

**Exploring Paediatric Indications for Off-patent  
Drug Substances – Strategic Input of  
Regulatory Affairs**

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## Preface

Case setting: a Regulatory Affairs Manager is working for a pharmaceutical company in Europe. The company is engaged in research and development concerning special therapeutic areas and holds various marketing authorisations for on-patent and off-patent drug substances. Within the responsibility of the Regulatory Affairs Manager falls to give strategic input into planning of development projects from a regulatory perspective. One morning the company's Head of Development sends the Regulatory Affairs Manager the following memo:

***Subject: Proposal for a paediatric development programme of ESTABLISH<sup>â</sup> – Regulatory evaluation required***

Dear colleague,

At the last meeting of the Senior Executive Committee a proposal for a paediatric development programme of our product ESTABLISH<sup>®</sup> has been discussed. The product is on the market since 17 years and faces generic competition. The current labelling restricts its therapeutic indication to the use in adults. We know, however, that the drug is widely administered to children in an off-label setting since many years.

The Executive Committee was aware of general discussions between medical society, industry and regulatory bodies about the need to explore paediatric indications. Hence it was assumed that the current evolution in the legislative environment could support efforts in extending our current labelling to children.

Of course, we are obliged to balance all investments into our products against the possible business benefit and to be transparent for our investors and shareholders. We therefore need information on time, resources and costs required for the proposed extension to the paediatric population. Furthermore, it is important to know whether it is possible to prevent our competitors from using our data for their generic products.

In order to support the decision process the Executive Committee asks you for a presentation about this topic at the next meeting. The following general questions should be discussed:

- ⇒What is the status of the current discussions within the EU about the exploration of paediatric indications for off-patent drug substances?
- ⇒Are there any other concepts, especially in the US?
- ⇒What incentives are proposed for companies making effort in this development?
- ⇒Which set of data is required for the application file?
- ⇒What are the expectations from the future evolution of the regulatory environment?

A 30-minute slot will be reserved for your regulatory evaluation on the agenda of the next meeting, which will take place on Monday next week.

Thanks!

The present master thesis is aimed to support the Regulatory Affairs Manager in answering these questions. It gives an up-to-date overview on the current status of this topic by addressing the relevant fields. This should enable the Regulatory Affairs Department to provide an adequate evaluation that is necessary for strategic decisions of the company.

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## Linguistic Notes

The British spelling ‘paediatric’ is used throughout the entire work. However, if the term is related to a fixed US expression like titles of legal texts or the name of departments of the FDA, the American spelling ‘pediatric’ is maintained.

In order to avoid confusion with the abbreviations, the Summary of Product Characteristics is abbreviated as ‘SmPC’ (instead of the also commonly used ‘SPC’), whereas for the Supplementary Protection Certificate the abbreviation ‘SPC’ is used.

## List of Abbreviations

AAP	American Academy of Pediatrics
ADR	Adverse drug reaction
AE	Adverse event
ANDA	Abbreviated New Drug Application
BA	Bioavailability
BE	Bioequivalence
BPCA	Best Pharmaceuticals for Children Act
COMP	Committee for Orphan Medicinal Products (at EMEA)
CP	Centralised Procedure (in the EU)
CPMP	Committee for Proprietary Medicinal Products (at EMEA)
DHHS	Department of Health and Human Services
DPDD	Division Pediatric Drug Development (at FDA)
ECJ	European Court of Justice
EMA	European Agency for the Evaluation of Medicinal Products
ENDIC	European Network for Drug Investigation in Children
EU	European Union
FDA	Food and Drug Administration
FDAMA	Food and Drug Administration Modernization Act
FDCA	Federal Food, Drug, and Cosmetics Act
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GP	General practice
ICU	Intensive Care Unit
IND	Investigational New Drug
INoPSU	International Network of Paediatric Surveillance Units
IP	Intellectual property
MRP	Mutual Recognition Procedure (in the EU)
NDA	New Drug Application
NICHHD	National Institute of Child Health and Human Development
NIH	National Institute of Health
ODS	Office of Drug Safety (at FDA)
OPT	Office of Pediatric Therapeutics (at FDA)
OTC	Over the counter (i.e. available without prescription)
PB	Paediatric Board (at EMEA, proposed)
PD	Pharmacodynamic
PdIT	Pediatric Implementation Team (at FDA)
PEG	Paediatric Expert Group (at EMEA)
PK	Pharmacokinetic
PPRU	Pediatric Pharmacology Research Unit
PSUR	Periodic Safety Update Report
RDP	Regulatory data protection
SMEs	Small and medium-sized enterprises
SmPC	Summary of Product Characteristics
SPC	Supplementary Protection Certificate
US	United States of America

## 1. Introduction

The aim of the present master thesis is to give an overview of various regulatory aspects to be considered when making a strategic decision on the exploration of paediatric indications. It is principally focused on the special situation for off-patent drug substances in the EU, and describes the status as of July 2003. Based on a presentation of the current regulatory environment and recent proposals for its evolution, an assessment is made in terms of the impact on stimulation of paediatric development and registration of generated data.

Off-patent drug substances are defined as having no intellectual property protection any longer and being used in medical therapy for many years. These substances usually have a well known efficacy and safety profile due to the long-term experience. However, they are often used even outside the approved labelling according to the SmPC (termed 'off-label'), e.g. in other indications or in other patient populations. This use is based more on historically generated knowledge rather than substantiated information from adequate and well-controlled clinical trials, which makes this situation unsatisfactory. On the other hand, without any intellectual property protection and in the absence of additional protection rights, generic companies are enabled to file applications by making full reference to the preclinical and clinical data of the innovator. Thus every extension of the labelling of the innovator's product on grounds of the necessary clinical trials could be directly claimed for the generic products.

It has been shown that medical treatment of children is often made by using substances, which are not licensed for that purpose. This is caused by the absence of approved products for the use in the paediatric population, a situation that refers to both on-patent and off-patent drug substances. Various reasons led to this situations, like the challenges in conducting clinical trials in children, the need to investigate various age groups, and the low return of investment due to the limited size of the patient population. However, concerns about the possible risks due to the lack of efficacy or safety data initiated discussions between authorities, governments, physicians and pharmaceutical industry to overcome this situation.

Getting paediatric indications into the labelling of medicinal products requires an application of the pharmaceutical company and the approval of the competent authority. Also for off-patent drug substances this approval is based on the presentation of evident scientific data with the need to invest time, money and resources for the generation. Of course, pharmaceutical companies have a humanitarian engagement due to their contribution to medical progress and public health. However, considering the required investments there is a strong business aspect in order to finance these contributions. It is therefore of utmost need that the strategic decision within a company considers the incentives for the efforts made.

There are various regulatory considerations to be made by a company in order to decide on a product-specific paediatric development programme for an off-patent drug substance. After a brief summary of general aspect of the exploration of paediatric indications for off-label drug substances, the following provides a description of the European regulatory initiatives together with information about the US programmes and national activities in selected Member States. To assess the impact of paediatric labelling changes in the US on EU product information, the results of a respective analysis are presented. A key section describes aspects of financing paediatric research once the patent is expired with special focus on incentives for the company through protection rights. Finally, basic information about possible data to be used for the registration of paediatric indications in the off-patent setting is summarised.

## 2. General Aspects

In order to assess regulatory aspects of paediatric development for off-patent drug substances, some basic facts should be recalled. This includes characteristics that make children special for medical therapy as well as the current use of drugs in the paediatric population. Furthermore, the current regulatory environment for development with off-patent drug substance is described making note of the relevant judgement of the European Court of Justice (ECJ).

### 2.1. Why represent paediatric patients a special population for medical therapy?

The key message is: Children are no small adults! There are significant differences between the paediatric population and adults that make a special designed drug therapy of utmost need. The following provides an overview to substantiate this statement by describing basic pharmacokinetic and pharmacodynamic characteristics and aspects of appropriate dosage forms.

#### *Pharmacokinetic characteristics*

In general, pharmacokinetic (PK) represents a simplified model to describe the effect of the body on the drug substance through a quantitative description of the time-dependent concentration profile of a drug substance and if necessary its metabolite(s). In consequence, differences in the physiology have direct impact on the PK. This is especially true for the paediatric population due to fast growing and maturation. In order to reflect different stages of paediatric development it is helpful to distinguish between various age groups. The categorisation scheme according to the ICH guideline E11, which is presented in Table 1, shall be used for that purpose recognising an overlap between the developmental stages across age categories.

Table 1 Categorisation of the paediatric population according to ICH guideline E11

Age	Category
---	pre-term newborn infants
0 to 27 days	term newborn infants
28 days to 23 months	infants and toddlers
2 to 11 years	children
12 to 16-18 years	adolescents

The most changes to the physiology occur within the first 12 months of living [1]. Therefore, individual adjustment of dose and dosing interval is of special importance in this period. But also the other age groups have important PK characteristics to be considered.

The rate and extent of the **absorption** of orally administered drugs can be altered in newborns and infants by changes in gastric pH and gastro-intestinal transit time as well as maturity of the intestinal mucosae and its colonisation of bacterial flora [2]. The following physiological alterations with possible effect on the absorption are described for various age classes [1]:

- ⇒ newborns: gastric pH > 5, irregular gastric emptying time; reduced intestinal surface and motility, immature biliary function → irregularly reduced oral absorption, reduced pre-systemic clearance
- ⇒ infants: gastric pH 2-4, increased gastric emptying time, increased intestinal motility → increased rate of oral absorption, increased pre-systemic clearance
- ⇒ children: moderate increased gastric emptying time and intestinal motility → increased pre-systemic clearance.



For administration routes other than the oral one the absorption is influenced by permeability and muscular perfusion [1]. The rectal administration is very efficient in newborns and efficient in young infants. In newborns and young infants the percutan absorption is increased. The intramuscular administration leads to variable kinetics in newborns and to increased absorption in young infants.

Regarding the *distribution* the ratio between body water and body fat is important. The total body water falls from 77% in newborns within 3 months to 73% and after one year to 59%, which is close to the value in adults of 55% [3]. The changes to body fat are nearly complete after the first year of living following continuous increase over that time [1]. Additionally, the protein binding capacity is of importance. In newborn the unbound fraction of drug substances with high protein binding is often increased due to lower concentration of plasma proteins and reduced binding capacity [1]. The alterations in physiology affecting the PK of drug substances can be summarised as follow [1]:

- ⇒ newborns: reduced plasma albumin binding, additional foetal albumin, reduced total protein and globulin, increased serum bilirubin, increased free fatty acids, blood pH 7.1-7.3, scarce adipose tissue → increased fraction of unbound drug substance, volume of distribution increased for hydrophilic drug substances and reduced for hydrophobic drug substances
- ⇒ infants: reduced total proteins and globulin, reduced adipose tissue → increased fraction of unbound drug substance, volume of distribution increased for hydrophilic drug substances and reduced for hydrophobic drug substances
- ⇒ children: generally reduced adipose tissue → slightly increased fraction of unbound drug substance, volume of distribution slightly increased for hydrophilic drug substances and slightly reduced for hydrophobic drug substances

The differences in *metabolism* between the various age classes are rather complex. They are usually related to phase I reactions, especially the activity of cytochrome P450. As an example, the alterations in CYP3A4, an important enzyme of the cytochrome P450 complex catalysing the biotransformation of well over 20 drug substances used in the paediatric population, are as follows [1]: The activity is very low at birth, reaching 30-40% after one month of living and full activity compared to adults after 6 months. Between 1-4 years of age the activity may exceed the adult activity and falls back to 100% level after puberty. It should be noticed that the changes for other enzymes of the complex like CYP2D6, CYP2C9 and CYP3A7 are different. Furthermore, phase II reactions may change over time, e.g. the activity of the N-acetyl transferase 2: poor activity up to 2 months and adult activity by 1-3 years. These physiological changes have an impact on clearance and half-life of the drug substances.

