compared to generic industry. The entry into the market of generic drugs will be delayed. Overall, originator drug companies gain substantially more than generic drug companies resulting in a shift in their competitive position in the market and an increase in the average price of medicines for use in children and adults.

This lack of balance between the two groups of pharmaceutical industry is reflected in the respective position papers - on the second publication cycle of the proposed Paediatric Regulation - of EFPIA (European Federation of Pharmaceutical Industries Associations) and

EGA (European Generic Medicines Association): The EFPIA paper basically reflects the current text of the Regulation and generally supports the introduced measures (although it suggests for off-patent products to grant market exclusivity instead of data protection and to grant extend the SPC for 12 rather than 6 months) whereas the EGA has repeatedly voiced its opposition against some of the provisions: In general the EGA welcomes the Commission proposals for improving medicines for children but is concerned that the draft proposal has not focused sufficiently on the off-patent sector and has created a model of rewards for on-patent products only, i.e. innovative products which would create an unnecessarily high cost burden on healthcare systems. In the view of EGA this would create an imbalance between originator and generic industry. The EGA's main demand is that the same incentives and reward model should be provided in both on-patent and off-patent sector, based on appropriate periods of market exclusivity covering the separate marketing authorisation for the separate paediatric medicinal product. Consequently, there would be no need for costly patent/SPC extension or any measure impacting on the adult product. [16, 17]

Since generic access to the market is delayed (and paediatric testing will increase) households will be faced with higher expenditures for medicines. In the future this may lead to higher reimbursement costs for insurance companies and households. The estimated shift in market share from off-patent medicines towards patented medicinal products will - according to the RAND analysis - increase European pharmaceutical expenditure by 0.06-0.25% and total health care expenditure by 0.01-0.04%.

### ***Risks and Uncertainties***

The incentive for off-patent medicines in form of data protection for a PUMA might not be recognised as a true incentive. The current system of marketing authorisation already allows for the application of a paediatric marketing authorisation. The only value added to the new form of PUMA is the marginal advantage to use the same brand name for the paediatric product and that the product's label will include a unique symbol to aid recognition and prescribing.

Since the 10-year period of data protection does not prevent access to the market by competitors, this incentive creates the danger of double testing: different companies can perform the same tests on children in order to gain market access, whereas double testing is considered unethical. Unnecessary testing in children may only be prevented by the PDCO who is responsible for assessing the entire range of Paediatric Investigation Plans for all products. Overall, the development of off-patent medicines may be insufficiently attractive for European pharmaceutical industry.

When the mutual recognition or decentralised procedure is used for products protected by a patent or SPC, the six-month extension will only be granted if the product is authorised in all EU Member States. This may prove difficult, especially for SMEs lacking of adequate capabilities and resources and regulatory knowledge but could even be worth in case it would be required to place the product on the market in each Member State. On the other hand this provision may stimulate a shift to the centralised procedure. [44]

### 5.4.3 Impact of Additional Requirements

The additional requirements describe the conditions under which the incentives and rewards are granted. They concern placing on the market, post-marketing obligations, labelling and pre-existing studies.

#### *Operationalisation*

Before a marketing authorisation is granted for a medicine for use in the paediatric population the label has to be revised in order to reflect the outcomes of the paediatric investigations. After marketing authorisation has been granted for a medicine for use in children the product must be placed on the market within two years following the date of approval of the paediatric indication.

The marketing authorisation holder must further describe the proposed measures to ensure the long-term follow-up of efficacy and of possible adverse drug reactions to the specific use of the medicinal product in the paediatric population. If the submission of results of paediatric testing was deferred, the MAH has to report annually to the Paediatric Committee an update on the progress with the realisation of the PIP. Companies must submit the results of pre-existing studies, if applicable, which have been completed by the date of entry into force of the Regulation (26.01.2007), for assessment to the competent authorities within one year thereafter.

The EMEA or a national competent authority will have to decide whether a risk management program should be established to cover specific paediatric needs and whether clinical post-marketing studies should be performed by the MAH. In general, regulatory authorities must monitor and enforce compliance with the additional requirements, including assessment of pre-existing studies, updates of the SmPC and package leaflets and a systemic registration of adverse drug reactions related to the paediatric use.

Health care professionals must report any ADRs and have to ensure that they will get the most recent scientific insights and adjust their treatment practice accordingly. Children may be enrolled in specific follow-up programmes.

#### *Short-term effects*

Since medicinal products tested for paediatric purposes will have to be placed on the market within two years following approval, health care professionals will gain a better knowledge in ADRs and, as a result, children will receive better and safer treatment. If all additional requirements will be adequately followed by the industry stakeholders the European paediatric population will considerably benefit.

There are also costs related to the design of plans for follow-up and progress reporting and to maintain pharmacovigilance and write annual reports. The level of costs is not known but may be estimated to be marginally because the main tasks represent adaptations to already existing systems within the companies, such as risk management plans and ADR reporting systems.

Governmental bodies will, however, be faced with an increased workload and a need for more experts as follow-up plans have to be assessed and compliance has to be monitored and enforced.

### ***Long-term effects***

As a long-term consequence of the new Regulation there will be a clear differentiation between adequately tested and authorised paediatric medicines and untested medicines for use in children and a continuous eradication of unlicensed and off-label paediatric prescriptions. Health care professionals will benefit from an increased transparency and will be able to choose between tested and untested medicinal products even though this may not be automatically translated into a change in prescription practices. In any case proper labelling of paediatric products will aid recognition and will help to create a sharper definition of paediatric and other segments of the market for off-patent products. Nonetheless the transparency advantage will also apply for children and their parents as far as OTC products are concerned.

Pharmaceutical companies may have to improve their internal processes in order to comply with the requirement to place the product on the market within two years. A two year period does not seem to be crucial to fulfil, but, this might become a hurdle particularly for small and medium sized companies which infrastructures may be limited in terms of international marketing and sales forces. For patented products the 6-months SPC extension will only be granted if the product is authorised in all Member States of the Community. As this does not mean that the product has also to be placed on the market in all EU Member States the two year deadline mentioned above will not be relevant. Nonetheless major efforts have to be made to approve the product in the entire Community.

The post-marketing requirement will force industry to develop an improved understanding of the safety, efficacy and quality of their paediatric medicine, which may result in the development of better medicines for children. Children can be treated more effectively and there will be most likely fewer cases of ADRs, suboptimal treatment or treatment failures.

### ***Risks and Uncertainties***

Theoretically a tested and in terms of paediatric use labelled medicine could have lower therapeutic benefit than an untested and unlabelled medicinal product for which paediatric testing is not required by the Regulation. In this case the choice of health care professionals to treat a paediatric patient would be in favour of the untested product and off-label use. The same effect may occur when parents buy OTC drugs and compare tested medicines (labelled) with untested drugs (unlabelled). This potential risk will likely become negligible when the number of untested products decreases over the next years, but this may take between 10 to 15 years, as estimated by RAND Europe.

