Make off-patent drugs available to children: Regulatory approaches in Europe and the US

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List of Acronyms and Abbreviations

03K	Oral off-patent oncology drugs for kids
AFSSAPS	Agence Française de Sécurité Sanitaire des Produits de Santé (French Medicines Agency)
AIFA	Agenzia Italiana del Farmaco (Italian Medicines Agency)
AMIS	Arzneimittelinformationssystem
AT	Austria
ATC	Anatomical Therapeutic Chemical
BE	Belgium
BG	Bulgaria
BPCA	Best Pharmaceuticals for Children Act
CMDh	Coordination Group for Mutual Recognition and Decentralised Procedure – human
CNS	Central Nervous System
CORDIS	Community Research and Development Information Service
CY	Cyprus
CYP	Cytochrome P450
CZ	Czech Republic
DDD	Defined Daily Doses
DE	Germany
DIMDI	Deutsches Institut für Medizinische Dokumentation und Information
DK	Denmark
EC	European Commission
EE	Estonia
EL	Greece
EMA	European Medicines Agency
EnprEMA	European Paediatric Research Network
EPC	European Patent Convention
EPOC	European paediatric oncology off-patent medicines consortium
ES	Spain
EU	European Union
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FI	Finland
FNIH	Foundation for the National Institutes of Health
FP7	Seventh Framework Programme
FR	France
HMA	Heads of Medicines Agencies
HU	Hungary
ICH	International Conference on Harmonisation
IE	Ireland
IT	Italy
LOULLA & PHILLA	Development of 6-mercaptopurine and Methotrexate oral liquid formulations for the maintenance treatment of Acute Lymphoblastic Leukemia in children.
LT	Lithuania
LU	Luxembourg

LV	Latvia
MAH	Marketing Authorisation Holder
MCRN	Medicines for Children Research Network
MCRN	Medicines for Children Research Network
MICE	Medicines Investigation for the Children of Europe
MS	Member State
MT	Malta
NEMO	Treatment of Neonatal seizures with medication off-patent: evaluation of efficacy and safety of bumetanide
NEOMERO	European multicenter network to evaluate pharmacokinetics, safety and efficacy of Meropenem in neonatal sepsis and meningitis
NEOOPIOID	No pain during infancy by adapting off-patent medicines
NEUROSIS	Efficacy and safety of inhaled budesonide in very preterm infants at risk for bronchopulmonary dysplasia
NICHD	Eunice Kennedy Shriver National Institute of Child Health and Human Development
NIH	National Institutes of Health
NIHR	National Institute for Health Research
NL	Netherlands
PAC	Pediatric Advisory Committee
PdAR	Paediatric Assessment Report
PDCO	Paediatric Committee
PEG	Paediatric Working Party (originally established as Paediatric Expert Group)
PeRC	Pediatric Review Committee
PERS	Paediatric European Risperidone Studies
PHSA	Public Health Servie Act
PIL	Patient Information Leaflet
PIP	Paediatric Investigation Plan
PL	Poland
PPdAR	Preliminary Paediatric Assessment Report
PPSR	Proposed Pediatric Study Request
PREA	Pediatric Research Equity Act
PSUR	Periodic Safety Update Report
PT	Portugal
PUMA	Paediatric Use Marketing Authorisation
RFP	Request for Proposals
RO	Romania
SE	Sweden
SI	Slovenia
SK	Slovakia
SmPC	Summary of Product Characteristics
SPC	Supplementary Protection Certificate
TINN	Evaluation of antibiotics (ciprofloxacin and fluconazole) for the treatment of infections in preterm and term neonates
UGT	Uridine 5'-diphospho-glucuronosyltransferase (UDP-glucuronosyltransferase)
UK	United Kingdom
US	United States (of America)
WHO	World Health Organization

1 Introduction

"Pediatrics does not deal with miniature men and women, with reduced doses and the same class of diseases in smaller bodies, but (...) it has its own independent range and horizon"
(Abraham Jacobi, 1889 [1])

Children are different. And not only in terms of size: Unlike an adult, children are growing and developing, physiological aspects and maturity of body systems may depend on age, and these factors may affect response to drug therapy. To complicate matters further: As "children" includes human beings from very preterm newborns to a 17 years old adolescent, they obviously are not a very homogenous group; children's each age group may have specific needs that have to be considered – and this is especially true when it comes to drug therapy.

Despite awareness for this problem has been rising over the years: For many medicinal products used in children, safety and efficacy have never been properly established. Because of ethical concerns, high complexity of clinical trials and financial considerations, pharmaceutical companies often refrained from testing their products in the paediatric population.

Because of the lack of paediatric medicines, off-label and unlicensed use of drug products is rather common in paediatric drug therapy. Paediatric doses are extrapolated from adult ones, with all risks for under- or overdosing and, as a result, ineffective therapy or an increased risk for adverse reactions. If the adult formulations commercially available are not suitable, with often unknown consequences with regard to dosing accuracy and quality aspects.

This is especially true for off-patent medicines, where paediatric development is even less attractive than within the on-patent sector, mainly due to expected low return on investment because of a combination of high costs for clinical development, small markets, and generic competition.

As market forces have not proven sufficient, specific approaches are required to improve paediatric labelling of off-patent medicines, explore paediatric indications and establish proper dosing recommendations and thus make these products available for children.

Aim of this thesis

This master thesis aims to examine the regulatory instruments in place in Europe and the US, respectively, that allow for the improvement of paediatric labelling and are intended to increase the availability of off-patent medicines appropriately tested in children.