The renal *excretion* in newborns is reduced although the number of nephrons is identical to older children and adults [3]. However, within the first two weeks the glomerular filtration rate increases significantly [1]. Tubular secretion may be developed with some delay leading to an initial imbalance between glomerular filtration and tubular secretion. At an age of 6-12 months the renal function may be considered to be comparable to adults. Special attention is to be paid for pre-term newborns, as the development of nephrons is usually not complete. Any reduction in renal excretion leads to prolonged half-life and reduced clearance.

### *Pharmacodynamic characteristics*

Some drug substances may also show considerable changes of the pharmacodynamic (PD) within the various age categories. Information about PD alterations is however more limited since the impact of the physiology on the PK needs to be evaluated prior to drawing any

conclusion on possible specialities in PD [4]. As an example, the grey baby syndrome caused by chloramphenicol was initially assessed as being a consequence of higher susceptibility in newborns but has been described later with an underlying PK process. An apparent PD difference was also assumed for famotidine in newborns, although this may have a PK basis [1].

The reason for PD alterations may be (a) qualitative or quantitative differences in the relevant receptors, or (b) differences in the endocrine system, or (c) differences in the anatomic composition of the organs [4]. E.g., differences in cholinergic and adrenergic receptors in newborns may have an impact on the blood circulation after administration of drug substances. For cyclosporin it has been shown recently that PD differences appear not only to be caused by PK alterations but rather true drug-receptor interactions [1]. A reduction of the inhibitory concentration ( $IC_{50}$ ) for the expression of the IL2-receptor was demonstrated. In addition to the PK alterations, which are already considered for therapeutic drug monitoring of cyclosporin [5], this additional aspect may be relevant for the correct therapy.

### ***Appropriate dosage forms***

The administration of drug substances to the paediatric population may require special dosage forms designed for that purpose. The reasons are the following:

- For the oral route either liquid dosage forms or solid dosage forms that may be mixed with drinks/food prior to administration are necessary for infants and children. Other routes of administration like parenteral or rectal use may be preferred for PK reasons or due to practical considerations (e.g. in an ICU setting).
- Due to the variability of the required dose for various age groups the dosage form should allow appropriate adjustment for accurate dosing. This includes the availability of measuring devices. In some situations a set of dose strength may be required to cover the entire range.
- The excipients need to be selected taking into account the patient population. Safety aspects of substances require consideration within the pharmaceutical development, e.g. the choice of preservatives. Furthermore, excipients may be selected for special aspects like masking of bad taste.

The absence of appropriate dosage forms may cause significant risks as this leads to extemporaneous dispensing or purchasing of unlicensed preparations [6]. Medication errors may result. Furthermore, there is no data on important characteristics like stability, solubility, and BA of the individually prepared formulation [7]. It should be noticed that a Concept Paper on paediatric formulations (CPMP/QWP/415/03) is already available that is supposed to be transformed in a draft guideline by December 2003.

## **2.2. What is the current situation regarding the use of drug substances in children?**

The issue of the lack of data on the use of drug substances in the paediatric population is commonly known and affects medical societies across the world [6][7][8]. In contrast to the adult population for which information on the use of the medicinal product is available through adequate and well-controlled clinical trials, there is often no information for the paediatric use. There are various reasons for this situation, e.g. the difficulties in the conduction of clinical trials in the paediatric population including ethical concerns, the variety of the paediatric population with the need to study subpopulations, and the low expectations for the return of investment in the clinical trials due to the limited size of the population. In consequence, either the off-label or the unlicensed use in this special patient population results. Off-label use means the use of the product outside the terms of the approved SmPC, i.e. the administration [6]:

- of a higher or lower dose
- in patients under the age for which the product is approved
- outside the approved indication
- in another route than the approved one
- in a condition that is listed as contraindication,

whereas unlicensed use describes:

- extemporaneous dispensing (e.g. to produce liquid formulations)
- preparation of unlicensed formulations manufactured under GMP conditions
- importation of drugs approved outside the country in question
- supply by a pharmaceutical company on a named-patient basis
- use of chemicals as medicinal products.

It is to be noticed that unlicensed use may follow specific legal limitations in each individual EU Member State. E.g. in Germany the supply on a named-patient basis is only possible within clinical trials, and the importation of medicinal products that are approved outside Germany is possible under specific conditions described in the German Drug Law.

In order to describe the extent of off-label and/or unlicensed use of drug substances in the paediatric population, various investigations have been performed. Table 2 provides a summary of some of these studies. It shows that off-label use is widespread and occurs in all clinical settings but with much greater extent in hospitals, i.e. in critically ill patients.

Table 2 Selection of published studies evaluating the extent of off-label and/or unlicensed use in the paediatric population

<b>Setting (Country)</b>	<b>Population (Number of patients)</b>	<b>Methodology (Duration)</b>	<b>Percentage of prescriptions (1) off-label (2) unlicensed</b>	<b>Refer- ence</b>
Hospital (5 EU countries)	4 days – 16 yrs. (624)	prospective (4 weeks)	(1) 38.5 % (2) 7.3 %	[10]
ICU (UK)	Neonates (70)	prospective (13 weeks)	(1) 54.7 % (2) 9.9 %	[11]
ICU (Israel)	Neonates (105)	prospective (4 months)	(1) 59 % (2) 16 %	[12]
GP (UK)	up to 12 yrs. (1175)	retrospective (1 year)	(1) 10.5 % (2) 0.3 %	[13]
GP (France)	under 15 yrs. (989)	prospective (1 day)	(1) 29 % (2) 4 %	[14]
GP (Germany)	up to 16 yrs. (455'661)	retrospective* (3 months)	(1) 13.2 % (2) not avail.	[15][16]

\* data base evaluation

Moreover, off-label use is more likely in newborns, a patient population that requires an extremely high level of caution. Regarding general practice (GP) it should however be noted that due to the large volume the total number of off-label prescription might be considerable high. Furthermore, none of the studies reflects the off-label use in OTC preparations.

Off-label and/or unlicensed use is commonly related to drug classes, which are widely used in paediatric therapy: analgesics, antibiotics, and bronchodilators [6]. This also includes a variety of off-patent drug substances, e.g. the well-known analgesic paracetamol and the bronchodilator salbutamol [10]. A subanalysis of generic substances with off-label use in a hospital setting provides the following ranking: paracetamol (15 %), beclomethasone (13 %), betamethasone (6 %), salbutamol (4 %) and amoxicillin-clavulanic acid (4 %) [17].

The consequence of using drug substances with limited data in the paediatric population may be a risk to the patients, either due to reduced efficacy or to safety concerns. There are various examples where drug administration led to safety issues [8], e.g. grey baby syndrome from chloramphenicol, kernicterus from sulphonamides, withdrawal symptoms after long-term use of fentanyl, or seizure and cardiac arrest because of bupivacain. Studies have been carried out to assess the risk for adverse drug reactions (ADRs) in relation to off-label use. The results of a French investigation in a GP setting [18] as well as the data of an UK study in a hospital setting [19] suggest an increasing safety risk being associated with off-label drug use in the paediatric population. However, as the current data is limited, further research regarding off-label and unlicensed use is required [20]. It should be noted that these studies only included short-term ADRs, statistical evidence data on the risk of long-term ADRs is lacking.

### **2.3. How about the current European regulatory environment regarding the development with off-patent drug substances?**

Development of medicinal products generally requires the conduction of extensive studies in animals and humans, i.e. the generation of pharmacological-toxicological and clinical data. These data shall ensure evidently that the medicinal product has the appropriate safety and efficacy for its intended use and it is therefore necessary to protect public health. On this basis the medicinal product shall be approved by the competent authority for placing on the market. This principle is applicable to both initial applications for a drug substance and further extensions, e.g. adding new indications to the labelling.

As the generation of the data is costly and takes a lot of time and resources, the approach of data protection has been introduced into the legislation for medicinal products. Data protection means the temporary prohibition on direct or indirect use of the safety and efficacy data, which has been used for registration purpose, by another applicant. This is to encourage companies to perform the required studies by offering incentives for the development work and is justified by the medical progress gained. It has to be clearly distinguished from patent protection, which is an important tool for granting exclusivity rights but is not relevant for the regulatory approval process (for the various types of protection rights see section 5.1).

Apart from the need to encourage the development there is an ethical concern that repetition of any studies in animals or humans is not acceptable. Once the patent of a drug substance has expired other companies may be interested in the registration of the same drug substances. For this purpose it should be possible to use the already available data for the registration of generic formulations. Consequently, the aforementioned protection of the initial data, which have been generated on the expense of the innovator, needs to be of limited duration.

The balance between protection and use of the data is laid down in the current European legislation with the provisions on so called abridged applications in Article 10(1)(a)(iii) of Directive 2001/83/EC. The principle has initially been introduced in 1987 by Directive 87/21/EEC and can be summarised as follows: An applicant shall not be required to provide the results of pharmacological-toxicological and clinical studies if it is demonstrated that the

product is essentially similar to another product, which has been authorised in the EU for not less than 6/10 years and is marketed in the Member State for which the application is made.

The two key elements are essential similarity and temporary protection period. The latter is currently not harmonised within the EU and depends on the type of registration procedure as well as - in case of national marketing authorisations - the Member State. For a product having been approved through the CP the duration is 10 years; national marketing authorisations (either through MRP or national procedures) lead in some countries to 10 years of data protection but in others only to 6 years.

With respect to the development of off-patent drug substances and the exploration of e.g. new indications after initial approval, the definition of essential similarity is of great importance. The legally binding text gives no further details and leaves space for interpretation. Therefore, a judgement of the 5<sup>th</sup> chamber of the ECJ in case C-368/96 dated 3 December 1998, which is also referred to as Generics I case, sets the current legal framework. The judgement covered several questions on the validity and interpretation of the provisions for abridged applications following a referral of three sets of proceedings between pharmaceutical companies (innovators and generics) and the British competent authority. On the basis of the divergent opinions of the three parties the ECJ created a definition of essential similarity with the following set of criteria (paragraph 36<sup>1</sup>):

- ⇒ same qualitative and quantitative composition in terms of active principle
- ⇒ same pharmaceutical form
- ⇒ bioequivalence
- ⇒ no significant difference as regards safety and efficacy.

If these criteria are met, essential similarity of a medicinal product with an innovator medicinal product is given and hence an abridged application is possible. It should be noticed that the content of the SmPC, especially the approved indication, is not subject to this definition of essential similarity. Furthermore, the judgement sets out that there is no further space for interpretation by the national competent authority (paragraph 37).

In the light of this basic definition, further determinations were made by the EJC regarding the extent of abridged applications (paragraphs 53, 56). As the content of the SmPC is not relevant for essential similarity, an abridged application may include all therapeutic indications, dosage forms, doses and dosage regimens already authorised for the innovator medicinal product. This is irrespective of whether the 6/10-year period is already expired for all of these details as only the first marketing authorisation initiates a data protection period. Consequently, there is no additional protection for any data, which has been filed after granting the initial marketing authorisation. The ECJ however made the following remarks:

- According to the ECJ the applicable legislation left no other possibility to decide, although an amended legislation could reinforce rules to protect innovations (paragraph 52).
- In their argumentation within the hearing of the case both the Commission and the authority stated that major innovations should be protected, however the ECJ considered the proposed demarcation systems as being not appropriate (paragraphs 48 and 51).

As a consequence it would be the task of the legislature to create effective solutions for the protection of innovations. This may also include a system for the definition of what is

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<sup>1</sup> The paragraphs refer to ECJ judgement in case C-368/96.

considered to be a relevant innovation with the sufficient legal certainty. However, at present the legal framework does not provide such protection of development activities. Any data would be only excluded from the access of a second applicant during the first 10-year period after the initial granting of a marketing authorisation in the EU. It is obvious that this leads to a discouragement of companies to invest in any further development for off-patent drug substances, especially if the innovations are not patented or patentable [9][21][22]. Once the criterion ‘essential similarity’ is fulfilled, the data used for the registration of innovative amendments or additions to the SmPC of off-patent drug substances can be used free of cost by an applicant for an abridged application at the expense of the first applicant. As there are no incentives to explore off-patent drug substances a lack of adequate and well-controlled studies of its use in clinical settings outside the initially approved marketing authorisation may result. The absence of data protection therefore causes not only a danger to the competitive power of European based pharmaceutical companies but also a threat to evident medical progress and adequate information in the labelling.