Deferrals may become a very long-term issue and post-marketing reporting may become difficult to improve. Regarding pre-existing studies, it will be a challenge to receive all data on negative trials. [44]

#### **5.4.4 Impact of Facilitating Measures**

There are three measures intended to facilitate the fulfilment of the requirements of the Paediatric Regulation, which are of specific importance during the early period of entry into force of the Regulation. They concern the waiver of the requirement to generate data, deferral to initiating or completing studies in the Paediatric Investigation Plan and the Community referral procedure for existing marketing authorisations.

##### ***Operationalisation***

Pharmaceutical companies will have to provide reasonable justifications and appropriate data to support their requests for a deferral or waiver in the context of a Paediatric Investigation Plan. Based on the conditions qualifying for a waiver (likelihood of the drug to be ineffective or unsafe when used in children, disease/conditions limited to adult population, no significant therapeutic benefit over existing treatments), the industry will have to allocate funds to collecting current evidence (e.g. literature searches, involving experts) in order to support a claim with respect to the therapeutic benefits, efficacy and safety of a drug when used in children. This may increase the costs in addition to the costs of clinical testing. These expenditures, however, are assessed to be minor. On the other hand, the PDCO will have to hire or contract the paediatric expertise to be able to judge on waivers and deferrals.

In case of deferrals companies will have to submit annual reports on ongoing studies providing an update on the progress with paediatric studies taking into account the need to avoid any delay of the authorisation of the product in adults. An additional obligation of the EMEA will be to establish and maintain a list of all waivers, including product-specific and class waivers. The list shall be regularly updated (at least every year) and made publicly available by the EMEA.

Regarding the Community referral procedure, pharmaceutical companies will be gaining an opinion of the CHMP, which will lead to a binding EC-decision, that has to be implemented by each Member State to reflect the agreed wording for the product information concerned.

##### ***Short-term effects***

The aim of deferrals is neither to reduce the workload of the Paediatric Committee and EMEA nor to lower the burden of pharmaceutical industry. Deferral does not mean deferral from requirements and does not prevent the need for a PIP. Deferrals refer to timing of initiation or completion of some or all studies and measures proposed in a PIP. By this means deferrals are intended to allow a medicine to be authorised for adults earlier in comparison to the paediatric indication and the results of studies in children to be presented at a later date (e.g. when a study in children is judged to be safer if delayed after first data and initial experience becomes available from adult studies or when studies in the paediatric population will take longer to perform than studies in adults). This will help both pharmaceutical industry in terms of timelines which are defined in the PIP and the Paediatric Committee during the transitional period when the number of applications is expected to be considerably high.

Waivers will quickly help to focus the work of the PDCO on those medicines and drugs that may be most valuable to be investigated for the use in children. It is estimated that for one third of all applications a waiver or partial waiver will be granted [4].

The possibility to use the Centralised Procedure for new applications and PUMAs provides a shorter or at least easier way to obtain approval in all EU Member States and thus represents an opportunity not to conduct the Mutual Recognition or Decentralised Procedure with all 27 EU Member States.

### ***Long-term effects***

Due to the facilitating measures paediatric testing will only be done when necessary. The possibility of deferrals allows the industry to adjust to the new requirements and/or to current knowledge in terms of evidence-based standard of care. When completion of paediatric studies is delayed further deferrals (if reasonable) allow ensuring the availability of medicines for use in adults.

Waivers will help to identify medicinal products that do not need to be tested in children. This may help health care professionals in their choice between different available medicines. Waivers will also prevent duplication of studies in children and unnecessary testing when a new paediatric medicine has no apparent or potential therapeutic added value.

### ***Risks and Uncertainties***

For some medicinal products it will be rather difficult to decide whether or not the drug or class qualifies for a waiver, particularly as far as the potential lack of significant therapeutic benefit in comparison to other available products or other standards of care is concerned. In any event, the Paediatric Committee has the power to deny the paediatric development for a product when it is of the opinion that there is no therapeutic need to initiate the proposed paediatric testing even though the company may believe that their product falls under the scope of the Regulation, e.g. when the 10<sup>th</sup> application for the same drug substance or class of products is submitted and no significant benefit can be expected [4].

Deferrals may become usual practice when standard Paediatric Investigation Plans are submitted. The latter case might become crucial when no time limit has been defined for the deferred paediatric studies or investigations. Enforcement measures may be limited to annual progress reports, fines and a naming and shaming policy.

Another risk might be the following: health care professionals may decide to prescribe the medicine for use in children based on the knowledge that the drug is intended or anticipated to be tested in the paediatric population, even though the clinical trial results may not be conclusive or even positive. [44]



#### **5.4.5 Impact of Support Measures**

Finally, the objectives of the new EU Paediatric Regulation are reinforced by mainly four support measures, namely the provision of free scientific advice, the Community network on the performance of clinical trials, the inventory of therapeutic needs for the paediatric population to identify research priorities and the establishment of a funding for research into paediatric development.

##### ***Operationalisation***

Companies can request scientific advice to discuss specific and general issues in the developmental process of the paediatric development or programme and to get scientific input and guidance from the agency's experts. EMEA will have to provide advice on the design and performance of various clinical studies necessary to demonstrate the quality, safety and efficacy of the product in the paediatric population.

Pharmaceutical companies, health care professionals and researchers may submit project proposals to the European Commission (according to the call for proposal deadlines and dedicated work programme) in order to participate in the Community Research Framework Programme (FP7). The respective funds have to be allocated and further annual working programmes will have to be identified by the European Commission involving external consultation. One of the tasks of the Paediatric Committee will be to identify research priorities and to establish the inventory of therapeutic needs ideally balancing acute and chronic diseases and to update the existing priority list for studies into off-patent paediatric medicinal products on a regular basis. EMEA is responsible for evaluating the functioning of the programme. Children and their parents or guardians can become involved in the work of the study programmes either as patients in trials by the research and study fund or by lobbying to influence the assignment of research priorities for paediatric testing.

The EMEA and the Paediatric Committee have to establish a network with specific expertise in the performance of paediatric clinical trials. They may build on the existing network of almost 3,000 experts maintained by EMEA, although it may have to be strongly enhanced to improve the quality of advice specific to the needs of the paediatric population. In addition, databases and online tools are needed to be put in place and the EMEA will have to hire in-house experts.

For industry and research organisations the clinical trial or paediatric research network will help improving the possibility to take part in clinical trials. The network will further help to identify investigators and centres with specific expertise, to coordinate studies relating to paediatric medicinal products, will help to avoid unnecessary duplication in the paediatric population and aims to build up the necessary scientific and administrative competences at European level.