The first part of this thesis explores the need for paediatric drug labelling and the reasons why children are different from adult patients when it comes to drug therapy. The regulatory environment for paediatric medicines in Europe and the US, respectively, is described, with a focus on off-patent medicines and the regulatory instruments in place that may lead to appropriate paediatric labelling and facilitate children's access to safe and effective off-patent medicinal products.

The second part deals with the situation as of August 2010: What has been achieved so far? The current status of the regulatory instruments in place in Europe and the US, respectively, is assessed in order to determine to what extend children have benefitted to date, i.e. whether or not the number of properly labelled off-patent medicines has significantly increased over the years since the implementation of the respective instruments.

All assessments are based on information made publicly available on websites of regulatory authorities, institutional websites, and in publicly accessible databases. Cut-off date is 15 August 2010, i.e. unless otherwise indicated, only information that had been published by then was considered for the analyses.

2 Medicines for children: General aspects

2.1 The need for paediatric labelling of medicinal products

Medicinal products intended to be used in human beings have to undergo extensive and well-controlled clinical testing and an elaborate authorisation process in order to prove safety, quality and efficacy for the intended use. Crux of the matter: Until recently, quite a lot of them had actually never been tested in the paediatric population; most medicinal products were developed in and for adults only, without regard of children and the special needs they might have. As a consequence, there is a significant lack of adequately tested and authorised medicinal products with age-appropriate formulations.

In 2009, there were 74.5 million children under 18 in the US (0 to 5 years: 25.5 million, 6 to11 years: 24.3 million, 12 to 17 years: 24.8 million), accounting for more than 24% of the total US population. This percentage is projected to remain fairly stable, with the absolute number of children likely to increase to about 101 million by 2050 [2]. Numbers are similar in Europe, where in 2005, 22.3% of the population was aged 0 to 19 years, representing more than 100 million individuals [3].

In general it may be true that morbidity increases with age; however, this does not mean that all children are necessarily in perfect health just because they are young: Data for 2003 to 2006 shows that almost 25% of US children under 18 had to take at least one prescription drug in the past month, 4% even had to be prescribed three or more medicinal products [4]. In 2008, almost 13% (i.e. around 9.5 million) of US children had to take prescription medication regularly for at least 3 months, with boys (15%) being more likely to need regular medication as compared to girls (10%)[5]. An analysis of German drug prescription data shows that on average, each of the 13.4 million German children and adolescents having statutory health insurance was prescribed 140.5 defined daily doses (DDD) in 2008 [6].

Because of the notable lack of information on paediatric use in many drug labels, many of these medicines are used off-label, and the use of unlicensed drugs is widespread. “Off-label use” means all uses outside the terms of the MA of an authorised medicinal product, i.e. all uses not detailed in the SmPC including therapeutic indication, use in age-subsets, appropriate strength (dosage), pharmaceutical form and route of administration. “Unlicensed use” is the use of a medicinal product that has not been granted a marketing authorisation in either adults or children; it includes modifications of authorised medicines, e.g. extemporaneous formulations such as solutions or dispersions of solid forms, as well as the use of imported drugs or chemicals [7].

Although percentages may vary depending on country, age of patients, and therapeutic area, by and large around half of the drugs prescribed for children are either off-label or unlicensed [8]. Neonatal hospital studies found that in neonatal wards, 55 to 80% of all prescriptions were off-label or unlicensed, and the percentage of patients that were given at least one off-label or unlicensed medicinal product ranged from 80 to 97% [9].

Because of missing paediatric information in the label, indications and paediatric dosing are often extrapolated from adult data and often doses are calculated from adult doses and adjusted according to a child’s body weight [10].

This does not necessarily mean that the respective product will actually harm the young patients, yet it carries many imponderables for prescribing paediatricians as well as for their patients, including risks such as inefficacy and/or unpredictable adverse reactions. However, without appropriate paediatric information paediatricians often have to treat children on a trial-and-error basis [10].

This has been an increasing concern over the years, and although there are many reasons why pharmaceutical companies refrained from developing medicines for children in the past (e.g. ethical concerns, scientific considerations, and commercial reasons like an expected low return on investment for paediatric medicines), consensus has developed that children also should have access to safe and effective medicines.

From a legislative point of view, the Clinical Trials Directive 2001/20/EC finally recognised that age- and development-related research is important; it made clear that the developmental, physiological and psychological differences between children and adults require medicinal products which are likely to be of significant clinical value for children and intended to be used in them to be fully studied [11].

Children are different

There are several reason why clinical trials in children as well as paediatric dosing are rather complex; one of it is that the paediatric population itself is not a homogenous group, but consists of a number of highly variable subsets (see Table 1). In general, based on age, there are five subsets, i.e. preterm newborn infants, newborn infants, infants and toddlers, children, and adolescents; it should be noted that sometimes the "children" group is further subdivided in pre-school children (2 to 5 years) and school children (6 to 11 years), as appropriate, and also the preterm newborn infant group may be split up in preterm, very preterm (28 to 32 weeks of gestational age) and extremely preterm (< 28 weeks of gestational age) neonates, as required [12].

Table 1: Paediatric subsets (according to ICH E11[13], modified).

Subset	Age	Development Phase[14]
Preterm newborn infants	≤ 36 weeks of gestation	Survival
Term newborn infants	0 to 27 days	Adaptation
Infants and toddlers	28 days to 23 months	Proliferation and growth
Children	2 to 11 years	Differentiation, Training
Adolescents	12 to 16-18 years (dependent on region)	Maturation

Each of these groups may be categorised by developmental stages, physiological and pharmacological characteristics, and there are numerous age- and development-associated changes that may influence drug response.