### **3. Initiatives to improve the inclusion of paediatric information into the labelling**

The following summarises regulatory initiatives aiming to address the issue of the lack of paediatric medicinal products. Besides the European approach the experiences in the US as well as activities in selected Member States are presented. The overview covers on-patent and off-patent drug substances, as the respective initiatives are usually complementary. However, the off-patent setting is reflected in more detail.

#### **3.1. Which are the current initiatives within the EU?**

At present there is no regulatory framework available in the EU that is specifically designed for paediatric medicinal products. There are, however, various discussions about future evolutions. In December 2000 the European Health Council adopted a resolution calling the European Commission to develop proposals regarding this issue. These should include incentives and measures for both new and existing medicinal products. In addition to these activities the status of the proposed amendments to the EU legislation on medicinal products (‘Review 2001’) regarding impact on research with off-patent drug substance shall be reflected as this is a general issue in the EU (see section 2.3).

##### **3.1.1. First proposals and the Consultation Paper**

As a first concretising step to create a regulatory framework for paediatric medicinal products, the European Commission published in February 2002 a consultation paper on proposed actions [23]. In this document reference is made to the experiences with orphan medicinal products in the EU and the paediatric programmes in the US. Based on the experiences a set of six objectives is described:

- (1) Increasing the availability of authorised medicinal products for the paediatric population (on- and off-patent drug substances as well as special formulations)
- (2) Developing pharmacovigilance mechanisms, in particular to follow-up long-term ADRs
- (3) Avoiding unnecessary studies by increasing transparency and exchange of data
- (4) Establishing a priority list for the investigation of existing marketing authorisations
- (5) Developing European excellence in paediatric studies by creation of expert groups at the regulatory bodies and promotion of expert networks in the medical society
- (6) Ensuring a high level of ethical standards including adherence to GCP requirements.

The approaches of the initial Consultation Paper were welcomed by all involved parties in principal. The European Commission published an overview of the comments [24] of which the following seem to be of special interest for off-label drug substances:

- A 'kid' marketing authorisation was supported (without any prefix/suffix) although it was questioned whether this idea would be sufficient. A system avoiding two companies embarking the same set of studies was seen as essential.
- The improvement and dissemination of available information on medicinal products authorised in only some Member States and feedback on experience in off-label and/or unlicensed settings was supported. For that purpose a central database was requested, which includes positive and negative results and avoids unnecessary studies.
- A network of excellence was supported with the proposal either by integrating already available networks or by using them as a model. A steering committee should manage the network including training. Furthermore, a register of paediatric studies was supported.

On this basis the plans for a regulatory framework have been developed further. As usual for the introduction of a new legislative initiative in the EU, an impact analysis of its effect needs to be performed. The invitation to the respective tender has been published recently. The current plans for the structure of the European regulations on medicinal products for paediatric use can be derived from that document [25].

### **3.1.2. Planned structure of the European regulations**

The technical specifications in section 4 of the tender document of the European Commission regarding the extended impact assessment [25] provide detailed insight into the status of the discussions. The principal approach is that two regulations are planned: one for drug substances with patent protection and another for off-patent products. This is due to the fact that incentives and obligations are considered to be different for the two groups of products. Furthermore, it is acknowledged that it shall be easier to find solutions for on-patent than for off-patent drug substances. It is hence assumed that the implementation of the regulations will be performed in two steps with the one for off-patent drugs to be issued later. However, considering the fact that today's paediatric off-label use affects many off-patent drug substances as outlined in section 2.2, the delay of its solution through adequate legal initiatives is critical from an ethical point of view and should be limited to a minimum time span.

#### ***Regulation for on-patent drug substances***

For drug substances that are still covered either by a patent or by a SPC the key elements of the planned regulation are

- ⇒ the obligation for a paediatric evaluation plan to be included in all applications for medicinal products containing a new active substance or applications for authorisation of new indications, new dosage forms and new routes of administration for already authorised medicinal products
- ⇒ the establishment of an advisory board within the EMEA termed Paediatric Board (PB) being responsible for the agreement on the paediatric evaluation plan and the decisions on deferrals and waivers
- ⇒ the extension of the SPC period by 6 months that is valid for the entire medicinal product if the results of the paediatric exclusivity plan are taken into account in the resulting marketing authorisation or amended marketing authorisation
- ⇒ further incentives like protocol assistance procedures as well as the possibility for fee reductions or waivers.

The 6-month extension protection period will only be granted if the paediatric exclusivity plan has been agreed with the PB prior to its execution and if it is completed as agreed. This means that studies resulting from the US exclusivity programme (see section 3.2.1) cannot be used for exclusivity qualification in the EU if they were conducted prior to the respective negotiations with the PB. The reason is that companies shall be discouraged from holding back available data at time of application.

When negotiating the paediatric evaluation plan the PB shall consider the expected significant benefit to the paediatric population. This is emphasised due to the concern that company's study proposals will be based more on the expected return of investment than on the therapeutic need. For the decision on the plan the PB should therefore take into account existing marketing authorisations available for the use in the paediatric population and draw up a priority list of drug substances for which there is a need for more information. The latter is also intended to be a preparation for the regulation on off-patent drug substances. A survey of all existing uses of medicinal products in the EU Member States is planned.

Further proposed elements of the regulation are the flexibility in using all available application procedures (i.e. national procedures including proceeding harmonisation procedures as well as CP), the publication of information about the paediatric evaluation plan and its results as well as the establishment of an European network for the conduction of paediatric clinical trials. Additionally, new pharmacovigilance requirements regarding long-term safety shall be implemented.

### ***Regulation for off-patent drug substances***

The level of information on a proposed regulation for off-patent drug substances is much lower than for the on-patent setting. A reason is that it is rather difficult to implement any incentive, which is one of the two basic elements. In general, there are two different approaches under consideration:

⇒ the establishment of a study fund

⇒ the creation of a new paediatric marketing authorisation.

The study fund is intended to finance clinical trials for the use of off-patent drug substances in the paediatric population leading to new marketing authorisations or to introduction of new information into the SmPC of available marketing authorisations. Both commercial and non-commercial sponsors may benefit from the study fund. Neither the size of the fund nor its source is fixed right now. A first proposal is a sum of €90 million for the first year. Member States as well as the industry are requested to contribute to the fund.

The idea with the new type of paediatric marketing authorisation is to adapt principal achievements of the available regulation on orphan drugs to the issue of the lack of paediatric information. Therefore, this marketing authorisation is proposed to be exclusively granted within the CP setting. The protection period, however, shall only last 5 years, whereas it is 10 years for orphan medicinal products. The reason is that the size of the population is assumed to be greater for the paediatric licenses with the result of a higher return of investment. Furthermore, as experiences and published data may also be used for filing the costs for data generation could be lower. The protection type itself is proposed not to be market exclusivity like for orphan medicinal products but a protection of the data filed with the application to introduce the paediatric information. This favour of granting a weaker type of protection for paediatric marketing authorisations is motivated by the opinion of the Commission that marketing exclusivity would block the market to similar products despite the fact that alternative therapies are likely to be available.



A final paragraph in the Commission's text mentions the requirement to carry out a paediatric study programme for off-patent drug substances if there is a public health need. However, there is no further information how this could be translated in a legally binding environment.

### **3.1.3. Evaluation of the 'Review 2001' regarding the development of off-patent drug substances**

According to Article 38 of Directive 2001/83/EC the European Commission was obliged to prepare a report on the experiences with the procedures laid down in that directive including proposals for their improvement; a similar obligation was set for the CP with Article 71 of Regulation 2309/93/EEC. In their report as of 2001 the Commission not solely reflected the procedures but also addressed various developments, amongst others the data protection issue. The entire project to revise the legislation on medicinal products is termed 'Review 2001', and the discussions are still ongoing within the pre-set legislative procedure.

With respect to Directive 2001/83/EC, which is the relevant framework for the discussion of data protection for developments of off-label drug substances, the Commission initially proposed amendments to Article 10 by harmonising the data protection period to 10 years, introducing the term 'generic medicinal product' according the ECJ judgement, and extending the data protection to 11 years for new indications authorised within the first 8 years. On the basis of the comments on their initial document the Commission published in April 2003 a revised proposal [26]. With this document the Commission either accepted or rejected the comments from the other involved parties. The aspects relevant for development with already authorised drug substances may be summarised as follows:

- The Commission rejected the introduction of an additional 3-year data protection period for the data submitted for registration of new indications for established substances (amendment 40<sup>2</sup>) as this was considered to be a disproportionate data protection period and to provoke disharmonisation between generics and reference products with the additional indication. Only data used for the switch of a medicinal product should be protected (amendment 92, 2<sup>nd</sup> part) with currently being one year in discussion.
- The Commission rejected the option to apply for and authorise generics within the initial 10-year data protection period and to extent the Bolar provisions (amendments 34, 39, 134 and 202)
- The Commission accepted the clarification that 11 years constitutes the maximum time of data protection (amendment 35). This refers to the proposal to introduce a 1-year extension to the initial data protection period if during the first 8 years an authorisation for a new therapeutic indication with significant clinical benefit was obtained.

Due to further interventions the Health Council agreed on 2 June 2003 on modifications to the revision text. The final position is now to allow the submission of generic applications already 2 years before the end of the data protection period if the marketing authorisation was received within an MRP or optional CP. Placing on the market cannot take place before the 10-year period expired (proposed Article 10 of the revisions for Directive 2001/83/EC) [27]. It is clarified that for the start of the protection period the granting of the initial marketing authorisation in the EU is of relevance (proposed second subparagraph to Article 6 (1) of the revisions for Directive 2001/83/EC) [27]. Only for compulsory CP procedures the protection period of 10 years remains relevant for submissions of generic applications, with a possible

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<sup>2</sup> The numbering of amendments refers to the document of the European Commission KOM (2003) 163 final.

extension of 1 year for new indications (proposed second subparagraph to Article 13 (8) of the revisions for Regulation 2309/93/EEC) [28]. Because of this compromise there is no longer an additional 1-year protection possible for data generated for new indications of off-patent drug substances. Final adoption of the revisions is scheduled for end of 2003.

Therefore, the initial proposals for the ‘Review 2001’ reflected some comments of the ECJ within the Generics I judgement by harmonising the protection period and offering protection for new indications, even if the latter was linked to the initial data protection period. The latest version makes, however, the data protection much more complex again. Furthermore, no significant stimulation of development with off-patent drug substances is expected from the ‘Review 2001’ as any proposal for data protection has been rejected due to the fear of disharmony between the labelling of generics, i.e. health political reasons. The revision stays well behind the ECJ’s call to change the legislation adequately and provides no step forward.

### **3.2. Which way was the US going?**

In the US there is a long history of various actions addressing the lack of labelling for the use of medicinal product in the paediatric population. After a brief review of the various initiatives in a chronological order, the following is focused on the off-patent drug substances especially in the light of the Best Pharmaceuticals for Children Act (BPCA).

#### **3.2.1. The various legislative actions**

The FDA issued a first rule aimed addressing the lack of paediatric studies and the respective labelling already in 1979 but this was not successful in improving the situation since it just introduced a paediatric use subsection into the labelling. The practical effect was for most products only the sentence “Safety and effectiveness in children have not been established” [29]. The following action referred to as Pediatric Rule of 1994 missed its aim due to the fact that this initiative was more requiring the companies to conduct a survey on the existing data rather than performing new clinical studies. The idea was that paediatric indications might be established in some cases on adult efficacy data and further information (PK, PD, safety data) supporting paediatric use. In the end this rule resulted in 430 submissions for labelling changes with 15 % and 8 % being adequate for all ages and for some age groups, respectively, but with 77 % of the changes providing no labelling improvements [29]. After these initial actions the following three initiatives were set up to lead to substantial improvements.