##### ***Short-term effects***

The inventory of therapeutic needs and the increased availability of relevant data on existing uses of medicines in children will help to raise awareness of current treatment best practice and identify research priorities, i.e. where future work can be carried out to best effect. Access to knowledge about paediatric medicines and paediatric clinical trials will be improved. This may help pharmaceutical companies since they can obtain prior information to the design of clinical

trials including the PDCO's assessment of the respective Paediatric Investigation Plan. The increased availability of information on medicinal products for paediatric use will help to create a good picture of each product in different countries that is currently available for the use in children. Free scientific advice may help to limit the costs for developing a PIP, particularly for small and medium-sized enterprises since they probably lack of paediatric expertise and/or clinical trial design in-house. On the other hand free scientific advice will cost time and money for the Agency and will considerably increase the EMEA's and PDCO's workload.

### ***Long-term effects***

All supporting measures foreseen in the Paediatric Regulation are generally considered to be highly valuable measures that will provide a strong stimulus to paediatric research in Europe.

Public health will gain faster access to new drugs and new forms of existing medicinal products and improved study designs will lower the risks for children enrolled in clinical trials. Once the Framework Programmes will generate results, tested paediatric medicines will become available also for rare diseases or conditions that would otherwise remain unavailable. Since almost all neonatal medicines are currently unlicensed and parents are highly reluctant to agree to enrol their child in a clinical trial, the Commission's Study Programme could act as a trusted party.

The Study Programme itself will support off-patent drug manufacturers for the investigations needed for a marketing authorisation. The projects will provide evidence for a better use of off-patent products in paediatric populations. The acquired knowledge should lead to new Paediatric Use Marketing Authorisations. The programme can further be used to strengthen pharmaceutical R&D in Europe. The study funds will be particularly useful for small companies whose work is usually restricted by a narrow knowledge base, small markets and a lack of access to capital.

Both the inventory of therapeutic needs and the priority list of off-patent medicinal products will help industry and researchers to identify opportunities, e.g. therapeutic gaps.

The period between trials, approval, and placing on the market may become shorter. Improving study designs and knowledge about paediatric testing may also result in more cost-effective trial designs and industrial savings and will prevent duplication of tests. These instruments of communication and coordination create a greater transparency and provide support for the self-regulating behaviour of pharmaceutical industry (which products to select) and health care professionals (which medicines to prescribe).

### ***Risks and Uncertainties***

One of the risks associated with these measures may be the reluctance of pharmaceutical industry and researchers to share proprietary information on medical R&D and testing.

As a consequence of current lack of knowledge in the field, it is uncertain whether a working group of the CHMP, which will be responsible for providing scientific advice, has sufficient expertise in the field of paediatric testing. This could work better if the scientific advice working group (SAWG) will consult the Paediatric Committee before giving its advice on e.g. draft protocols as this would help ensuring consistency.

The main challenge of support measures concerns the financing of the work commissioned by the study fund. Since funding will be limited to certain projects the majority of organisations, industry and individuals will not gain support. For those who will participate in the Framework Programme, the EU may only support them on the basis of 50% co-financing, which means that applicants for the fund need to have alternative or additional sources of funding (e.g. national government, industry, charities). This is most likely a more prominent issue for academic researchers and health care professionals as their work is generally not destined for the market. [44]

## 6 COMPARISON WITH US EXPERIENCES

### 6.1 PEDIATRIC RULE AND PEDIATRIC EXCLUSIVITY PROVISION

In the US, the FDA implemented a number of largely voluntary measures already in the early 1990s to encourage the availability of appropriate paediatric labelling information<sup>7</sup>. However, these failed to produce significant increases in paediatric drug development and did not result in the desired labelling changes.

The FDA has thus proposed specific legislation to encourage the performance of clinical trials in children which was introduced by the so-called “**pediatric rule**” and “**pediatric exclusivity provision**” adopted in 1998 and 1997 respectively. These pieces of legislation are complementary.

The *pediatric rule*, which was proposed in 1997, finalised in 1998 and became effective on 1 April 1999, requires companies to perform paediatric studies and/or to develop paediatric formulations for new and already marketed medicinal products if the product is likely to be used in a “substantial number of paediatric patients<sup>8</sup>” or if it would provide a “meaningful therapeutic benefit<sup>9</sup>” to paediatric patients over existing treatments. The requirements in the paediatric rule are mandatory but are not directly linked to any incentives or rewards for the pharmaceutical industry, although it may be possible for companies to satisfy the requirement while also being granted the incentive described in the following paragraphs detailing the US exclusivity provisions. In October 2002 the US District Court overturned the *paediatric rule*, however, on 3

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<sup>7</sup> 1) *1997 Pediatric Labeling Regulation*: In 1994, FDA issued a regulation requiring drug manufacturers to survey existing data and determine whether those data were sufficient to support additional paediatric use information in the labelling of their drugs. If a manufacturer determined that existing data permitted modification of the label’s paediatric use information, the manufacturer was required to file a supplemental new drug application to FDA seeking approval of a labelling change. The response to the 1994 rule was disappointing and did not substantially increase the paediatric use information for marketed drugs and biological products. 2) *Pediatric Plan*: In December 1994, FDA’s Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation and Research (CBER) implemented a Pediatric Plan designed to focus attention on and encourage voluntary development of paediatric data both during the drug development process and after marketing. These voluntary activities did not substantially increase the number of drugs with adequate paediatric labelling.

<sup>8</sup> FDA considers the term *substantial number of patients* to mean 50,000 paediatric patients in the U.S. with the disease or condition for which the drug or biological product is indicated (63 CFR 66636)

<sup>9</sup> The term *meaningful therapeutic benefit* is defined as a significant improvement in the treatment, diagnosis, or prevention of a disease, compared to marketed products adequately labelled for that use in the relevant paediatric population (CFR 314.55(c)(5)).

December 2003 the “paediatric rule” requirements were again passed into US law via the **Paediatric Research Equity Act (PREA)**. The PREA provisions are detailed in section 6.2.

The *pediatric exclusivity provision* is part of the 1997 Food and Drug Administration Modernisation Act (FDAMA) and provides an economic incentive to manufacturers who conduct studies of drugs in children in accordance with the requirements of FDAMA. This law, which provides six months added to the market exclusivity or patent protection on the active moiety in return for companies who perform clinical studies in the paediatric population had a sunset date of 01.01.2002. The incentive is granted when the studies, conducted in accordance with a Written Request from the FDA based on public health needs, are submitted to the FDA (details are provided in section 6.3). As it applies for the new EU Regulation the incentive is granted irrespective of whether the results have demonstrated safety and efficacy. Similarly to the EU Regulation the Act required the FDA to draw up guidelines and a paediatric list, i.e. a list of drugs for which additional paediatric information is expected to be beneficial with the aim to prioritise research activities and to close therapeutic paediatric gaps. [45, 51]

The *pediatric exclusivity provision* further includes a requirement that the Secretary report by 1 January 2001, on the experiences under the new law including the effectiveness of the program in improving information about important paediatric uses for approved drugs, the adequacy of the incentives provided and the economic impact of the program on taxpayers and consumers. As described in this report, the *pediatric exclusivity provision* has been highly effective in stimulating new paediatric studies on many drugs and in providing useful new information in US product labelling. After entry into force of the law until December 2000, the FDA has received 191 proposals from industry, issued over 157 Written Requests, asking for 332 studies that would potentially involve well over 20,000 paediatric patients. In less than 3 years, over 58 paediatric studies have been conducted, study reports submitted and exclusivity granted to 25 drugs.