Developmental pharmacology

As pharmacokinetics and even pharmacodynamics of a given drug varies with age and stage of maturity, growth, development, and physical maturation are important aspects that need to be considered in paediatric drug therapy. Pharmacokinetics in adolescents is often similar to that in adults, but in younger patients, particularly in neonates and young infants, immaturity of body systems and age-related changes in pharmacokinetics may account for variable and unpredictable drug response [10, 15, 16].

a) Absorption

Although the **absorption** of orally administered drugs is relatively similar in older children and adults, developmental changes such as gastric acid secretion and gastric motility can affect the absorption of certain drug substances especially in newborn and young infants. Gastric pH is elevated in neonates, leading to increased plasma levels of acid-labile drugs (e.g. penicillin G, ampicillin, erythromycin) following oral administration; thus the dose has to be reduced [17, 18]. On the other hand, the absorption of weak acids such as phenobarbital is reduced in these children, i.e. larger doses will be required to achieve therapeutic plasma levels [17].

Rectal administration may be useful when treating neonates; however, rectal absorption is rather slow and unpredictable, especially in children, and is influenced by factors such as e.g. the increased number of rectal contractions in neonates as compared to adults that may enhance repulsion and reduce absorption [15, 18].

Following cutaneous administration, the absorption in children generally exceeds the absorption in adults, due to a thinner stratum corneum in preterm neonates and a greater extent of cutaneous perfusion and hydration of the epidermis in all children [17]. A child's ratio of body surface area to body mass is much greater than that of an adult, and this may lead to a greater systemic exposure to cutaneously administered drugs in young children, with an increased risk for toxicity [15].

b) Distribution

Body composition is one of the factors that influence drug **distribution**. The most dramatic changes occur in the first year but continue throughout childhood and adolescence, particularly with regard to body fat [15].

Extracellular and total-body water spaces are relatively larger in neonates than in adults, plus they have adipose stores with a higher water to lipid ratio, and this results in a larger apparent volume and lower plasma levels of drugs that distribute in these compartments for the same weight-based dose [15, 17].

In neonates and young infants, the quantity of total plasma proteins is reduced, resulting in lower plasma protein binding and increases in the free fraction of highly protein-bound drugs. Changes in the composition of the plasma protein may also have an effect on distribution [17].

In addition, the affinity of many drugs for albumin seems to be lower in newborn children than in adults [18]. In neonates, the bilirubin-binding capacity of albumin is reduced; in combination with a blood-brain barrier that is still immature and thus enables greater perfusion in the CNS, highly protein-bound drugs, particularly sulphonamide antibiotics, may cause CNS toxicity and kernicterus [14, 15, 18].

c) Metabolism

When it comes to **biotransformation** of drugs, specific enzymes are required for the metabolisation of drug substances. Enzyme expression often varies with age, and distinct patterns of isoform-specific developmental expression of many drug-metabolising enzymes, causing considerable changes in the biotransformation of drugs, have been observed in neonates [17, 18].

So there are, for example, age-dependent changes in the expression of **cytochrome P450** (CYP) isoforms. Some become detectable soon after birth, some take a week, others three months to appear; and on the other hand, there is one isoform, CYP3A7, whose expression peaks shortly after birth and then declines rapidly to levels that are undetectable in most adults [17].

Such peculiarities of enzyme expression affect the metabolic clearance of many drug substances. As Carbamazepine clearance, mainly dependent on CYP3A4, is greater in children than in adults, children need higher weight-adjusted doses (i.e. milligrams per kilogram of body weight) to achieve therapeutic plasma levels [17].

Caffeine and theophylline are both substrates for CYP1A2. Theophyllin half-live decreases from 8 to 18 hours in the term infant to 3 to 4 hours in infants 48 weeks old [15]. Caffeine clearance in infants older than 4 months is similar to that in adults; in infants that are six months old, the rate actually may exceed that in adults [17].

Conjugation reactions such as **glucuronidation** or **sulfatation** also depend on expression and activity of specialised enzyme systems. Glucuronosyltransferase (UGT) isoforms show age-related expression patterns, and lacking capacity of certain isoforms in known to cause serious incidents: The „Grey baby syndrome" in neonates treated with chloramphenicol has been known for decades [19]; due to the immature UGT system, the drug is not properly metabolised and in combination with insufficient renal excretion, this leads to an accumulation of toxic metabolites causing cardiovascular collapse and a grey colour of skin, hence the name [20]. Morphine, on the other hand, is the substrate of a different UGT isoform and its glucuronidation can be detected in premature neonates as young as 24 weeks of gestational age [17], thus there is no room for generalisation.

d) Excretion
Glomerular filtration and tubular secretion are the most important mechanisms for renal clearance of drugs. Both mechanisms are immature at birth, especially in preterm neonates, and this may lead to extended half-lives and accumulation of drugs. However, adult capacity is reached during the first year of life [17].