#### ***Paediatric exclusivity according to FDAMA 1997***

With section 111 of the Food and Drug Administration Modernization Act (FDAMA) of 1997 the instrument of granting exclusivity rights as an incentive for the inclusion of paediatric information into the labelling has been introduced. The newly created section 505A of the Federal Food, Drug, and Cosmetics Act (FDCA) provides a 6-month period of so called paediatric exclusivity, which is added either to the patent protection or to the data exclusivity. The latter may be granted on the following grounds [30]:

- 5 years exclusivity for a NDA containing a new molecular entity<sup>3</sup>
- 3 years exclusivity for a supplemental application of the ‘new use’ of an already approved molecular entity if the application contains new clinical data other than BE data essential for approval of the application and conducted and sponsored by the applicant<sup>3</sup>

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<sup>3</sup> Hatch-Waxman Amendments (Drug Price Competition and Patent Term Restoration Act), 1984

- 7 years exclusivity for an orphan drug (i.e. a drug for the treatment of a disease affecting fewer than 200'000 inhabitants of the US)<sup>4</sup>

The prolongation of protection rights is then applicable to all marketing authorisations of the same active substance held by the company, i.e. all indications and all formulations. It requires, however, the existence of valid patent and/or exclusivity protection. This means that for a product that is broadened by paediatric information in the labelling paediatric exclusivity may only be claimed for if it is either on-patent or within any exclusivity provision.

The key element of the paediatric exclusivity provisions is the Written Request issued by the FDA. In this letter the authority outlines specific criteria like the type and objectives of the studies to be performed, the indications to be studied, the number of patients including age groups and the timeframe. Only if the company in response to the Written Request submits the studies within either a NDA, a supplemental application or an amendment to an application, and if the studies –with some exceptions- have been initiated after the issuing of the Written Request paediatric exclusivity will be granted.

Besides the Written Request procedure the Pediatric Priority List is a tool implemented with FDAMA. In this listing approved products for which additional paediatric information would be of value for public health are presented. For products on the list the probability of the FDA issuing a Written Request is increased. Companies were encouraged to propose products that should be listed. The overview is available in public domain. It should, however, be noticed that it is the Written Request that is essential for any exclusivity rights.

The entire paediatric exclusivity provisions of FDAMA were implemented with a sunset by 1 January 2002. As of 1 April 2001, 414 studies had been requested in 188 Written Requests, 28 drugs had been granted paediatric exclusivity extensions and the labelling of 18 drugs had been revised to provide new information for paediatric use [30]. In January 2001 a report of the FDA to the Congress was requested about the experiences made regarding effectiveness of the programme, adequacy of incentives, economic impact and suggested modifications. The overall conclusion were that “the paediatric exclusivity provision has been highly successful in generating paediatric studies on many drugs and in providing useful new information in product labelling”. However, two gaps in the statute were raised:

- to encourage the studies in younger age groups, including neonates
- to encourage studies on drugs that lack patent protection or exclusivity.

Further reports claimed for faster implementation of information into the labelling as well as better dissemination of the data [30]. All of these aspects were considered with the follow-up exclusivity programme referred to as Best Pharmaceuticals for Children Act (BPCA).

### ***Paediatric Rule 1998***

The most stringent programme having been set up in the US was the so called Pediatric Rule, which came into effect in April 1999. This programme needs to be clearly separated from the paediatric exclusivity according to Section 111 of FDAMA (and the BPCA) as it made the determination of paediatric data mandatory for all new drugs and biological products, i.e. new active ingredients, new indications (except orphan indications), new dosage forms, new dosing regimens, and new routes of administration. The requirement to present the data is triggered by a meaningful therapeutic benefit for paediatric patients (i.e. significant

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<sup>4</sup> Orphan Drug Act, 1983

improvement in medical therapy with the need for additional options) or the substantial use for the labelled indications defined by more than 50'000 paediatric patients [29]. The assessment is requested for all paediatric subpopulations in all indications that are claimed for the product with the aim to support dosing and administration recommendations. This could either be made through adequate and well-controlled trials in paediatric patients, extrapolation of adult data to paediatric patients, or analysis of data of adult trials having enrolled paediatric patients. Either partial or full waivers are granted in special circumstances, like the option for interpolation of data between various age groups, evidence of the drug being ineffective or unsafe in paediatric patients or the treated disease not being relevant to paediatric patients. The Pediatric Rule also includes the requirement for the development of a paediatric formulation if necessary.

However, the Pediatric Rule was challenged in court. On 17 October 2002 the US District Court for the District of Columbia ruled that the rule was “incompatible” with the BPCA and that the FDA lacked the authority to require paediatric studies [30]. The key aspect was that the “FDA cannot regulate the paediatric use of a drug when the indication is not claimed in the labelling”. The FDA nowadays is therefore barred from enforcing the Pediatric Rule. They solely encourage the holders of an approved NDA to submit a paediatric plan that describes the development of the product in the paediatric population where it may be used. Furthermore, in March 2003 a bill has been introduced in the US Senate with the aim to amend the FDCA authorising the FDA to require certain research into drugs used in children. This act, which may be cited as Pediatric Research Equity Act of 2003, would reinforce the ideas of the Pediatric Rule.

### ***Best Pharmaceuticals for Children Act (BPCA) 2002***

The BPCA was signed into law on 4 January 2002 and re-authorises the paediatric exclusivity provisions of FDAMA. This follow-up initiative addresses the issues that have been raised with the former legislation. Again paediatric exclusivity incentives are applied for drugs approved under Section 505 of FDCA. The sunset date of the initiative is 1 October 2007. The highlights of the BPCA are the following (summary of [32]):

- Process for studying off-patent and on-patent drugs
- Collaboration between FDA and NIH on drug development process for drugs that may be administered to children
- Addition of neonates to the programme
- Requirement for adequate representation of racial and ethnic groups
- Establishment of an Office of Pediatric Therapeutics (OPT) at the FDA for ethical issues and post-marketing safety
- Mandate for the public dissemination of paediatric information

The BPCA eliminated the priority list of FDAMA as it was assessed to be too resource-incentive with little effect in terms of prioritisation and to lead to the mistaken impression that only drugs on the list would qualify for incentives. However, a different kind of list has been introduced, which contains mostly off-patent and no-exclusivity drugs (see section 3.2.2). It should however be noted that the priority list may also include on-patent drugs if the company declines to conduct studies in the paediatric population in response to a Written Request and the authority still deem the information to be necessary for the drug.

Regarding the pharmacovigilance system the BPCA established a new safety reporting system. A review of all AE reports for a one-year period after a drug is granted paediatric exclusivity is required that has to be prepared by the Office of Pediatric Therapeutics (OPT)

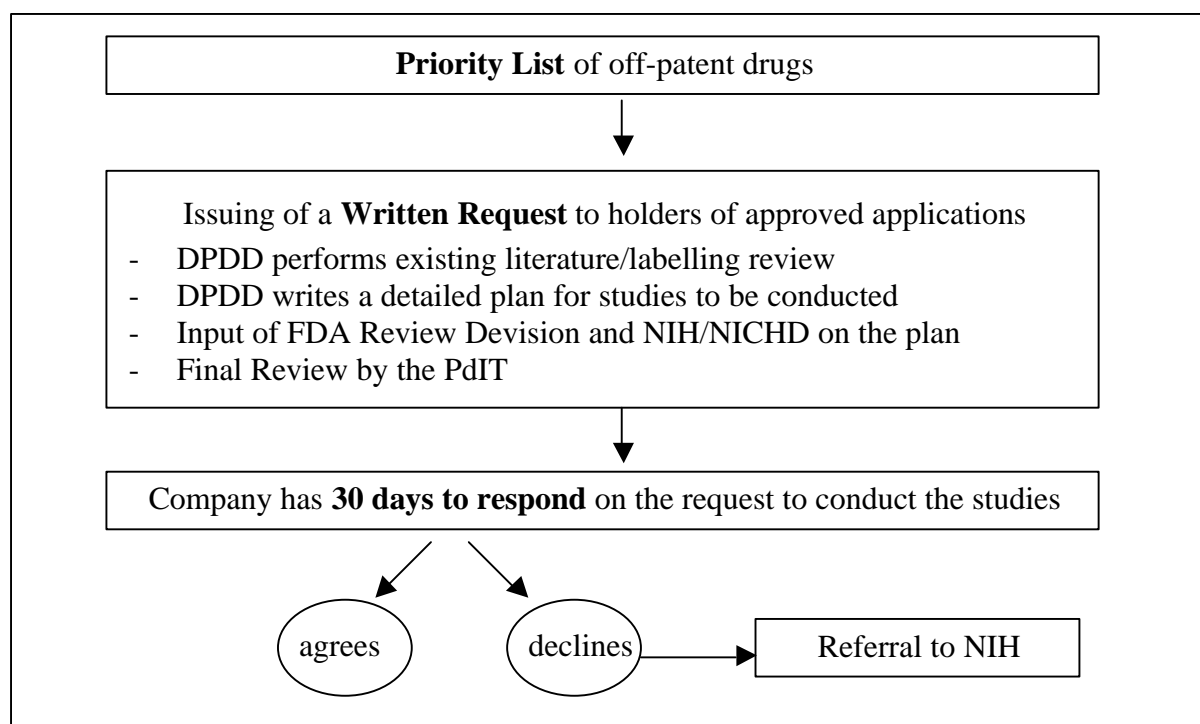
and needs to be submitted to the Pediatric Advisory Sub-Committee for review and recommendations. The system is currently in evolution with review through and improvement by the relevant functions over time [33].

Public discussion about the BPCA is wide and reflects various views [30]. For the most part, paediatrician groups like the AAP support the BPCA as they acknowledge the increase in the number of clinical trials since the passage of FDAMA and credit exclusivity with an increase in information available about medicines used in children. Other groups however criticised that the conduction of the trials is (still) not assured, financial burden is put on customers due to the delay in generic drugs and that there is no guarantee for the respective label changes. The report about the BPCA that is scheduled for 6 October 2007 will present its results.

### 3.2.2. Special attention to off-patent drug substances

Established substances that are off-patent and have no exclusivity were covered for the first time by the BPCA. It has been recognised that a funding process as well as the involvement of third-parties is required. The key element of the BPCA in terms of addressing this issue is the partnership between the FDA (represented by the DPDD) and the NIH (represented by the NICHD). The research fund has been created by amending the Public Health Service Act. The process for the study of off-patent drugs is presented in Figure 1. It starts with the issuing of a priority list of drugs for which paediatric studies are needed. The BPCA required this being published not later than one year after enactment of the legislation. The main considerations for the inclusion of a drug to the list are (1) the availability of information concerning the safe and effective use of the drug in the paediatric population, (2) whether additional information is needed, (3) whether new paediatric studies concerning the drug may produce health benefits in the paediatric population, and (4) whether reformulation of the drug is necessary.

Figure 1 Process for the evaluation of off-patent drugs



The Division Pediatric Drug Development (DPDD) performs for a selected drug from the list a review of existing literature and labelling and writes a detailed plan of studies to be

conducted. The FDA Review Division and NIH/NICHD give input to the plan. After final review through the PdIT the Written Request is issued to all holder of approved applications under section 505 of FDCA. They now have 30 days to respond and either to agree to the conduction of the studies or to decline. In the latter case (and also if no response will be received within the 30-day period) the matter will be referred to the NIH for collaboration with third parties by publishing a request for contract proposals. Entities for contract are required to have expertise to conduct paediatric clinical trials including qualified universities, hospitals, laboratories, contract research organisations, federally funded programmes such as paediatric pharmacology research units, other public or private institutions, and individuals. For funding of these studies the BPCA grants an amount of US\$ 200'000'000 for fiscal year 2002 and again such sums as are necessary for each of the five succeeding fiscal years.