Although the incentives provided by the *pediatric exclusivity provision* has clearly been adequate for many drugs and products, it has naturally tended to produce paediatric studies on those products where the exclusivity has the greatest value and thus the provision has left some important categories of drugs (e.g. old antibiotics, drugs with low sales and other drugs lacking market exclusivity or patent protection because these products are not eligible for any exclusivity) and some age groups (especially the neonatal age group) unstudied or inadequately tested and as a consequence some significant gaps in paediatric labelling information remained.

Most important to note, the economic incentives under US law only apply to drugs with existing patents or exclusivity. For these drugs, the incentives have resulted in a significant increase in the number of paediatric studies performed. Unfortunately, many medicines used in children (but never specifically properly studied for use by children) are not eligible for this kind of incentive because they no longer have patent protection or exclusivity. Contrary, in Europe efforts have been made to implement incentives also for off-patent medicinal products in form of a 10-year period of data protection via a new type of marketing authorisation, the PUMA, which covers exclusively therapeutic indications which are relevant for use in the paediatric population.

FDA believed that the incentives provided by the *paediatric exclusivity provision* would encourage sponsors to conduct paediatric studies for all drugs. Since this was not sufficiently achieved the FDA stated that the *paediatric rule* and the elements codified in the PREA were still necessary to address some of the gaps left.

Nonetheless, due to its success in stimulating new studies on medicinal products to treat children the *paediatric exclusivity provision* has been retained in the **Best Pharmaceuticals for Children Act (BPCA)** in 2002. The new Act which became effective 4 January 2002 provides a new mechanism to help study off-patent products, providing for a prioritised annual listing<sup>10</sup> of medicines (with no patent or market exclusivity protection) for which paediatric studies are needed and federally-funded testing of these drugs [3, 51]. Working with FDA and the *American Academy of Pediatrics* and other experts, HHS' National Institute of Child Health and Human Development (NICHD), part of the National Institutes of Health (NIH), has developed and published that list (called the "List of Approved Drugs for Which Additional Pediatric Information May Produce Health Benefits in the Pediatric Population"), which is updated at least annually on the FDA's website. [51]

Also in Europe similar approaches have been introduced with the new Regulation aiming to stimulate research and development for off-patent medicines: On the one hand through the "Priority List of Off-patent Medicinal Products for Paediatric Studies" of the PEG and on the other hand through the European Community Research Framework Programmes.

## 6.2 PAEDIATRIC RESEARCH EQUITY ACT (PREA)

PREA is the most recent of more than a decade of legislative and regulatory attempts to address the lack of paediatric use information in drug product labelling codifying many elements of the 1998 *paediatric rule*.

The requirements of the 2003 *Pediatric Research Equity Act* apply retrospectively for all applications submitted between 1 April 1999 and the present. PREA requires the conduct of paediatric studies for all new drug applications (NDAs) and biologic license applications (BLAs) (or supplements to those applications) for a new active ingredient, new indication, new dosage form, new route of administration, or – in contrast to the EU Regulation – also new dosing regimen to contain a paediatric assessment (i.e. a dataset of study results characterising safety, efficacy, dosage and administration) unless the applicant has obtained a waiver or deferral (see below). It also authorises FDA to require MAHs for already approved products who are not intending approval for one of the changes listed above to submit a paediatric assessment. Designated orphan medicinal products and generic drugs, i.e., abbreviated new drug applications (ANDAs) are exempted from the PREA provisions, in other words for those applications a

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<sup>10</sup> Generally, an active moiety is included in the priority list if: (1) The drug, if approved for use in the paediatric population, would be a significant improvement compared to marketed products labelled for use in the treatment, diagnosis, or prevention of a disease in the relevant paediatric population (i.e., a paediatric priority drug); or (2) The drug is widely used in the paediatric population, as measured by at least 50,000 prescription mentions per year; or (3) The drug is in a class or for an indication for which additional therapeutic or diagnostic options for the paediatric population are needed

submission for a paediatric assessment or an application for a waiver or deferral is not needed. In the EU this is only the case for generics or similar biological medicinal products, homoeopathic medicines, traditional herbal medicinal products and products authorised through the well-established medicinal use procedure but not for orphan medicinal products. [31]

The paediatric assessment under PREA contains data gathered from paediatric studies using appropriate formulations for each age group for which the assessment is required, and other data that are adequate to assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant paediatric subpopulations (unless waived or deferred) and that are adequate to support dosing and administration for each paediatric subpopulation for which the product has been assessed to be safe and effective.

In general, PREA applies only to those drugs and biological products developed for diseases and/or conditions that occur in both the adult and paediatric populations. Products intended for paediatric-specific indications, like a PUMA in the new EU legislative environment, will be subject to the requirements of PREA only if they are initially developed for a subset of the relevant paediatric population.

There is a noteworthy distinction between the scope of the studies requested under the *paediatric exclusivity provisions* or BPCA and what is required under PREA. For paediatric exclusivity, FDA's authority to issue a Written Request extends to the use of an active moiety for all indications that occur in the paediatric population, regardless of whether the indications have been previously approved in adults or approval for those indications is being sought in adults, which refers only to "information relating to the use of a new drug in the paediatric population". Under PREA, on the other hand, a paediatric assessment is required only on those indications included in the pending application which addresses "the safety and effectiveness of the drug or biological product for the claimed indications". Therefore, to qualify for paediatric exclusivity, the paediatric studies conducted to satisfy the requirements of PREA must also satisfy all of the requirements for paediatric exclusivity under BPCA. [31]

### ***Waivers and Deferrals***

Both the EU and US legislative framework include facilitating measures in form of waivers and deferrals. **Waivers** for paediatric studies in the US are common and typically represent these scenarios:

- The drug or biological product (1) does not represent a meaningful therapeutic benefit over existing therapies for paediatric patients (e.g. an antibiotic) and is not likely to be used by a substantial number<sup>11</sup> of paediatric patients [45]
- Studies would be impractical or impossible in the specified population (because, for example, the number of patients is so small or the patients are geographically dispersed, such as neonates) [45]

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<sup>11</sup> PREA does not define a "substantial number". In the past, FDA generally considered 50,000 patients to be a substantial number of patients.