As immature **excretion** mechanisms dramatically affect the plasma clearance, renal function must be taken into account when deciding on dosing regimens, especially for drugs with extensive renal elimination; e.g. dosing intervals for tobramycin, eliminated predominantly by glomerular filtration, are 36 to 48 hours in preterm newborns and 24 hours in term newborns. Inappropriate aminoglycoside dosing regimens may lead to potentially toxic serum levels, with all associated risks of adverse reactions including renal impairment and loss of hearing [17].

e) Pharmacodynamics
Paediatric patients may even show different pharmacodynamic responses, e.g. when treated with cyclosporine or with warfarin where differences in drug-receptor interaction caused augmented response in prepubertal children despite plasma levels comparable to those in adults [17, 21]. Age-dependent differences were observed with regard to the relation between plasma concentrations and pharmacologic effect of a drug, e.g. concerning midazolam-associated sedation [17]. For erythromycin, there is evidence that the age-dependent expression of intestinal motilin receptors and the modulation of antral contractions might have implications with respect to the prokinetic effects of erythromycin in preterm infants [17].

Formulation matters

Another important aspect in paediatric dosing, in addition to developmental pharmacology, is the availability of age-appropriate formulations of the drugs needed in paediatric drug therapy.

Even if proper dosing recommendations exist, it is often hard to achieve paediatric dosing with commercially available medicinal products intended for adult use. Thus paediatricians often have to fall back on extemporaneous preparations and parents are faced with the problem how to correctly administer medicines to their children.

Common **manipulations** of adult dosage forms include breaking scored or cutting un-scored tablets, crushing tablets or opening capsules, often to mix the resulting powder in food or drink to facilitate ingestion, dispersing tablets or capsules to take proportions, and cutting transdermal patches and suppositories, with all associated risks of dosing inaccuracy and therapeutic failure, especially e.g. with regard to prolonged-release formulations [22, 23].

More than 90% of paediatric dosage forms are intended for oral administration; it is the predominant route despite all limitations [23, 24]. For children who are not yet able to swallow capsules or tablets, liquid formulations such as solutions, syrups, suspensions, and emulsions are most appropriate [22]. For infants up to two years of age, concentrated liquid formulations are suited best, due to the reduced volume that has to be administered; for children 2 to 12 years of age, dosage forms such granules and chewable tablets may also appropriate [23].

To ensure accurate dosing of liquid formulations, appropriate dose delivery **devices** are required that allow for exact dose measurement and simple, controlled administration [22]. For infants under 2 years of age, calibrated droppers or oral dosing syringes are suited best [23]. As children from 2 to 12 years of age usually need to be administered larger volumes, graduated dosing cups or spoons are commonly used [23]. To enhance paediatric compliance, task-masking strategies such as the addition of sweeteners and/or flavours might be considered [23, 24].

But even though oral liquids are preferred formulations in paediatric drug therapy, not all liquid preparations are actually suitable: Some **excipients** commonly used in formulations intended for adult patients may cause harm in at least some of the more vulnerable paediatric age groups.

In children younger than 6 months of age, polysorbates may cause liver and kidney failure; the solvent propylene glycol can cause adverse reactions such as seizures, neurotoxicity, and hyperosmolarity [24]. Ethanol, used as solvent in many oral liquid preparations, may be a cause of drug interactions and has neurotoxic potential; concerns include acute intoxication with accidental overdose as well as chronic toxicity [22, 24]. Benzoic acid, sodium benzoate and potassium benzoate may increase the risk of jaundice in neonates [22] and in paediatric patients with reduced renal function, aluminium salts may cause e.g. encephalopathy, microcytic anaemia, and osteodystrophy [24].

Benzyl alcohol, a preservative widely used in multidose injections, is known to cause the “gasping baby syndrome” in neonates whose immature enzyme systems do not have the capacity to metabolise this substance properly. Thus plasma concentrations of benzyl alcohol increase, leading to severe adverse reactions including metabolic acidosis, seizures, encephalopathy, and death [24].

All things considered formulation issues add to the problem of safe and effective paediatric drug therapy, which is why there is a clear need for paediatric formulations that permit accurate dosing and enhance patient compliance.

2.2 Off-patent drugs: particular challenges

There has been a considerable lack of paediatric drug development in the past. Although the market for paediatric medicines is not as large as the market for adults, significant resources are required in order to study a medicine for use in children; thus looking at expected revenues, pharmaceutical companies have often been rather reluctant to invest in this field. And there are numerous additional challenges e.g. when it comes to clinical research involving children.

Conducting clinical studies in children is more challenging than in adults; it faces specific ethical, scientific, and practical issues. For example, parents are often concerned about the risk and often reluctant to permit the inclusion of their child in a clinical trial. Children, namely the younger ones, cannot give legal consent or assent; as a consequence, many paediatric studies can only include children who have the condition of interest and are likely to benefit from the treatment [10]. For many diseases, there is only a small number of children affected, therefore recruiting enough patients for a clinical study often is more difficult and takes longer than for adults and e.g. international, multi-centre trials are required [10, 25, 26].

Compared with the size of the potential market, paediatric clinical studies are cost-intensive. There have been assumptions that, in academic centres, the conduct of a pharmacokinetics study in Europe would be about 200,000€, a dose-finding study about 500,000€, and about 1.7 million € might be required for safety and efficacy studies [27]. For the US, the National Institute of Child Health and Development (NICHD) has estimated a pharmacokinetic study to cost from $250,000 to $750,000 per age group, the cost of a safety and efficacy study may range from $1 million to $7.5 million [28]; figures are rising and there have been reports that there was an 8-fold increase of mean costs for completing a US Written Request study programme from 2000 to 2006 [29]. The expenditure is further increased if age-appropriate formulations have to be developed. Depending on the formulation, these costs can be quite significant, yet widely variable; there have been assumptions that 750,000€ will have to be spent for the development of a formulation [27], but there have also been reports that this might add to several million in some cases [29].