The development of the list of drugs for which paediatric studies are needed is a long, iterative process that obtains input from Advisory Committees, FDA Divisions, NIH Divisions, the American Academy of Pediatrics, the United States Pharmacopoeia and other experts in paediatric research. The NIH published the first list in January 2003 and included the twelve drugs listed in Table 3. It will be updated annually by the NIH.

Table 3 US list of drugs for which paediatric studies are needed [31]

Azithromycin	Dopamine	Lorazepam
Baclofen	Furosemide	Rifampicin
Bumetanide	Heparin	Sodium Nitroprusside
Dobutamine	Lithium	Spironolacton

In addition to the initiation of generating the required data the BPCA also lays down regulations for the respective labelling changes with clear timelines to be followed by the various involved parties. This is an important tool as it guarantees that the results obtained through third party contracts with national funding will lead to adequate improvements of the labelling. After the requested studies have been conducted and the study reports have been submitted to the NIH and the FDA, the process for subsequent labelling changes should be concluded within a 180-day period. On the basis of a review of the reports negotiations with the holders of approved applications will be initiated through the FDA with the request to apply for a labelling change. Additionally, the report and any requested labelling changes will be placed on a public docket file with a summary being published in the Federal Register in order to promote public dissemination of new information. If the company does not comply the matter will be referred to the Pediatric Advisory Subcommittee for reviewing the data and giving recommendations of labelling changes within 90 days. A 30-day period is then set for the FDA to request from the holder of approved applications the recommended labelling change. If the company does not follow this request the FDA may deem the drug to be misbranded under the FDCA. Furthermore, if a study completed under public contracts indicates the need for a formulation change, a non-binding letter requesting for a respective change will be send to the holders of approved applications.

Overall, the FDA's enforcement authority is strengthened by the BPCA. In best case scenarios with all parties respecting the given timelines a labelling change will be effective within one year after the FDA receives the final study report [30]. There are however some issues that are not fully reflected by the BPCA and needs further discussion during its implementation. Regarding the involvement of third parties one might question about the motivation since the monetary aspects will be low so that perhaps the prestige effect give the required incentive. Furthermore, the ownership of the data generated through third parties is

not clear as trade secrets or patent infringements may be asserted by drug companies. For the conduction of the studies it is not clear whether an investigational new drug exemption (IND exemption) is necessary. Since one condition for an IND is the intention to report to the FDA for significant changes to the labelling (i.e. a filing of a supplemental NDA) this cannot be fulfilled if the trial is conducted by a third party. Also the regulatory procedures for label changes are not fully solved if an abbreviated new drug application is applied since this approach requires full reference to a listed drug. And finally, an important issue is whether the holder of an approved application will qualify for 3-year Hatch-Waxman labelling exclusivity based on third party studies with the additional option to attach 6 months of paediatric exclusivity. It is the current understanding that Hatch-Waxman only apply if the company conducts the study so that also additional exclusivity can be granted, but not if the company declined to follow the request. All of these issues need to be addressed during the 5-year implementation of the BPCA [30].

### **3.3. Are there any national initiatives in the EU Member States?**

Besides the activities on an European level, national programmes regarding paediatric medicinal products have already been initiated in some Member States. The following provides a summary of what has happened in Germany, France and the UK. These examples show that excellence has been build up, which should be used adequately in the future European system.

#### **3.3.1. Germany**

In April 2002 the Ministry of Health created an expert committee on medicinal products for children and adolescents at the health authority (BfArM). It is planned that this committee gets an official status through the next amendment of the German Drug Law (proposed § 25(7a)). The tasks are (1) to support of the authority in licensing of new products and (2) the compilation of relevant information on the use in paediatric population for medicinal products with and without paediatric use in the labelling. The idea with the latter is that the committee elaborates listings based on the information available in public domain [34] although further details about structure and publishing are still under evolution.

At present the Expert Committee meets 2-monthly and has created an organisational structure. Recently, a special web site informing about the tasks has been created on the authority's homepage. The first publishing of information on paediatric use is expected for drug substances for neurological disorders. In general, interested parties requested that the published information should be useful for regulatory filings. Plain listings are not considered to be helpful. Considering the experiences with the German re-registration monographs summarising the available data but providing additionally a list of references may be appropriate.

#### **3.3.2. France**

A paediatric expert committee has been set up at the level of the health authority (AFSSAPS) and internal structures of the authority have been linked to co-ordinate the activities. The task of the committee is to assess current unmet medical need in the paediatric population. For that purpose a staggered evaluation process has been created.

In March 2002, a preliminary list of 39 drug substance of the following 8 therapeutic classes has been published [35]: analgesics, anti-infectives, oncology drugs, cardiovascular drugs, gastro-enterologic drugs, neurologic drugs, psychiatric drugs, and anti-rheumatics. The list includes information on further demands for the use in paediatrics for each individual substance and shall be extended by the available data. Further to these activities at authority

level a group at industry association level (LEEM) with industry delegates, paediatricians, a representative of the health ministry and patient organisations meets regularly for information exchange and to raise awareness about the issue.

### **3.3.3. United Kingdom**

The Royal College of Paediatrics and Child Health together with the Neonatal and Paediatric Pharmacists Group created the national paediatric formulary 'Medicines for Children' in 1999. The aim of the formulary is to offer guidance on the use of drug substances given to children. Besides the information on approved paediatric medicinal products it is the unusual with the formulary that it also covers the use of medicinal products for unlicensed applications and lists a few unlicensed medicinal products necessary for the treatment of children. In a policy statement the Standing Committee on Medicines, which is a joined committee of the above mentioned associations, advocates for the need of off-label use in paediatric practise [36]. The requirement should be that a respectable, responsible body of professional opinion needs to assess the use adequately. The created formulary provides such a basis.

On an authority level (MHRA), the scientific advice committee includes a paediatric sub-committee. Furthermore, a paediatric task force has been established by the MHRA to review the availability of paediatric labelling on commonly used drugs. Individual requests to companies have already been sent out by that group but until now there are no publications or reports available.

## **4. Analysis of the impact of US labelling changes on EU product information**

The idea with the following analysis is to get an impression on how the US activities have an impact also on marketing authorisations in the EU. Labelling changes qualifying for paediatric exclusivity under FDAMA require the compilation of data in accordance with FDA's written request. Once these data is submitted in the US it could be that it will be introduced in other countries, too. Therefore, the investigation whether paediatric exclusivity label changes in the US lead to the respective modifications of the European licenses may be of interest.

Of course, the national marketing authorisations for identical medicinal products may differ within the EU if they were not subject to either the MRP or a harmonisation procedure. Therefore, Germany was selected as reference country. Labelling changes in the US were assessed regarding their inclusion in the present labelling of the respective product on the German market that is either approved nationally (including MRP) or via the CP.

### ***Methodology***

Basis for the analysis was the public available list Pediatric Exclusivity Labelling Changes<sup>5</sup> as of 1 April 2003, which covers the period April 1999 to February 2003. For each medicinal product the labelling of the correspondent German marketing authorisation containing the same active substance with comparable indication was identified by using the Compendium of Medicinal Products<sup>6</sup>. It was then assessed whether the US information on the paediatric use

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<sup>5</sup> <http://www.fda.gov/cder/pediatric/labelchange.htm>

<sup>6</sup> Rote Liste 2003, Editio Cantor Verlag



is included in the German labelling. If the information in the compendium was considered not to be sufficient for this decision the Physician's Data Sheet<sup>7</sup> was used in addition.

The criterion was: Is the entire information on the use of the drug substance in the paediatric population from the US labelling, which was submitted to qualify for paediatric exclusivity, included in the German labelling, i.e. either

- is the use of the drug substance approved for the modified age range (usually down to a lower age) or
- if there was no change to the range in the US labelling, is the additional information on the use in the paediatric population included in the German text (e.g. the new PK data).

Each comparison was made with the marketing authorisation that is held by the same company, which also applied for paediatric exclusivity in the US. If, however, this company was not a holder of a respective German marketing authorisation the alternative approach was to identify the product with the same trade name like in the US since this could be an indicator for license agreements. Only if this approach also failed a review of all relevant German marketing authorisations with the same drug substance was performed.

In an additional evaluation it was recorded whether the German product faces generic competition. This was used as an indicator whether the product contains an off-patent drug substance. For each class, i.e. labelling with and without paediatric information, the generic competition status was recorded separately.

### **Results**

A total number of 52 labelling changes are reported in the US listing with 50 different drug substances / drug combinations being affected. In 7 cases paediatric exclusivity was granted for a paediatric formulation. Of these 50 drug substances / drug combinations 6 are not listed in the German compendium. Another 2 drug substances are not approved in Germany either in the special paediatric formulation or the respective general therapeutic area, so that they are not further considered. The remaining 42 drug substances on the German market contain the following information in the labelling:

- ⇒ 18 marketing authorisations include the paediatric information (age range and/or additional information) in accordance with the US labelling
- ⇒ 24 marketing authorisations **NOT** include the paediatric information (age range and/or additional information) in accordance with the US labelling

Examples of drug substances, for which the paediatric information that resulted from the US programme is also included in the European marketing authorisation, are fluvoxamine (Luvox<sup>®</sup>/Fevarin<sup>®</sup>), omeprazole (Prilosec<sup>®</sup>/Antra<sup>®</sup>) and insulin glargine (Lantus<sup>®</sup>). On the other hand, examples for drug substances lacking in the European labelling the paediatric information of the US marketing authorisation are oxaprozin (Daypro<sup>®</sup>/Dayrun<sup>®</sup>), ketorolac (Acular<sup>®</sup>) and pravastatin (Pravachol<sup>®</sup>/Pravasin<sup>®</sup>).

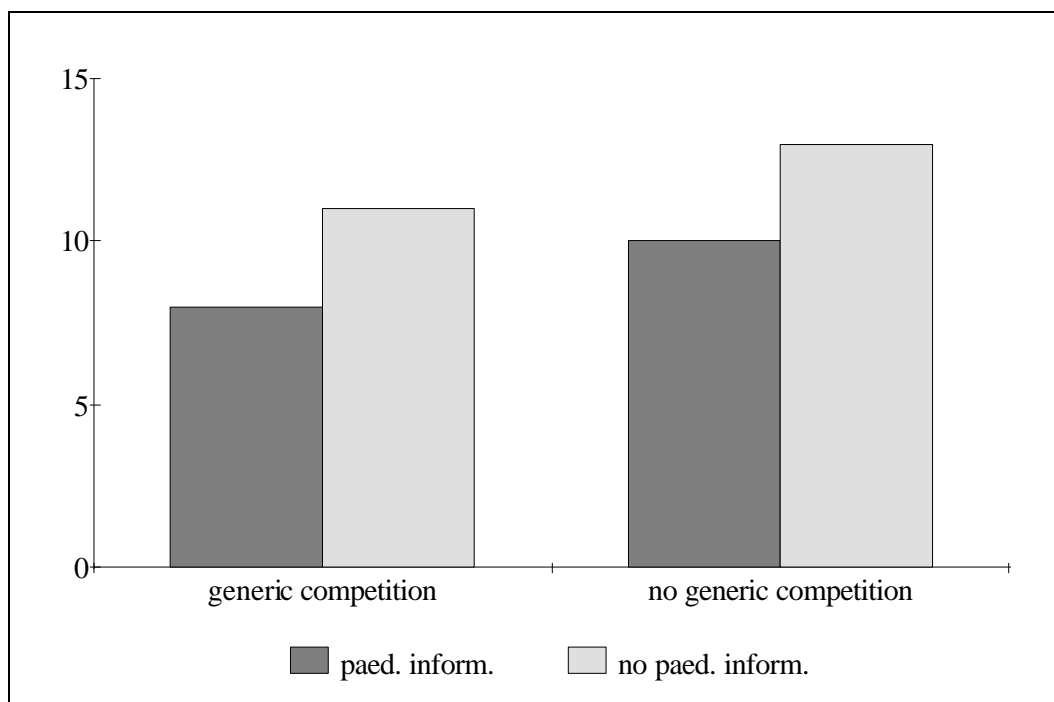
Consequently, about 57 % of the US labelling changes did not lead to subsequent changes to the product information of the European marketing authorisations. It should, however, be noted that restrictions to the use in children due to safety concerns, which have been identified with the paediatric exclusivity studies, are all reflected in the European marketing authorisations. The imbalance is hence focused on the available efficacy information in the labelling.