Another example is a drug or biological product for an indication that has extremely limited applicability to paediatric patients because the pathophysiology of these diseases occur for the most part in the adult population. FDA would be likely to grant a waiver for studies on products developed for the treatment of these conditions without requiring applicants to provide additional evidence of impossibility or impracticality. For a list of adult-related conditions that may be candidates for a disease-specific waiver

- There is already existing evidence of ineffective or unsafe use in all paediatric age groups section

If a waiver is granted based upon evidence that the drug is unsafe or ineffective in paediatric populations, the applicant must include this information in the labelling for the drug or biological product. [45]

A **partial waiver** may be granted if there is evidence of reasonable, yet unsuccessful, attempts to develop a paediatric formulation. Sometimes a partial waiver is granted instead of a full waiver for any of the parameters listed above.

The reasons qualifying for a full or partial waiver are almost identical to those in the EU. The only difference is that the EU Paediatric Regulation does not specify a number of paediatric patients where a product is likely to be used. Further a waiver in the EU may not be based on feasibility reasons as it is possible under US legislation.

A **deferral** acknowledges that a paediatric assessment is required, but permits the applicant to submit the paediatric assessment after the submission of a NDA, BLA, or supplemental NDA or BLA. On its own initiative or at the request of an applicant, FDA may defer the submission of some or all of the paediatric studies until a specified date after approval of the drug or issuance of the license for a biological product for adult use.

FDA may defer the timing of submission of some or all required paediatric studies if it finds one or more of the following:

- The drug or biological product is ready for approval for use in adults before paediatric studies are complete
- Paediatric studies should be delayed until additional safety or effectiveness data have been collected
- There is another appropriate reason for deferral (e.g., development of a paediatric formulation is not complete). [45]

In addition, to obtain a deferral the applicant must submit certification of the reason(s) for deferring the assessments, a description of the planned or ongoing studies, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time [45].

All of these grounds would also qualify for a deferral in accordance with the EU Paediatric Regulation.

### ***The Pediatric Plan***

In order to enable FDA to evaluate the proposed paediatric development for a drug or product, applicants are obliged under PREA to submit a ***Pediatric Plan***. A *Pediatric Plan*, which is largely comparable to a PIP in the EU legislative framework, is a statement of intent that outlines the paediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that the applicant intends to conduct. The plan should also address the development of an age-appropriate formulation. Furthermore, it should detail the grounds for requesting a waiver or deferral under PREA, if applicable. FDA encourages applicants to discuss the *Pediatric Plan* at an early stage of product development. Early consultation and discussions are particularly important for products intended for life-threatening or severely debilitating illnesses. For these products, applicants should aim to seek for scientific advice from FDA at pre-IND meetings and end-of-phase 1 meetings. For products that are not intended for treatment of life-threatening or severely debilitating illnesses, consultation of FDA should occur no later than the end-of-phase 2 stage of product development, i.e., in end-of-phase 2 meeting. These recommendations are quite similar to those laid down in the EU Paediatric Regulation. In the US, free scientific advice is generally provided for any advice given by the FDA whereas the EMEA's free scientific advice is limited to questions related to paediatric drug development. [31]

### ***Compliance with PREA Requirements***

If a paediatric assessment or a request for approval of a paediatric formulation is not submitted by an applicant in accordance with the above mentioned requirements, the drug or biological product may be considered misbranded solely because of that failure and subject to relevant enforcement action. But the failure to submit a paediatric assessment or request for waiver or deferral will not be the basis for withdrawing approval of a drug or the revocation of a license for a biological product. However, the FDA could bring injunction or seizure proceedings if a product is found to be misbranded under these provisions.

In the EU, the Paediatric Investigation Plan (PIP) is the document upon which the development and authorisation of medicinal products for the paediatric population should be based and which itself will be the basis upon which compliance with the requirement is judged. Non-compliance with the requirements of the EU Paediatric Regulation results in non-validation of applications, non-inclusion of the compliance statement by EMEA or the national competent authority and thus leads to ineligibility for the rewards and incentives.



### **6.3 BEST PHARMACEUTICALS FOR CHILDREN ACT (BPCA)**

The issuance of a FDA Written Request is a prerequisite for obtaining the additional 6-months paediatric exclusivity for patented products. Before issuing a Written Request FDA will evaluate the need for studies for all paediatric subpopulations and for all indications for which the active moiety is being used in the paediatric population and might not issue a Written Request for every drug that for which additional paediatric information may create health benefits for children. Similar to the objectives of the EU Paediatric Regulation, in order to prevent duplication of paediatric testing and unnecessary testing in children FDA might not request additional paediatric studies if sufficient paediatric information has already been submitted to the NDA, if sufficient paediatric information exists in the literature and the active moiety can be labelled appropriately based on submission of a NDA/BLA supplement that contains the relevant literature or if information from the population for which the drug is labelled is sufficient to label the drug for all relevant paediatric age groups based on submission of a supplement that proposes such extrapolation.

The Written Request has to be issued before the approval of a new drug application (NDA) and the applicant has to provide the reports of the requested studies to the NDA or BLA after the FDA made the Written Request. The submitted studies must respond completely to the Written Request in order to gain the exclusivity [32]. In the EU the situation is comparable: An applicant can only obtain the 6-months patent (SPC) extension when the respective application includes the results of all studies conducted in compliance with an agreed PIP. As laid down in both the new EU and the US Regulation the incentive is granted irrespective of whether the results have demonstrated safety and efficacy.

Upon a Proposed Pediatric Study Request (PPSR) submitted by a pharmaceutical company, any other interested party or on FDA's own initiative, the FDA may issue a Written Request.

Issuance of a Written Request to a sponsor does not require the sponsor to conduct paediatric studies described in the Written Request since this is voluntary in the US. In contrast to the requirements in the EU Paediatric Regulation (where the results of all studies performed and details of all information collected in compliance with an agreed PIP are obligatory to be part of a new MA application and where penalties will be applied for infringement of the provisions and implementing measures of the Regulation), in the US, it is the sponsor's decision whether to conduct the studies and possibly gain paediatric exclusivity.

As it applies for the EU Paediatric Investigation Plan, it is also possible to amend the FDA's Written Request based on scientific or medical justifications (including timelines). Concerning the timelines of the procedure, there are some differences between EU and US Regulation: FDA estimates that it could take approximately 120 days after submission of a proposed paediatric study request to issue an appropriate response and to issue a Written Request. Sponsors should plan to submit their request with sufficient time to permit FDA to review the proposal, discuss with the sponsor as necessary, issue a Written Request, and permit sponsors to initiate, complete and file reports of studies before expiration of a patent or exclusivity period. In contrast, the EU Paediatric Regulation defines a fixed 60-day procedure which might be extended to a maximum of 120 days in case supplementary information is requested to be provided by the applicant.