Because of these expenses and the small financial benefit that is to be expected, appropriate incentives, e.g. patent extensions or paediatric exclusivity, are required to make paediatric research more attractive. There have been reports that, as a result, patent-protected blockbusters are more likely to be studied for children because paediatric exclusivity delays generic competition and thus increases the revenues significantly [28, 29].

As incentives such as patent extensions naturally only apply to on-patent products, the problems of cost and complexity aggravate when it comes to off-patent medicines. Off-patent medicines in Europe are those not covered by a patent or by a supplementary protection certificate (SPC). According to Article 63(1) of the European Patent Convention (EPC), the term of a European patent is 20 years from the date of filing of the application. The SPC, originally introduced by Council Regulation (EEC) No 1768/92 [30], may extend this period; it was established as a compensation tool for the long time required for development and regulatory approval of medicinal products. With an SPC, an overall maximum of 15 years of patent exclusivity from the time the medicinal product in question first obtains a marketing authorisation in the EU, but not more than five years after patent expiry, may be obtained. An SPC application may be considered for a medicinal product that is protected by a basic patent in force, had not been the subject of an SPC before and has been granted a marketing authorisation that needs to be the first marketing authorisation in place for said product [31]. There is no cross-recognition of SPCs among EU member states, hence SPC applications must be filed and approved on a country-by-country basis. Therefore a given drug substance may be on-patent in one and off-patent in another Member State.

Developing these older medicines for children is even less appealing in most cases, as there is no protection of intellectual property rights. There is no patent to be extended, and although there is data protection period foreseen for new medicinal products, this period however depends on the granting date of the initial marketing authorisation in the EU and is not renewed upon authorisation of a new indication, even if paediatric. Thus, if e.g. an originator develops an off-patent medicinal product for paediatric use, generic competitors may refer to the paediatric data and include the new paediatric indication in their labels without delay. This of course is an important disincentive that makes pharmaceutical companies refrain from investing resources and effort in new paediatric clinical studies for older products.

In the US, with regard to paediatric development, a drug is considered “off-patent” in case it is not covered either by a patent or by marketing exclusivity such as Waxman-Hatch exclusivity granted for new drug applications and for supplemental applications for a new use of an authorised medicine, or orphan drug exclusivity. Especially the supplemental application part is why in the US a drug that is “off-patent” now may change status and become “on-patent” again, thus making the whole process more complicated.

But paediatric drug therapy cannot do without off-patents: Many of the drugs that are used off-label or unlicensed in children are older, off-patent drugs. The medicines most frequently prescribed for children are anti-infectives/antibiotics, analgesics/antipyretics, drugs to treat respiratory diseases, gastroenterological drugs, and cardiovascular drugs [32]. These drug classes include many off-patent substances, and although not all of them are used off-label, there is a significant lack of paediatric information for some of them; for example, cardiovascular drugs commonly prescribed off-label with regard to age and/or indication include e.g. several off-patent β-blocking agents such as metoprolol and propranolol and calcium channel blockers such as nifedipine [32].

In the field of paediatric oncology, more than 75% of the drug substances used in paediatric cancer chemotherapy are off-patent. Pharmacological information regarding the use in infants is sparse, available formulations of oral anticancer drugs are not age-appropriate for young children who cannot swallow capsules or tablets, and little is known about long-term toxicity that might affect survivors in later life (e.g. with regard to second malignancies and fertility issues) [33].

Because of this situation there clearly is a paediatric need for off-patent medicines. As market forces alone have not be sufficient to stimulate development in this field sufficiently, special instruments and approaches are required in order to increase safety and efficacy of paediatric drug therapy with off-patent medicinal products, either providing appropriate incentives that encourage pharmaceutical companies to invest resources and effort in paediatric development of older drugs or, where this is not feasible, utilising the knowledge that has been gained in many years of off-label use to improve paediatric labelling of off-patent medicines.

3 How to achieve paediatric labelling for off-patent drugs

3.1 Current Situation in Europe

3.1.1 EU Regulatory Environment for Paediatric Medicines

When on 26 Jan 2007 Regulation (EC) No 1901/2006, the so-called Paediatric Regulation [34], entered into force, this marked the beginning of a new era as this new piece of legislation considerably changed the European landscape of paediatric drug development.

The objectives of the Paediatric Regulation are to facilitate the development and accessibility of medicines for use in the paediatric population, i.e. in that part of the population aged between birth and 18 years (Article 2(1)), to ensure that medicines used in children are subject to ethical research of high quality, to ensure that these medicines are appropriately authorised for use in children as well as to improve the information available on the use of medicines in the various paediatric populations. Unnecessary clinical trials in children are to be avoided, and the authorisation of medicines for adults should not be delayed (recital 4).

In order to achieve these aims, a system of obligations as well as rewards and incentives is foreseen. Which obligations or incentives actually apply for a given medicinal product largely depends on whether the product is still under development or has already been authorised and, in the latter case, if the product is still covered by some kind of patent or SPC.

Obligations

One of the key requirements according to the Paediatric Regulation is the obligation to provide results of studies conducted in compliance with an agreed **Paediatric Investigation Plan (PIP)** when applying for a new marketing authorisation (Article 7; Article 30) or for new indications, pharmaceutical forms, or routes of administration for authorised medicinal products (Article 8). This does not apply in case a waiver or deferral (see below) has been granted; applications related to generics, hybrid medicinal products, biosimilars, well-established use medicines, tradional herbal medicinal products, and homeopathics are exempt (Article 9).