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<sup>7</sup> <http://www.fachinfo-service.de>

Figure 2 presents for either group (i.e. marketing authorisations with and without paediatric information in the labelling) the partition between drug substances facing generic competition in Germany and those which does not. Of the 42 marketing authorisations with US labelling change about 45 % contain drug substances with generic competition. The ratio between medicinal products with and without the paediatric information in the labelling is however similar for drug substances with and without generic competition.

Figure 2 Number of German marketing authorisations with and without the paediatric information according to the US labelling, stratified by drug substances with and without generic competition, respectively (N = 42)



### Conclusions

The results of this analysis show clearly that the available information on the use of a product in the paediatric population will not directly be logged in EU marketing authorisations. The US labelling and the product information in the EU might remain substantially different in terms of the data on the use in children, especially regarding the use in a lower age.

There may be various reasons for this situation. The company may not have applied for a respective amendment of the labelling (e.g. through variation procedure) by using this paediatric data. Another reason may be that various authorities assess identical data differently. As an example, this is obvious for lamivudine used in hepatitis B virus treatment. The US license Epivir-HBV<sup>®</sup> contains paediatric patients with 2 to 7 years of age in the indication section with the note that information is limited. Additionally, special dose recommendations that were investigated in a clinical trial are given. The EU license Zeffix<sup>®</sup> however just mentions the results of the clinical trial in the pharmacodynamic properties section of the SmPC with the additional note that further data for justification of the dose is necessary. The indication section only contains the use in adults. It is clear that the identical data was submitted by the company but that different assessments of the authorities led to these significant differences in the labelling.

The issue of differences in the approved paediatric labelling due to different assessments of the authorities in the US and the EU has specifically been investigated for products that have gone through the CP in Europe, i.e. innovative drug substances [37]. Within the evaluated time frame (January 1995 to September 2001) a total of seven drug substances have been detected that differ in paediatric labelling resulting from either EMEA/CPMP or FDA assessment. Although harmonisation should have been reached through the ICH guideline on the clinical investigation of medicinal products in the paediatric population, the results show that different opinions of the assessors on the data may lead to a different labelling. This needs to be clarified to avoid confusion due to different information provided to the medical society. It is of utmost need that the requirements on paediatric data should reflect the special aspects of this patient population that clearly differs from adult (see section 6.1). Obviously, the principal aim for drug development and registration needs to be the adequate investigation leading to registration and hence availability of the drug substance for medical treatment. The level of paediatric data required for approval in that population should keep the balance between the needs for adequate assessment and the possibility to generate the data.

Another reason for the differences in the labelling between the marketing authorisation in Europe and the US may be the matter of standard texts for specific drug substances issued by the competent authority (core SmPCs). These harmonised texts are strongly recommended for the company but do often not include the paediatric information. As these texts are issued in the context of generic products this explanation may be valid for off-patent drug substances.

The present analysis has its limitations due to the selection of only one reference country as well as using indicators for the decision on the protection status. However, it is adequate to provide the overall impression that information qualifying for paediatric exclusivity in the US is not introduced in half of the respective European marketing authorisations. This is independent of whether or not the drug substance is still under data and/or patent protection in the EU. Of course, all drug substances for which paediatric exclusivity was claimed were under protection in the US since this is the principle of the procedure of FDAMA (see section 3.2.1). It could be expected that encouragement to include the available data in the European marketing authorisations with paediatric information is higher if also in the EU the drug substance is still protected, but this cannot be confirmed. An interesting finding is the status of loratadine in Germany: although it faces generic competition this is limited to the tablets and covers neither the dispersible tablet nor the syrup. Only the latter two formulations are indicated for children down to 2 years with the US paediatric exclusivity labelling. The tablets of the innovator and the generic companies are approved with a threshold of 6 years. It remains open whether this is caused by formulation patent or by low generic business interest.

## **5. Aspects of financing paediatric development for off-patent drug substances in the EU**

Paediatric development requires the investment of money, time, and resources. Assumptions have been made that the cost for a PK study of 15 patients and an efficacy study of 15 patients are US\$ 100'000 and US\$ 150'000, respectively, per affected age group [25]. A development of a paediatric formulation costs US\$ 500'000 to US\$ 3.5 million. Adequate measures to finance these investments are therefore needed, which may include either incentives for the sponsoring company (i.e. protection rights) or funding. The following describes the various systems that are available today and that may be created with the new legislation. For the latter comparisons are made with the respective US programmes.

### **5.1. Which options for financing through protection rights for paediatric development are currently available?**

A general approach to stimulate the investments for research and development is granting intellectual property (IP) rights. In the field of drug regulatory affairs, the following types of IP rights are currently in place within the EU:

- patent protection (20 years) with the addition of a SPC protection, which is applicable after granting of the first marketing authorisation within the EU (maximum of 15 years but not more than 5 years after patent expiry)
- regulatory data protection (RDP) of the data submitted in support of a marketing authorisation preventing a second applicant to file abridged applications
- protection through market exclusivity rights requiring the authorities to reject other applications for similar medicinal products (applicable for orphan medicinal products).

Once the patent of a drug substance is expired this type of protection including any additional period through a SPC (according to Regulation 1768/92/EEC) is no longer applicable. Offering incentives for these substances is therefore limited to either data protection or market exclusivity, for which the key elements are summarised in Table 4. Although both types of protection have significant impact on competition they differ in terms of power:

1. RDP prevents generic applications but does not have an impact on the possibility that a second company may file an application with a full dossier, i.e. a dossier containing a full set of preclinical and clinical data, which is normally not done by generic companies. In contrast market exclusivity blocks the market for other products completely.
2. The criterion 'similarity' as applied for market exclusivity includes a broader range of products than the criterion 'essential similarity' relevant for data protection. The latter has been defined through an ECJ ruling as being characterised by the same composition of the active principle, the same pharmaceutical form, (if necessary) bioequivalence, and no significant differences regarding efficacy and safety. On the other hand, similar medicinal product just requires a similar active substance (intended for the same therapeutic indication), which means an identical active substance but also an active substance with the same principal molecular structural features acting via the same mechanism.

Consequently, market exclusivity offers a more powerful protection than data protection. This is justified by the fact that it is only applied to special medicinal products for which granting of very attractive incentives were considered to be necessary: the orphan medicinal products. It should, however, be noted that the broad definition of similarity leaves a lot of space for discussion and is expected to be challenged in court once leading to a more concrete definition like it has happened with essential similarity.

As discussed in section 2.3, data protection does generally not apply to any extension of the therapeutic indication. Therefore, if paediatric research and development for off-patent drug substances just leads to a new claim in the SmPC of the already approved product, there will be no protection of these data. An open question at present is whether the (necessary) development of a different pharmaceutical form will induce a separate data protection period. The final ECJ ruling on this matter (currently termed Generics II case) is still pending.

Within the current regulatory environment the use of the market exclusivity rights through an orphan drug designation is mainly the only option to receive incentives for the paediatric development work in an off-patent setting. In the following this approach will therefore be discussed in more detail. For the sake of completeness another option by using the centralised procedure is presented although this way may only be possible in very rare cases.

Table 4 Key elements of data protection and market exclusivity

	<b>Data protection</b>	<b>Market exclusivity</b>
Legal basis	Article 10(1)a(iii) of Directive 2001/83/EC	Article 8(1) of Regulation 141/2000/EC
Applicable to	Marketing authorisations granted in the EU on the basis of full dossier (i.e. MA of an innovator)	Orphan medicinal products approved in the EU after having received an orphan drug designation
Protection against	Products with essential similarity → abridged applications making reference to the innovator's data (i.e. generic applications)	Similar medicinal products → any filing of applications for marketing authorisation
Protection period	6 or 10 years, depending on the type of approval procedure and –in case of national/MRP approval- the Member State	10 years (possible reduction to 6 years if designation criteria are no longer met)
Start of the protection period	First marketing authorisation in the EU	Approval in the entire EU, either through CP or through MRP with all Member States being involved

### 5.1.1. Using the epidemiology: Orphan Drug Designation

In the EU, a specific legislation on orphan medicinal products has been introduced in 2000 in order to stimulate the development and registration of medicinal products for rare conditions that are life-threatening or serious / debilitating. The legal basis is Regulation 141/2000/EC in conjunction with Regulation 847/2000/EC. According to these legal texts an orphan drug designation may be granted either on grounds of either epidemiological or economic criteria. The first criterion defines the condition affecting not more than 5 in 10 thousand persons in the EU; the second criterion requires that a sufficient return of investment is unlikely to be generated. It should be noted that the economic criterion requires a full transparency of the company's financial structure and is hence of less importance. A further general requirement for the designation is that either no medicinal product for diagnosis, prevention or treatment of the condition is already approved in the EU or the product for which orphan drug status is applied offers a significant benefit to other products available. This is an important difference to other comparable legislation like in the US where there is no such additional requirement.

Applications for orphan drug designation are handled through the Committee for Orphan Medicinal Products (COMP). The maximum duration for the adoption of a COMP Opinion is 90 days but most procedures are already completed after 60 days. Based on the opinion a Commission Decision is adopted and the product enters the Community Register of Orphan Medicinal Products. This designation may, however, not be mixed up with an approval for marketing of the product. It just says that the criteria for orphan medicinal products are met

and that the use of the medicinal product is plausible. At time of application usually only limited data on efficacy, and in very rare case even only assessments based on theoretical consideration are available. The data may be more limited if there is no satisfactory alternative approved in the EU for the condition in question. If significant benefit to an alternative is claimed, the scientific basis is expected to be much more validated. Efficacy aspects are usually discussed instead of safety concerns, as the latter is usually not substantiated enough at time of application. In contrast to this evaluation for the orphan drug designation the application procedure for the marketing authorisation requires to prove the benefit-risk ratio of the medicinal product by presenting the entire data for quality, safety and efficacy.

Besides the above described protection through market exclusivity an orphan drug designation offers further incentives to the applicant. These are:

- protocol assistance during the development, with involvement of the CPMP
- priority access to research programmes in the EU
- the access to the CP (independent of any list A/B status)
- fee reduction for the centralised application and maintenance activities.

The protocol assistance is much more supportive than the classical scientific advice procedure with the option of more open discussion about the development programme. Regarding the research programmes the EU Framework Programme for Research and Technological Development offers foundation for research in special areas. The access to the CP is important as marketing exclusivity is only granted after approval in the entire EU, which is achieved with the approval by Commission Decision. Furthermore, as the CPMP is also involved in the protocol assistance the continuity of assessors and opinions may be maintained by selecting this way of application. The size of fee reduction is dependent on the fiscal year.

It should be noted that the orphan drug designation does not require the applicant to go CP for the marketing authorisation approval. It is still possible for the company to select the MRP. However, marketing exclusivity is only granted after approval in the entire EU, which may be more difficult to obtain with the MRP, especially for off-patent drug substances with long-term use [38]. And fee reductions for initial and maintenance applications are not expected to be available in all national fee regulations of the Member States. For 2003 the EMEA have set fee exemptions of 100% for protocol assistance and of 50% for all other fees in the CP (marketing authorisation applications, variations, inspections, and annual fees) [39]. It is therefore highly recommended to select the CP for the approval of orphan medicinal products.