Generally, FDA's request will seek all necessary paediatric information for an active moiety whereas in the EU a PIP is required for a product to be developed for paediatric use. Further an EU PIP may only be targeted at indications and is intended to be written for a medicinal product to be investigated for the use in the paediatric population. Both Written Requests and PIPs will have to include information on e.g. type and objective of studies to be performed, indications to be studied, age groups in which the studies will be performed, dosage form, drug-specific safety concerns to be monitored and most important to note timeframes for submitting reports of the studies. [32]

#### **6.4 SUMMARY AND IMPACT OF US REGULATIONS ON EUROPEAN PAEDIATRIC INITIATIVES**

A comparison of the main proposals in the European Paediatric Regulation to the provisions in the US is given in Table 3.

In the last decade, several steps have been taken regarding medicines for paediatric use in the US. Earlier efforts were widely regarded as not sufficient, but, learning from experience, and despite some challenges over the years, the 1997 FDA Modernization Act and one of the succeeding acts, the Paediatric Research Equity Act of 2003 has been seen as working.

The combined measures of obligations and incentives, which are often called “the stick or the carrot”, have been extremely successful in the US in stimulating the development of medicinal products for paediatric use. Under the US Regulations the originating drug manufacturer sector is a winner and the generic sector is a loser as it is expected for the new EU Paediatric Regulation. [44]

Both acts FDAMA and PREA have successfully increased paediatric investigations, specific medical knowledge and prescribing information for US children. Until 31 March 2007, 793 studies have been requested by the pharmaceutical industry, 340 Written Requests have been issued by FDA leading to 514 studies to be conducted (which will approximately include a number of 47,000 paediatric patients) and to a number of 151 paediatric exclusivities granted for approved active moieties. Paediatric studies conducted in response to US legislation have led between 1 July 1998 and 22 June 2007 to 131 labels containing new paediatric information for established medicines submitted in response to a Written Request. The new labels include important new information concerning dosing/pharmacokinetics or safety which has an impact on the safe and effective use of the medicine in the paediatric population and are published on the FDA's website. Without specific studies in children this important information would not have been available. [36]

During the time of finalisation of US Regulations and before the new EU Regulation was implemented in 2006 some EU Member States have tried to introduce national measures to increase the availability of information on the use of medicines in the paediatric population and to increase the availability of authorised medicines that are specifically adapted for use in the paediatric population. Their efforts have been largely unsuccessful. Furthermore, it is disappointing to note that despite the trends towards globalisation in the area of pharmaceuticals, the success of the measures taken in the US has brought little benefit to the children of Europe.

International companies did not appear to be willing to voluntarily submit data collected in the US to support the authorisation of paediatric indications in the EU.

Therefore it was assessed to be unlikely that there will be any substantive progress in this area in the European Union until there is a specific legislative system in place. This was recognised in the Council Resolution of 14 December 2000 which called on the Commission to make proposals in the form of incentives, regulatory measures or other supporting measures in respect of clinical research and development. As described in sections 1, 3.1 and 3.2 of this Master Thesis, after long debates and extensive consultations, the new European Paediatric Regulation was introduced as a legislative response to this Council Resolution.

It remains to be seen what the terms of engagement of the EMEA Paediatric Committee will be and whether they will be similar to or in contrast with those of FDA's Paediatric Advisory Committee. In general, there is the potential for significant discussion between the two bodies about drug development matters. The Confidentiality Arrangements between the agencies, concluded on 12 September 2003, establish a framework for the possible exchange of information on advance drafts of legislation and regulatory guidance documents.

As stated in the most recent press release of 18.06.2007, the ultimate goal of the initiative is to promote and protect public health, reducing regulatory burden and costs and bringing innovative products to patients in a timely manner. At a meeting occurred on 14-15 June 2007, the FDA, the European Commission and the EMEA have agreed to expand their current cooperative activities in the areas of paediatrics. Based upon the newly adopted Paediatric Legislation in the EU, the already existing US Paediatric Regulations, and in the context of the Confidentiality Arrangements, the three parties have taken a further step in agreeing on principles for interactions in relation to paediatric matters that will facilitate the timely exchange of information on scientific and ethical issues for paediatric medicinal products and therapies. [29, 30]

The New Paediatric Regulation in the EU – Development, Implications and Comparison with US Experiences in Paediatric Drug Development

Table 3: Comparison of Paediatric Drug Regulations EU vs. US

Topic	USA	EU	Comment
<b>Legislation</b>	<p>2003 Pediatric Research Equity Act (PREA) “<i>Pediatric Rule</i>”</p> <p>2002 Best Pharmaceuticals for Children Act (BPCA) “<i>Pediatric Exclusivity Provision</i>”</p>	<p>Regulation (EC) No 1901/2006, amended by Regulation (EC) No 1902/2006</p>	
<b>“Stick”</b>	<p>PREA: A <i>Pediatric Plan</i> (incl. waivers and/or deferrals) must be submitted for already claimed indications</p> <p>BPCA: Submission of PPSRs strongly encouraged to obtain FDA’s Written Request and/or Written Agreement</p> <p>BPCA: FDA issues Written Request for an active moiety for an already approved indication (for adults or parts of paediatric population) that occurs in children and appears on FDA’s “Priority List”</p>	<p>A PIP (incl. waivers and/or deferrals) must be submitted for all new applications and certain line extensions for on-patent products</p>	<p>Agreed PIP is mandatory for adult approvals (exemption: waivers) (a PIP is required for a product intended to be developed for paediatric use)</p> <p>Written Request is not mandatory for approval of adult products (a Written Request is issued for an active moiety)</p>

The New Paediatric Regulation in the EU – Development, Implications and Comparison with  
US Experiences in Paediatric Drug Development

*Table 3: Comparison of Paediatric Drug Regulations EU vs. US – continued (1)*

Topic	USA	EU	Comment
<b>“Stick” -continued-</b>	<p>PREA (mandatory for all new and already marketed drugs and biologics): Submission of paediatric data in every application for a new ingredient/dosage form/dosing regimen/route of administration (as of 01.04.1999)</p> <p>Does not cover generics or orphan drugs</p>	<p>Paediatric study results mandatory as an integral part of MA application to be submitted for all new drug applications (as of 26.07.08) and already authorised patented products for new indication/route of administration/pharmaceutical form (as of 26.01.09)</p> <p>Does not cover generics, biosimilars, products with well-established use, homoeopathic products, traditional herbal medicinal products</p>	
<b>“Carrot”</b>	6 months of an additional market protection for conducting clinical trials in children if trials are conducted in compliance with all conditions of a Written Request (incl. timing of studies)	<p>6 months SPC-extension (i.e. additional market protection) for conducting clinical trials in children:</p> <ul style="list-style-type: none"> <li>- when applications include the results of all studies conducted in compliance with an agreed PIP (incl. timing of studies)</li> <li>- when EU-wide MA</li> <li>- relevant information included in the labelling</li> </ul>	BPCA: Exclusivity is entirely voluntary. A sponsor can decide not to conduct the studies in the Written Request. SPC-extension is only granted when studies are in full compliance with Written Request
<b>- Off-patent Products</b>	No regulation	PUMA (10 years data protection)	PUMA qualifies for the Centralised Procedure
<b>- Orphan Medicinal Products</b>	Not regulation	2 years added to 10-year market exclusivity when application is in compliance with an agreed PIP	