A PIP, as defined in the Paediatric Regulation (Article 2(2)), is a research and development programme that aims to generate the data required to authorise a product for the use in the paediatric population. It is possible to include studies initiated before the Paediatric Regulation was enforced (Article 45(2); rewards and incentives will however only be granted if the significant studies in the PIP were completed afterwards (Article 45(3)).

PIPs have to be agreed in advance with the **Paediatric Committee (PDCO)**, an independent scientific committee established within the European Medicines Agency (EMA; Article 3(1)). This committee is composed of 33 members (plus alternates) who are appointed for a renewable period of three years; five of them are CHMP members, 22 are appointed by the Member States not represented by these CHMP members, three of them represent health care professionals and another three members represent patient organisations (Article 4). The Member States have to ensure that the final composition of the PDCO covers all fields relevant to paediatric medicines, such as pharmaceutical development, paediatric pharmacology, pharmacovigilance, ethics and so on [35].

In addition to the assessment of PIPs, the tasks assigned to the PDCO include e.g. to assess waivers, and deferrals, to assess PIP compliance, to support and advise the Agency on establishing the European network, to establish a specific inventory of paediatric needs, and to provide advice on any question related to medicinal products for use in the paediatric population (Article 6(1)).

The PIP application must be submitted to the PDCO no later than on completion of the pharmacokinetic studies in adults. Form and content (see Table 2) of such an application are specified in Commission Guideline 2008/C 243/01 [36], the so-called “PIP-guideline”, that provides detailed information regarding all aspects of a PIP.

Table 2: Organisation of a PIP application

Organisation of a PIP application (acc. to PIP guideline [36])	
Part A	Administrative and product information
Part B	Overall development of the medicinal product including information on the conditions
Part C	Applications for product specific waivers
Part D	Paediatric investigation plan
Part E	Applications for deferrals
Part F	Annexes

The Paediatric Regulation aims to meet therapeutic needs of children. As it is acknowledged that there may be conditions that do not occur in children or that a given medicinal product will not represent a significant benefit for the paediatric population or a subgroup thereof or will even be unsafe or ineffective, **waivers** may be issued, i.e. no clinical studies have to be done for the product, condition, or age-group waived. There are class-waivers covering a class of medicinal products such as medicines to treat Alzheimer’s disease or age-related macular degeneration and product-specific waivers the applicant or marketing authorisation holder has to apply for in the PIP application, if considered appropriate.

Under certain circumstances, on the one hand a waiver is not justified as children are likely to benefit from e.g. a new medicine, but it on the other hand paediatric studies might take longer than studies in adults, thus delaying the authorisation of the product for adult patients, or it would not be safe or ethical do start paediatric studies before data from adults is available. In this case, a **deferral** may be applied for (Article 20 of EC/1901/2006), so that the initiation or completion of some or all paediatric studies will be deferred as appropriate.

As all age subsets must be considered, a PIP application may contain e.g. a proposal for a clinical trial involving school children and adolescents with a deferral application for pre-school children plus a waiver application for the remaining subsets.

Upon receipt of a PIP application, PDCO assigns a rapporteur and takes care of the request; when the assessment procedure is completed, PDCO issues an opinion whether or not the proposed studies are justified by the expected therapeutic benefit and will ensure the generation of the data required and formulations proposed are age-appropriate (Article 17(1) of EC/1901/2006).

All measures agreed must be conducted in accordance with the PIP decision in order to achieve PIP compliance. Should changes to the PIP be deemed necessary, it is possible to apply for a PIP modification in accordance with Article 22 of the Paediatric Regulation.

When all measures not deferred have been completed, a compliance check is required. The compliance check, too, is performed by the PDCO, upon request (Article 23 of EC/1901/2006). PIP compliance is a prerequisite for a marketing authorisation application or line extension application to be valid, i.e. by the time of submission of such an application all measures agreed in the PIP must have been conducted in accordance with the PIP decision and within the agreed timelines [37]. Moreover, PIP compliance is also required to be eligible for the incentives (Article 24 of EC/1901/2006).

Rewards and incentives

For new medicinal products or for line extensions of authorised products covered by an SPC or a patent that qualifies for an SPC, an SPC extension of six months is granted as a reward, provided the prerequisites are met, i.e. the study results presented with the application are PIP-compliant, no one-year patent extension on the grounds of significant clinical benefit has been granted for the paediatric use, and the product is authorised in all Member States (Article 36 of EC/1901/2006).

An important aspect is that this exclusivity extension is granted regardless of the outcome of the paediatric studies, i.e. it applies even if the studies do not lead to an authorisation for the paediatric population; however, relevant information has to be included in the product information in any case.

Orphan medicines are exempt; these products will be rewarded with an extension of the market exclusivity period from ten to 12 years instead (Article 37 of EC/1901/2006).

As off-patent medicines obviously do not qualify for a patent extension, Article 30 of the Paediatric Regulation provides the legal basis for a more specific incentive: the **Paediatric Use Marketing Authorisation (PUMA)**. This is a new kind of marketing authorisation specifically designed for drugs lacking intellectual property rights intended to stimulate development of off-patent drugs exclusively for paediatric use. A PUMA is associated with a set of incentives such as 10 years of data protection (Article 38), eligibility for the centralised procedure (Article 31), and brand name retention (Article 30(4)), if applicable. Please refer to section 3.1.2.1 for more details regarding PUMA. Funding of research into paediatric drug use that may eventually lead to a PUMA application may be provided through Community research programmes such as the EU Framework Programme (Article 40).