### ***Use of orphan drug designations for paediatric indications***

Considering the general aspects of orphan medicinal products it could be possible to use this available legal environment also for paediatric indications. The following three key aspects should however be considered for an application:

- (1) The main criterion is supposed to be the epidemiology of the condition. This is usually assessed on the basis of an intensive literature review. The assessment needs to cover the entire EU. If there is already an assessment for the US available, this set of data may additionally be used provided the applicant can demonstrate the possibility to transfer the data to the EU, e.g. by comparing the ethnology together with condition-specific aspects.
- (2) It is unlikely that only the prevalence in the paediatric population leads to an orphan drug designation if the identical medicinal product is already approved for the same indication for the use in adults with higher prevalence. The COMP might consider this being an invalid subset of patients. In this case a special benefit for the paediatric population needs to be elaborated, e.g. by the development of a special paediatric dosage form.

- (3) To restrict the indication to a special stage of the condition is generally not acceptable, as the condition needs to be seen as a whole. The only option is that distinct evaluable characteristic of the restricted patient population with link to the condition can be determined if such characteristics are essential for the effectiveness of the product and their absence would lead to ineffectivity. As an example, if a medicinal product in oncology is indicated for a subpopulation with a defined physiologic characteristics like the expression of a special receptor on the surface of the target organ this may be considered as being a valid restriction of the population leading to lower frequency rates within the epidemiological assessment.

In consequence, due to these limitations it is obvious that

- ⇒ the approach of orphan medicinal product application is only applicable to some paediatric indications.
- ⇒ this can hence not considered to be a general option to solve the issue.
- ⇒ in addition to the limitations in the epidemiology criterion it is important that of course a basic requirement for the designation is that the condition is life-threatening or serious.
- ⇒ therefore, mild to moderate diseases that also require paediatric research are not eligible for this approach.

Two other provisions may be important especially for off-patent drug substances. First, the application for an orphan drug designation shall be made before the application for marketing authorisation. The applicant needs to check carefully that no application for the paediatric indication has been filed in the past, even if rejected. Second, for an already approved product the designation can only concern unapproved indications. Regarding paediatric indication for off-label drug substances this means that the outcome of an approval procedure following orphan drug designation will be a separate marketing authorisation for the paediatric claim, i.e. an introduction of the labelling under the brand of an already available marketing authorisation (e.g. for adults) is not possible.

#### ***Current status of orphan drug designations for paediatric indications***

At present, 12 % of all orphan drug designations are for conditions that are exclusively related to the paediatric population [40]. About half of the designations (55 %) covers conditions, which affect both adults and children. The remaining third of designations is related to conditions specific for treatment of adults only.

An example for an off-patent drug with exclusive paediatric indication is the orphan drug designation for benzoic acid, sodium salt (EU/3/02/111, 11 September 2002). The orphan drug designation relates to the use for the treatment of non-ketotic hyperglycinaemia, a condition that may lead to accumulation of glycine in the tissue including the nervous system. In severe cases in newborns neurological complications may be caused. Benzoic acid is expected to lower increased glycine levels by reacting with glycine to hippuric acid that may be eliminated through the kidneys. In order to mask the unpleasant taste of benzoic acid the applicant developed a special preparation by microencapsulation. This designation represents two important aspects: the use of a substance being without any patent protection *and* the development of a special dosage form for children. It could hence give an idea how orphan drug designations may be used for paediatric indications if the conditions and limitations mentioned above are met.

### 5.1.2. The special way: Centralised Procedure

For completeness, the following possibility shall be mentioned, although it is limited to very rare cases (if any) to introduce protection rights for paediatric data generated for an off-patent drug substance. The principal idea is that medicinal products having been approved through CP obtain 10 years data protection. For an off-patent drug substance access to the CP may be reached if the CPMP considers the medicinal product being eligible for list B status. Criteria may be the innovative character of the route of administration or a therapeutic indication with high medical interest. An example for an off-patent drug substance for which this strategy has been applied is memantine approved for Alzheimer's disease (EU/1/02/218/001-006). After CP approval the older national marketing authorisations were renounced. The probability to apply this strategy to paediatric medicinal products is considered to be extremely low. Furthermore, the impact of the ECJ's decision on abridged applications on this situation is not fully clear at present.

### 5.2. How about the proposed regulatory initiatives currently in discussion – Do they provide adequate options for financing?

As outlined in section 3.1.2, the current proposals for an European regulation on paediatric medicinal products for off-label drug substances contain two basic elements: the establishment of a study fund and the creation of a new paediatric marketing authorisation. In Table 5 these approaches are compared to corresponding initiatives of the current US programme. The idea of a study fund can be found in both programmes. Protection through a special paediatric marketing authorisation is only available in the plans for the EU. However, it is important to note that in the US a supplemental application for a new paediatric indication may qualify for a 3-year period of new indication marketing exclusivity in accordance with Hatch-Waxman.

Table 5 Approaches for financing the exploration of paediatric indications for off-patent drug substances in the EU and the US

<b>EU</b> <i>according to the outline of proposed regulations presented in [25]</i>	<b>US</b> <i>established by BPCA</i>
Establishment of a paediatric study fund: - either €90 million for the first year or – if aimed to fund 12 substances per year – €42.5 million - source of the fund under active consideration (Member States, possibly requesting industry profits)	Establishment of a paediatric study fund: - US\$ 200 million for 2002, such sums as are necessary for the succeeding five years - NIH Foundation established under the Public Health Service Act
Creation of a paediatric marketing authorisation with 5-year data protection period	no comparable approach

#### 5.2.1. Funding paediatric research

Due to the US experience funding is necessary for adequate stimulation of paediatric research. Neither the size nor the source of the EU fund is fixed. The industry associations claim for a



similar size to the US fund and for the financing through public health and research budgets [43][44]. Regarding the latter a supply by tax or clawbacks on paediatric incentives are considered to be counterproductive.

As an example for funding in the EU, the EU Framework Programme for Research and Technological Development shall be presented, which is the main instrument for funding of research in Europe and is open to all public and private entities. The current 6<sup>th</sup> Framework Programme lasts 2003 – 2006 and consists of an overall budget of €17.5 billion [41]. Some topics of the current programme may also be applicable to paediatric research:

- Combating cardiovascular disease and diabetes by using genomic approaches
- Combating resistance to antibiotics and other drugs by using genomic approaches
- Combating cancer by using genomics and other fields of basic research and translates into contributing applications
- Realising the benefits of pooling Europe's research sources for tackling rare diseases

It is recognised that these topics are only to be eligible for off-label drug substances if some aspects of genomics are incorporated. Another interesting aspect of the programme may be the specific schemes for SMEs in the form of Horizontal Research Activities [42]. This is independent of a topic and aims to facilitate transnational and co-operative relations in research. It should, however, be noticed that due to the criteria for SMEs a lot of the smaller European pharmaceutical companies are not covered by the official EU definition.

The programme therefore is a system for funding research that may be applicable for paediatric research. The new legislative environment for paediatric medicinal products should generally offer priority access to research programmes in the EU like it is applicable for orphan drug designations. Furthermore, it would be an option for future developments if the succeeding programme would contain a special funding for paediatric research, as this would avoid the need for the introduction of specific paediatric programme.

### **5.2.2. Granting protection rights**

As neither the current regulatory environment nor the future developments through the 'Review 2001' provide any options to protect data generated for off-patent drug substance, the idea to create a paediatric marketing authorisation is of high value. However, industry associations advocate for market exclusivity for a minimum of 10 years to promote investments [44]. Special reference is made to SMEs that are specialised in this niche market.

It should be noted that the paediatric population as well as the volume of the relevant therapeutic indications is very heterogeneous. E.g. the neonates represent a subpopulation for which return of investment may generally be difficult to obtain. The current proposals of the Commission only support a 5-year data protection, which may be too weak. A more differentiating approach is required like it is available for orphan drugs for which 10 years protection are granted that need to be justified (and may be turned down) after 6 years.

## **6. Data required for the registration of paediatric use of off-patent drug substances**

The requirements on the data for the registration of paediatric use of off-patent drug substances need to reflect adequately the special situation that there is often a long history of medical use even in an off-label setting leading to a variety of available data. Of course, appropriate clinical trials are necessary to gain evident and credible medical data on the safe

and effective use of a drug. However, the balance between the generation of new data according to the latest standard and the use of existing information needs to be maintained in order to prevent unnecessary trials.

This is especially true for the paediatric population that deserves special protection. Directive 2001/20/EC laying down the principal framework for Good Clinical Practise (GCP) provides in Article 4 information on investigations in the paediatric population. It requires that clinical trials in minors are only be undertaken “where such research is essential to validate data obtained in clinical trials on persons able to give informed consent or by other research methods”. Clinical excellence is required to guarantee the adequateness of any intervention.

Table 6 provides an overview of the key elements of the proposed European regulations on paediatric medicinal products relevant for clinical trials using off-patent drug substances, and compares them to the US initiatives. There is the general need to create a central forum for handling the matter (currently represented by the Paediatric Expert Group (PEG) at EMEA) and to strengthen the networking in medical practise. Furthermore, improvements of transparency and special pharmacovigilance measures are proposed, even if the latter differ.

Table 6 Key elements of the legislation regarding paediatric development for off-patent drug substances in the EU and the US

<p style="text-align: center;"><b>EU</b> <i>according to the outline of proposed regulations presented in [25]</i></p>	<p style="text-align: center;"><b>US</b> <i>established by various legal initiatives</i></p>
<p>Establishment of an advisory board at the EMEA (Paediatric Board, PB)</p>	<p>Key institutions within the current organisational structure:</p> <ul style="list-style-type: none"> <li>- Division of Pediatric Drug Development (DPDD)</li> <li>- Office of Pediatric Therapeutics (OPT)</li> </ul>
<p>Drawing up of a Priority List of products for which there is a need for adaptation for paediatric use, which is used for</p> <ul style="list-style-type: none"> <li>- decisions on paediatric development plans</li> <li>- shall be used for the Regulation on off-patent drug substances</li> </ul>	<p>Development of drug listings:</p> <ul style="list-style-type: none"> <li>- FDAMA Pediatric Priority List of approved drugs for which additional paediatric information may be required was eliminated by BPCA</li> <li>- BPCA established a new type of list designed to capture off-patent and no-exclusivity drug substances</li> </ul>
<p>Establishment of a European network with specific expertise in the performance of clinical trials in the paediatric population</p>	<p>Network of Pediatric Pharmacology Research Units (PPRUs) established in 1993, which includes today 13 centres and receives financial support from NIH/NICHD</p>
<p>Introduction of additional pharmacovigilance requirements to collect long-term safety data in the paediatric population</p>	<p>New safety reporting system introduced by BPCA: one-year report of all AEs to be prepared by the OPT</p>

Relevant aspects of clinical development of off-patent drug substances are highlighted below. Special attention is paid to the fact that a variety of excellence in the field of paediatric development already exist. This is to give a principal idea on the various options that may be used by all parties, i.e. industry sponsoring trials, health authorities requesting expertise within evaluation procedures and legislative bodies establishing new European structures.

### **6.1. What are the special aspects of clinical trials in children?**

As laid down in Directive 2001/20/EC clinical trials in children require special care to ensure adequate protection of this vulnerable population. Therefore, the conditions for conduction go further than the requirements of the European Convention on Bioethics [45][46]. E.g., one important aspect is that a benefit needs to be guaranteed either for the individual patient or the patient population. Further guidance on the conduction of clinical trials in the paediatric population is given in the ICH guideline E11. Additionally, it should be noticed that a Concept Paper has been released aimed to initiate the work on a Points to Consider document on PK studies in the paediatric population (CPMP/EWP/968/02). The entire topic of clinical trials in children has been discussed in a previous master thesis [47].