The New Paediatric Regulation in the EU – Development, Implications and Comparison with  
US Experiences in Paediatric Drug Development

Table 3: Comparison of Paediatric Drug Regulations EU vs. US – continued (2)

Topic	USA	EU	Comment
<b>Additional Requirements</b>	PREA: FDA is allowed to require paediatric data for already marketed products submitted prior to 01.04.1999	Submission of pre-existing paediatric studies (completed by 26.01.2007) to NCA	Studies may be included into PIP and qualify for being granted incentives/rewards (when completed after 26.01.2007 and assessed to be significant)
	No requirement	Additional post-marketing pharmacovigilance requirements	
	No requirement	For already approved products: placing on the market within 2 years after approval of the paediatric indication	
<b>Support for Research</b>	Funding from NICHD	Community Funding Programmes (FP7)	

## 7 OVERALL CONCLUSIONS AND OUTLOOK

The absence of paediatric testing and appropriate labelling poses significant risks for children, including adverse reactions and ineffective treatment through underdosing, that could be avoided if such information were provided. Inadequate labelling information may further deny paediatric patients the ability to benefit from therapeutic advances because physicians choose to prescribe existing, off-label or unlicensed products, which might be less effective in the face of insufficient paediatric information about a new medication. The failure to produce drugs in dosage forms that can be used by young children (e.g., liquids or chewable tablets) can also deny them access to important medicinal products.

It may safely be assumed that more than 50 percent or more of medicines used in children in Europe have never been actually studied in this population and are not authorised for such use [2, 51]. Viable mechanisms to enhance paediatric medicinal research in Europe was lacking for a long time. The attempts and efforts made in the US resulted in great benefits for US children. Europe has been slow to follow. Although clearly based upon the US experience, the EU Paediatric Regulation incorporates a similar “carrot” but a larger “stick” to ensure companies will undertake paediatric development work for new drugs in Europe.

All the key measures in the new EU Paediatric Regulation build on or strengthen the existing framework for the Regulation of medicinal products: the Paediatric Committee is established and the procedures for agreeing Paediatric Investigation Plans, waivers and deferrals will operate, within the existing EMEA; the requirement for data in children applies to the current procedures for marketing authorisation applications; the reward for compliance with the requirement is a six-months extension to the existing supplementary protection certificate; for orphan medicinal products the reward for compliance with the requirements is two years added to the existing market exclusivity; the new type of marketing authorisation, the PUMA, utilises the current marketing authorisation procedures; measures are put in place to increase the robustness of the current pharmacovigilance system for children; an EU inventory of therapeutic needs of children and an EU network of clinical trials will be coordinated by the EMEA which will also be responsible for the provision of free scientific advice for the industry; the EudraCT database set up to support the existing EU Clinical Trials Directive will provide the database of paediatric clinical trials and study funds will be provided via the European Framework Programmes.

The implemented core requirements in the EU Regulation will definitely ensure that medicines are appropriately tested and authorised in the various paediatric populations. The development of medicines for paediatric use will be stimulated by a number of incentives and rewards. The additional requirements, facilitating and support measures provide strong support for research by smoothing procedures, providing information and ensuring availability.

The Regulation will definitely cost money: Industry will have to pay for complying with the various requirements, government has to provide adequate infrastructures to make the Regulation work, households, health care professionals and insurers will be faced with slightly higher drug prices, as a result of added paediatric testing. Producers of patented medicines will benefit substantially more than the generic industry. The potential sharing of confidential drug development information between EMEA and FDA hopefully will mean that there will be less

duplication of effort for those companies intending to obtain a new product approval in Europe and the US, ultimately resulting in a greater benefit to both paediatric populations.

The overall objective of the EU Paediatric Regulation is to improve the health of the children in Europe. Based on the successful experiences in the US and the comparable approach made in Europe it is concluded that the Paediatric Regulation provides one half of the solution. By changing the economics and legal preconditions, the European Commission hopes to steer consumers, involving health care professionals and households, towards tested and, hence, safer and more effective medicines. If the products are developed and the tested products are indeed prescribed, children will benefit through better treatment, shorter hospitalisation and lower drug consumption and will at the end enjoy a better quality of life. A number of risks and uncertainties related to possible delays in drug development, authorisation and market entry remain. But choice remains the most uncertain factor: the readiness of the industry to focus on the development of paediatric medicines, the response of generic manufacturers to the incentives of a PUMA and the willingness of health care professionals to prescribe tested medicines in disfavour of off-label and unlicensed medicinal products. The final piece – regulating prescription practices – will have to be provided by policy makers in the health care domain.



## 8 LITERATURE REFERENCES

1. Ad hoc Group for the development of implementing guidelines for Directive 2001/20/EC. Ethical Considerations for clinical trials performed in children – Recommendations of the Ad hoc group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use. 6 October 2006
2. Arlett P. Proposed regulation on medicinal products for paediatric use – Overview and explanation of the proposal. September 2004
3. Best Pharmaceuticals For Children Act, Public Law 107-109, 107th Congress. An Act to amend the Federal Food, Drug, and Cosmetic Act to improve the safety and efficacy of pharmaceuticals for children. 4 January 2002
4. Brasseur D. The New Paediatric Regulation – Establishment and Role of Paediatric Committee (PDCO). 9<sup>th</sup> DGRA Annual Congress. Bonn 12 June 2007
5. Brauholtz D, Edwards S, Lilford R. Are randomised clinical trials good for us (in the short term)? Evidence of a ‘trial effect’. *J. Clin. Epidemiol.* 2001; 54: 217-224
6. Chalumeau M et al. *Arch Dis Child.* 2000; 83: 502-5
7. CMD(h) Best Practice Guide EU Work Sharing Procedure in the Assessment of Paediatric Data, Revision 3. March 2007
8. Commission guideline on the format and content of applications for agreement or modification of a Paediatric Investigation Plan and requests for waivers or deferrals and concerning the operation of the compliance check and on criteria for assessing significant studies for public consultation, Draft Version January 2007
9. Conroy S, Choonara I, Impicciatore P, Mohn A, Arnell H, Rane A, et al. Survey of unlicensed and off label drug use in paediatric wards in European countries. *BMJ* 2000; 320: 79-82
10. Council Regulation (EEC) No 1768/92 of 18 June 1992 concerning the creation of a supplementary protection certificate for medicinal products. Luxembourg 18 June 1992
11. CPMP/EWP/462/95 Note for Guidance on Clinical Investigation of Medicinal Products in Children. London 17 March 1997
12. CPMP/ICH/2711/99 ICH Topic E 11, Clinical Investigation of Medicinal Products in the Paediatric Population. London January 2001

13. Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 on the approximation of the Laws, Regulations and Administrative Provisions of the Member States relating to the Implementation of Good Clinical Practice in the conduct of Clinical Trials on Medicinal Products for human use. Luxembourg 4 April 2001
14. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use. Brussels 6 November 2001
15. Dunne J. Medicines for Children – Regulation on medicines for paediatric use EC No 1901/2006. 9<sup>th</sup> DGRA Annual Congress. Bonn 12 June 2007
16. EFPIA. Position Paper EFPIA, Views on the European Commission’s Proposal for a Regulation on Medicinal Products for Paediatric Use. Brussels April 2005
17. EGA Position Paper EGA Comments on the Proposed Regulation on Incentives for the Development of Medicines for Paediatric Use (in response to the second public consultation). Brussels 8 April 2004
18. EMEA/175192/2004/rev2 EMEA/PEG Procedure for identifying paediatric needs. London 29 June 2005
19. EMEA/197972/2007 Updated priority list for studies into off-patent paediatric medicinal products. London April 2007
20. EMEA/197972/2007 Updated priority list - revised for studies into off-patent paediatric medicinal products. London June 2007
21. EMEA/252232/2007 Press Release European Medicines Agency’s Management Board elects new chair and vice-chair. London, 8 June 2007
22. EMEA/27164/98 Rev.1 Report on the Experts Round Table on the Difficulties related to the Use of New Medicinal Products in Children held on 18 December 1997. London 30 July 1998
23. EMEA/520085/2006 Frequently asked questions on regulatory aspects of Regulation (EC) No 1901/2006 (Paediatric Regulation) amended by Regulation (EC) No 1902/2006, last updated on 12 January 2007. London 12 January 2007
24. EMEA/9224/2007 Press Release: EMEA prepares for entry into force of new legislation on paediatric medicines. London 12 January 2007
25. European Commission Better Medicines for Children Proposed regulatory actions on Paediatric medicinal products Consultation document. Brussels 28 February 2002

26. European Commission C (2007) 560. Cooperation Work Programme 2007 In accordance with Articles 163 to 173 of the EC Treaty, and in particular Article 166(1) as contextualised in the following decisions: Decision 1982/2006/CE of the European Parliament and of the Council of 18/12/2006 concerning the 7th Framework Programme of the European Community for Research, Technological Development and Demonstration (2007 – 2013) and the Council Decision 971/2006/CE of 19/12/2006 adopting a Specific Programme for Research, Technological Development and Demonstration: 'Cooperation' (2007 – 2013). 26 February 2007
27. European Commission COM (2002) 278 final. Communication from the Commission Action plan "Simplifying and improving the regulatory environment". Brussels 5 June 2002
28. European Commission Research Directorate-General. The Seventh Framework Programme (FP7), Taking European Research to the Forefront. Brussels 2007
29. FDA, European Commission, EMEA. Press Release, Regulatory Cooperation Expanded. 18 June 2007
30. FDA, European Commission, EMEA. Principles of Interactions: Between EMEA and FDA Pediatric Therapeutics. June 2007
31. Guidance for Industry, How to Comply with the Pediatric Research Equity Act, Draft Guidance. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) September 2005. Rockville September 2005
32. Guidance for Industry, Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER). Revised, September 1999. Rockville September 1999
33. Guiton SD, Reith M, Isitt VL. Off label prescribing in children. BMJ; 2002: 325:338
34. <http://cordis.europa.eu/en/home.html>
35. [http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2002/feb/cd\\_pediatrics\\_en.pdf](http://ec.europa.eu/enterprise/pharmaceuticals/pharmacos/docs/doc2002/feb/cd_pediatrics_en.pdf)
36. <http://www.fda.gov/cder/pediatric/index.htm>
37. <http://www.hyksinstituutti.fi>
38. <http://www.mcrn.org.uk>

39. <http://www.paed-net.org>
40. <http://www.rand.org>
41. Jacqz-Aigrain E, Kassai, Behrouz. The French network of Paediatric Clinical Investigation Centres (CICPs). Assessment of activities over a three year period, 2004–2006. *Paediatric and Perinatal Drug Therapy*; 2007: 8 (1)
42. Joint European Commission / EMEA Document: Priorities for Implementation of the Regulation on Medicinal Products for Paediatric Use (based on common position of the Council amended by second reading agreement). September 2006
43. Lantos J.D. The ‘inclusion benefit’ in clinical trials. *J. Pediatr.* 1999;134: 130-131
44. Oortwijn WJ., Horlings E, Anton S, van het Loo M, Kahan JP. Extended Impact Assessment of a draft Regulation on medicinal products for paediatric use. Rand Corporation 2004
45. Pediatric Research Equity Act of 2003. One Hundred Eighth Congress of the United States of America, At the First Session, Begun and held at the City of Washington on Tuesday, the seventh day of January, two thousand and three, An Act To amend the Federal Food, Drug, and Cosmetic Act to authorize the Food and Drug Administration to require certain research into drugs used in pediatric patients. Washington D.C. 7 January 2003
46. Regulation (EC) No 141/2000 of the European Parliament and of the Council of 16 December 1999 on orphan medicinal products. Brussels 16 December 1999
47. Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. Strasbourg 12 December 2006
48. Regulation (EC) No 1902/2006 of the European Parliament and of the Council of 20 December 2006 amending Regulation 1901/2006 on medicinal products for paediatric use. Brussels 20 December 2006
49. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency. Strasbourg 31 March 2001

50. Saint Raymon, A. The Paediatric Regulation – Paediatric Team, Scientific Advice, Paediatrics & Orphan Drug Sector EMEA 2007. 9<sup>th</sup> DGRA Annual Congress. Bonn 12 June 2007
51. Status Report to Congress. The Pediatric Exclusivity Provision, January 2001, Status Report to Congress, Department of Health and Human Services U.S. Food and Drug Administration. January 2001
52. Thorsen T. and Mäkelä M. (Editor) Changing Professional Practice - Theory and Practice of Clinical Guidelines Implementation. Danish Institute for Health Services Research and Development. Copenhagen 1999
53. T Jong GW, Vulto AG, De Hoog M, Schimmel K, Tibboel D, van den Anker JN. Unapproved and off label use of drugs in a children's hospital. N Engl J Med 2000; 343: 1125
54. Turner S, Longworth A, Nunn AJ, Choonara I. Unlicensed and off-label drug use in paediatric wards: prospective study. BMJ 1998; 318: 343-345

## **Erklärung**

Hiermit erkläre ich an Eides statt, die Arbeit selbständig verfasst und keine anderen als die angegebenen Hilfsmittel verwendet zu haben.

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Unterschrift