Rewards and incentives granted for paediatric drug development are mostly associated with marketing obligations: If marketing of a medicinal product with a paediatric indication and for which the MAH has benefited from rewards or incentives is discontinued after the protection periods have expired, the MAH has to transfer the marketing authorisation or allow a third party to refer to the relevant data to obtain a marketing authorisation based on informed consent (Article 35 of EC/1901/2006).

Further to the above, as foreseen in the Paediatric Regulation, EMA provides free **scientific advice** (Article 48) for paediatric aspects of drug development; in addition the services of the PDCO with regard to the assessment of PIPs, waivers, deferrals, and PIP compliance are free (Article 47(3)). Member States are free to offer rewards and incentives for paediatric drug development in addition to those provided for in the Paediatric Regulation (Article 39(1)).

Other provisions of the Paediatric Regulation

Other provisions of the Paediatric Regulation include for example those related to **EU Paediatric Worksharing**: Article 45(1) of the Paediatric Regulation required all available information from paediatric studies already completed by 26 Jan 2007 be submitted to the competent authorities by 26 Jan 2008; the authority may then assess this data and decide on an amendment of the SmPC. MAH-sponsored paediatric studies related to an authorised medicinal product that have not been completed by then have to be submitted within six months after completion (Article 46)

Furthermore there are provisions regarding the establishment of a European network for paediatric clinical trials (Article 44; see section 3.1.3.2)). Clinical trials involving children that are part of an agreed PIP and carried out in third countries are to be included in the Eudra-CT database; parts of the information will be made public (Article 41). **Penalties and sanctions** on both EU and Member State level are foreseen in Articles 49 and 50 of the Paediatric Regulation.

Originally the Paediatric Regulation foresaw a provision for paediatric medicines to be identified by a special **symbol**, to be selected by the Commission on PDCO's recommendation (Article 32). However, following extensive discussions that could not allay concerns that there is a considerable risk of misinterpreting the symbol and that this might lead to medication errors, the PDCO finally stated that it was not able to recommend a symbol for which the benefits would outweigh the risks [38]. Therefore, Article 32 could not be implemented.

List of Paediatric Needs

In order to establish an inventory of paediatric therapeutic needs, a thorough review of paediatric drug use and gaps in this field was performed some years ago. This was coordinated by the predecessor of the PDCO, the Paediatric Working Party (PEG), that was established in 2001 as Expert Group on Paediatrics and transformed into a temporary working party in 2005. PEG had established a procedure for identifying unmet pediatric needs in the different therapeutic areas [39]:

Based on drug lists originally drawn up by the French Medicines Agency (AFSSAPS) and information gathered in collaboration with National Authorities and recommended experts as well as societies from the relevant therapeutic areas, PEG prepared lists of paediatric needs for about 15 disciplines such as anaesthesiology, anti-infectious therapy, cardiology, diabetes, epilepsy, pain, and chemotherapy.

These lists include both on-patent and off-patent drug substances and have been published on the EMA website. There are some substances that appear on more than one list (fentanyl, for example, is included in both the list related to anaesthesiology [40] and the one related to pain [41]). For every drug substance, the available paediatric information (i.e. authorised indication, age group, dose and formulation, if applicable) has been summarised; moreover the list indicates which kind of data would be needed for the respective drug substance whether or not there is a need for an age-appropriate formulation of the drug.

As foreseen in Article 43 of the Paediatric Regulation, PDCO should attend to an revised inventory of therapeutic paediatric needs, based in information communicated from the Member States in accordance with Article 42 of the Paediatric Regulation, and ensure regular updates; the paediatric needs as adopted by the PEG will serve as a basis for this exercise [42].

Priority List for Studies into Off-Patent Drugs

Based on the established pediatric needs, PEG created a priority list of off-patent medicinal products in 2003, following a two-step procedure, i.e. first prioritising conditions based on e.g. severity of disease, non-availability of treatment alternatives and paediatric subsets affected and then identifying off-patent drugs for each condition according to published therapeutic reviews [43, 44].

The list has been updated on several occasions, in the beginning by PEG and later, after its establishment, by PDCO; the current version was originally adopted on 21 May 2010 [45]; an updated version with minor amendments was published in July 2010 [46]. A draft version of the 2011 version of the list was released for public consultation in June 2010 [47].

The objective of the list of off-patent drugs is to provide the basis for the respective calls under the EU Framework Programme, as funds should be directed into fields with the highest therapeutic needs [48]; therefore the list may be a valuable instrument in paediatric drug development.

3.1.2 Off-patent drugs for children: Procedures in the EU

3.1.2.1 Off-patent drugs only: The Paediatric Use Marketing Authorisation

Developing drugs for use in the paediatric population is challenging and requires a lot of resources while being less financially rewarding than developing products for adult use. Therefore, special instruments are required to foster paediatric drug development in the off-patent field and thus increase children's access to safe and effective medicines.

One approach, and one of the key measures of the Paediatric Regulation, was the introduction of a new type of marketing authorisation, the **Paediatric Use Marketing Authorisation (PUMA)**. The PUMA is intended to establish incentives for the development of authorised medicines exclusively for the use in children and applies only to products that are no longer covered by intellectual property rights (i.e. patent or SPC) and are therefore ineligible for incentives like SPC extension.

As set out in Article 2(4) of the Paediatric Regulation, a PUMA exclusively covers therapeutic indications which are relevant for use in children (i.e. all age-groups or one or more subsets), including the appropriate strength, pharmaceutical form or route of administration for that product.