In order to address the issue of high level paediatric protection adequately, clinical excellence and transparency of clinical trials are of utmost need. It has been recognised that close networking of various functions is required for the conduction of paediatric trials [6]. E.g. the conduction of population PK trials aimed to reduce blood sampling needs special expertise. Like in the US, where PPRUs have been created, the proposals for the European regulations includes a respective network. In this context it is important to be aware that substantial efforts have already been made by establishing networks either on a national or an international level. The European Network for Drug Investigation in Children (ENDIC) includes members of various EU Member States and holds contact to the PPRUs [48]. On a national level, a network termed PAED-Net has been created in Germany to promote an efficient infrastructure for paediatric research [49]. It includes amongst others a co-ordination centre for the conduction of multi-center trials. In other Member States like the UK and France further regional or local networks exist. Regarding transparency there is the need for databases in discussion. They may be used for recruiting of paediatric patients for specific studies like the US database ClinicalTrials.gov, which is a service of the NIH available in the Internet. Furthermore, in order to avoid unnecessary trials a dissemination of information of data from completed trials is requested although careful considerations to avoid misuse or misinterpretation of the data are needed [44].

Any European initiative should recognise available structures for further evolutions of networking and create adequate transparency. Furthermore, industry may collaborate with the already available networks to ensure high quality standard of the trials. This could be a very important option for SMEs with low internal resources for clinical research.

### **6.2. Could other data be used for the registration?**

Besides clinical trials other data may be evaluated and used for the registration. A general prerequisite for the possibility to use these data is the availability in public domain. Therefore, concepts to improve transparency are needed. This may either be databases of specific aspects or comprehensive evaluations prepared by expert committees. Exemplary data usable for registration purpose may be the following:

- ***Surveillance programmes***

Various surveillance programmes are already in place in different countries. The International Network of Paediatric Surveillance Units (INoPSU) provides an efficient and effective framework to study rare conditions in children and offers a platform for experience exchange [50]. These systems may support either the conduction of prospective studies in post marketing surveillance settings or the compilation of data for further evaluation. As an example, vitamin K deficiency bleeding has been monitored over a period (April 1993 – March 2001) in which the oral standard dose was increased from 1 mg to 2 mg and the results demonstrated improved prevention rates. The current German labelling of oral vitamin K preparations acknowledges these results.

- ***Publications***

As stated above excessive data may be published due to a wide off-label use of a drug substance in the paediatric population. This may include small trials, individual reports, etc. usable for further analysis. E.g. for the use of carboplatin 166 and 274 publications are available for children under 12 years and 18 years, respectively. It is, however, necessary to assess the data with special care, especially if historical controls are used [51].

- ***Registries***

Registries are available for many topics and may provide substantial data. As an example, the Pediatric Toxicology (PedTox) Registry collects case reports of drug substances detected in children. In terms of safety evaluation the registry may serve as a source [52].

- ***Expert evaluations***

Some expert associations or official committees publish assessments on the adequate paediatric use of off-label medicinal products. These compilations are of great value if a highly qualified body of experts is responsible for the generation. An important source is the formulary Medicines for Children (see section 3.3.3). Other future publications may be the assessments of the French and the German expert committees (see section 3.3).

- ***PK/PD modelling***

Efforts have been made to improve the possibility to use PK/PD modelling in drug development [53]. If it is reasonable that the disease process is similar in adults and children and a pharmacological effect marker is available, the development of concentration effect relationships may enable the simulation. Within the limits of the model it could hence avoid the conduction of extensive clinical trials.

All these examples show that there are various options to obtain data on the paediatric use of a drug substance. This is more likely the longer the drug substance is already used in off-label settings. Of course, every approach need careful consideration of its adequateness to provide evident information that could lead to a registration. For each drug substance an individual set of data is needed. This compilation illustrates, however, that flexibility in the registration of paediatric indications is required from both the industry and the authority. In order to prevent unnecessary clinical trials and protect the paediatric population, a high level of excellence based on intensive experience exchange is of utmost need.

### **6.3. And after approval: Are there special pharmacovigilance requirements?**

With the future legislation on paediatric medicinal products new pharmacovigilance requirements shall be implemented (see section 3.1.2). Additionally, the EMEA's Concept Paper on Conduct of Pharmacovigilance for Medicines used by Children (CPMP/PhVWP/4838/02), which provides further information on the current plans, is already available. It is acknowledged that at time of approval the safety and efficacy data base may be very limited. Moreover, children may experience other AEs/ADRs than adults, especially in

terms of developmental and growing disorders. The introduction of post-authorisation data collection mechanisms and risk reduction strategies is therefore suggested. Post-authorisation safety studies with special focus on long-term AEs/ADRs may be requested. It will also be considered whether the extension of an indication to paediatric use should trigger re-starting of the PSUR clock.

The concept paper is intended to initiate the work on a Paediatric Pharmacovigilance Guideline. Regarding the statement on additional pharmacovigilance requirements in the proposed paediatric regulations the industry feels that there is no need to cover this aspect therein as general pharmacovigilance also includes paediatric medicinal products [44]. Any product-specific requirements to conduct post-marketing studies should be part of an agreed development plan. This topic needs special attention and follow-up of future developments.

## 7. Conclusion and Outlook

Regulatory initiatives in the EU are urgently needed to overcome the issue of marketing authorisations lacking of adequate information on the paediatric use. The current proposals for a new legislation reflect the experiences that have been made in the US. They need, however, to address the complexity of the EU with its differences in medical culture as well as the specificity of the Community market and the regulatory framework. This is especially of importance for off-patent drug substances as there may be substantial differences in terms of their medical use between the Member States.

Any strategic decision of a company concerning a paediatric development programme needs a balanced and reliable legal framework to assess the investments that are necessary for the efforts in medical progress.

Neither the current nor the future regulatory environment offers any possibility to protect data generated within further development of off-patent drug substances. This is disappointing as it represents an important difference to the US system in which exclusivity rights for the 'new use' may be granted. Therefore, the only possibility of the present European system to obtain protection rights for paediatric development with off-patent drug substances is the (mis)use of the framework of orphan medicinal products. There are, however, strict limitations for its application and hence this approach cannot solve the general issue. E.g. common diseases like asthma are not covered although data is needed.

With the proposals of the Commission for regulations on paediatric medicinal products a system of requirements and incentives is suggested [25]. Due to the differences in options to provide protection rights any stimulating system for off-patent drug substances needs to differ from the one for substances still under patent protection. The idea to create a paediatric marketing authorisation that obtains protection rights is considered to be a step forward. In general, the issue of off-label would be addressed best by offering incentives for the development [54]. It needs further discussion whether the proposed 5-year data protection period is sufficient. A more differentiating approach is recommended.

Like in the US the establishment of a study fund is an alternative. This approach may use available funding structures in the EU. However, in the light of public health economics it is assumed that the granting of adequate incentives for paediatric development is the better way than financing the research by study funds [34]. Furthermore, there should be a process how the data that have been generated at the expense of study funds will be introduced into the

labelling. The US experience showed its difficulties. Another alternative for financing may be the division of the research costs to all holders of approvals for the drug substance but the legal basis to oblige companies to participate is lacking.

In order to receive incentives, a general approach of a company might be to develop a paediatric formulation for an off-patent drug substance, as this should receive adequate protection in either system. It should be acknowledged that paediatric research might be an interesting field for SMEs as it requires specific knowledge in a niche area. Any incentive and funding programmes should hence consider these addressees adequately.

Regarding the data for the registration of paediatric use a lot of flexibility is required from both industry and authority. For off-patent drug substances various data sources should be explored to avoid unnecessary clinical trials in the paediatric population. In addition, the analysis of the impact of US labelling changes on EU product information clearly demonstrates that available data may not get across. The adequate use of all sources is of high value.

This, however, needs specific expertise in each individual therapeutic area. The number of experts is assumed to be limited and hence independent expert panels that may be approached by both industry and authority is necessary. Experiences have already been made by the COMP with orphan medicinal products, for which the committee has established ways to handle the special situation of less medical experts. Furthermore, the PEG has already started creating a network by identifying additional paediatric experts for ad-hoc expert groups. Both groups share experiences in the paediatric field [40]. The new paediatric system with the proposed Paediatric Board should build upon these experiences available at EMEA. For that purpose the available expert networks should be integrated as much as possible in order to concentrate the excellence pool. Furthermore, herbal medicinal products are widely used in paediatric treatment and may require special attention. Close co-operation with the respective experts at EMEA for herbal medicinal products is required.

Due to the urgency of the matter pragmatism is generally needed. Any too complex structure should be avoided. E.g. the idea of publishing a list of drug substances with the need for paediatric research should be handled with care. The priority list of FDAMA was eliminated with the BPCA as it was considered to be too resource intensive and less effective. Any European approach should hence reduce the complexity of the list to a minimum. Moreover, there is a lot of data available that can be used for that purpose, if not instead of a new list. Various investigations identified three therapeutic classes of high priority even in GP: analgesics, antibiotics, and bronchodilators. National committees have created further lists. The use of these data is recommended.

Besides the regulatory aspects other relevant topics should be reflected within the discussion of off-label paediatric use. Reimbursement issues may be caused by the off-label use leading to financial discussions within the health assurance system, and liability in the off-label setting is a topic that may cause legal cases. Therefore, it is necessary to solve the issue soon.

Overall, the regulatory framework for paediatric medicinal products is developing but needs further discussion. The time of implementation of the new regulations cannot be foreseen yet, but concretising steps are not expected before the availability of the results of the impact analysis. The duration of the tender, which is due to be signed in September 2003, shall be 6 months and any legal initiative cannot be started before its completion. Consequently, proposals for the paediatric regulations may be expected by mid-2004 with the one for off-patent drug substances being likely to be issued later. Close follow-up of the discussions on the new regulatory environment is of high interest.

## 8. Summary

The issue of the lack of information on the paediatric use of drug substances is commonly known. Various investigations have shown that paediatric treatment suffers to a great extent from off-label and/or unlicensed use of medicinal products. Typical drug classes are analgesics, antibiotics, and bronchodilators. The situation gets worse especially in critically ill patients like newborns in an ICU setting, but is also of significant interest in general practice.

A variety of off-patent drug substances with a long history of medical use is affected by this issue. However, as these medicinal products face generic competition, stimulation of their paediatric development requires special initiatives. The current European regulatory environment provides in general no incentives through protection rights for the exploration of e.g. new indications of off-patent drug substances. The recent proposals of the 'Review 2001' regarding the amendment of the regulatory environment also offer no improvement of this situation. Development of off-patent drug substances is hence a general issue in the EU.

Regarding paediatric development the use of the framework for orphan medicinal products could be an option. Under its criteria for an orphan drug designation this system may offer market exclusivity as an incentive as well as further advantages. However, as this regulatory framework is exclusively applicable to rare conditions that are life-threatening or serious / debilitating it may not be applicable to the issue of the lack of paediatric data in general.

In the US exist a lot of experience with initiatives to stimulate paediatric development. Recent evolutions specifically address the aspects of off-patent drug substances. This system is complementary to other initiatives applicable to on-patent drug substances.

Discussions on the creation of a new European legislation for paediatric medicinal products have already been started. The current proposals consist of two separate regulations for on-patent and off-patent drug substances. In general, the experiences with the US programmes as well as the framework for orphan medicinal products represent the basis of these proposals. The paediatric development of off-patent drug substances shall be stimulated by the creation of a paediatric marketing authorisation and the establishment of a study fund.

With respect to the registration of paediatric use of medicinal products special attention needs to be paid on the various sources of medical data for off-patent drug substances. This is of utmost need as the avoidance of any unnecessary trials in the paediatric population is generally required. Flexibility of both industry and authority is requested to handle this matter adequately. Moreover, it is acknowledged that a high level of clinical excellence is required. The use of available structures for networking and expert consultation is recommended.

The master thesis offers an up-to-date compilation of the regulatory aspects to be considered for a strategic decision on a paediatric development plan for an off-patent drug substance. An assessment of the planned regulatory initiatives in the EU in terms of their stimulation of paediatric development is made. The impact of US labelling changes from paediatric exclusivity programmes on EU product information is analysed. Key aspects of the data necessary for registration are highlighted under consideration of the off-patent setting. Special emphasis is laid on already existing clinical networks and respective examples are given. In conclusion, an individual assessment for each drug substance is required to decide upon the investment into a paediatric development as it could be an interesting opportunity for both the company and the medical society due to the evolving regulatory framework.

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