The PUMA utilises existing procedures for granting marketing authorisations. Any submission of an application for a PUMA is automatically eligible for the centralised procedure, i.e. without prejudice to Article 3(2) Regulation (EC) No 726/2004 (Recital 21, Article 31; [49]). However, any PUMA application may also be made through the established national/decentralised/mutual recognition procedures and basically they follow the normal processes in terms of e.g. prerequisites, costs, and timelines, although of course special provisions like accelerated assessment or fee reductions may be applied by a member state's national competent authority.

Like for any medicinal product, quality, safety and efficacy of PUMA medicines have to be demonstrated. Data required to establish safety, quality and efficacy in children may be derived from published literature or from new appropriate studies conducted in children or be a combination thereof. In addition, applicants may cross-reference to data contained in the dossiers of a medicinal product which is or has been authorised in the Community (according to Article 14(11) of Regulation (EC) 726/2004 and Article 10 of Directive 2001/83/EC, respectively), provided data and market protection periods have expired (Recital 20, Article 30(3)). Thus a PUMA is the only type of marketing authorisation where it is possible to submit new data in an otherwise generic-type application.

The information required for PUMA applications includes **data** concerning the use of the product in children, collected in accordance with an agreed PIP, as well as data supporting an appropriate strength, pharmaceutical form or route of administration for the product; thus, as pointed out in CMD(h)'s "Recommendations of Paediatric Use Marketing Authorisations" [50], the PUMA submission should comprise:

- Application form
- Demonstration of compliance with a PIP (i.e. provision of a PDCO opinion on compliance)
- Cross-references to existing data
- Quality documentation to support age-appropriate strength, form, route of administration
- Pre-clinical documentation to support safe use in children (Module 4)
- Clinical safety and efficacy studies (Module 5)
- Details of measures to ensure follow-up of efficacy and safety (Risk Management Plan)

All documentation should be provided as designated in the approved PIP, with appropriate crossreferenced data.

For products that are already marketed for other indications, the MAH is obliged to actually market the product with the new paediatric indication/information within two years following the date of approval. This measure does *not* apply to medicinal products authorised via a PUMA (Recital 22); the PUMA incentive is only realised if the respective medicine is actually on the market, thus launching the product is the MAH's interest.

Rewards associated with PUMAs

In order to encourage paediatric research into off-patent drugs and subsequent authorisation of paediatric medicines, PUMAs are associated with a number of incentives, as set out in the Paediatric Regulation (see Table 3):

Table 3: Incentives associated with PUMA

PUMA: the Incentives
▸ Brand name retention
▸ Data protection
▸ Eligibility for centralised procedure
▸ Fee reduction (centralised procedures only)
▸ Free assessment of PIP applications*
▸ Free assessment of PIP compliance*
▸ Free Scientific Advice*
▸ Funding under EU Framework Programme

* these apply to on-patent paediatric medicines as well

What is supposed to be the most valuable incentive is the **data protection** period that is granted upon authorisation and covers all new information regarding paediatric formulation and indication. The usual data protection periods apply, i.e. protection is granted for 10 (8+2) years (Article 38 of EC/1901/2006). Data protection is a kind of intellectual property right yet it is not dependent on the patent system and therefore may be applied to off-patent drugs. For this period, other MAHs must not refer to the protected parts of the dossier to obtain a marketing authorisation of their own. It should however be noted that, hypothetically, data protection does not prevent competitors from conducting their own research and develop a product of their own in case the respective market segment is sufficiently attractive, which is why data protection is not to be mistaken for market exclusivity (as the latter is not guaranteed).

A second incentive: In order to capitalise on existing brand recognition, the **brand name** of the corresponding medicinal product authorised for adults may be retained, provided both marketing authorisations are held by the same MAH (Recital 19; Article 30 (4)).

Incentives with immediate financial impact include the **fee exemptions** that apply for both on- and off-patent drugs, i.e. free paediatric scientific advice provided by the EMA as well as PDCO's free assessment of PIP applications and PIP compliance (Article 47(3)).

Additional PUMA-only incentives are a 50% **fee reduction** for initial marketing authorisation applications and pre-authorisation inspections for PUMAs authorised through the centralised procedure; also reduced by 50% are annual fees and fees for variations, extension applications, and inspections in the first year from granting of a PUMA (Article 47(1); [51]).

In addition to the incentives provided for by the Paediatric Regulation, medicines authorised via PUMA may be eligible for additional incentives provided by either the Community or the EU Member States (Article 39). Another incentive that may facilitate paediatric development of off-patent medicines in some cases potential funding of PUMA-related research under Community research programmes, e.g. through the Community Framework Programmes (Recital 12; Article 40).

3.1.2.2 EU Paediatric Worksharing

In order to improve paediatric labelling of medicinal products that are already authorised, a second approach was provided for in the Paediatric Regulation: It may be assumed that for a certain number of medicines, MAHs have some information related to the use of their product in the paediatric population that has never been published, study results that were never used for any regulatory action or the like; to collect these bits and pieces, to assess them and make relevant paediatric information available for paediatricians and patients – or their parents, respectively – the EU Paediatric Worksharing procedures were established.

Although not specifically designed for off-patent medicines, this regulatory instrument may nevertheless offer a chance for the improvement of paediatric labelling of off-patent medicinal products that have been authorised for long time and are not attractive any more to be subject to new paediatric studies due to the lack of intellectual property rights.

Article 45 Worksharing

As set out in Article 45(1) of the Paediatric Regulation, MAHs are obliged to submit all paediatric clinical studies that had been completed by the date of entry into force (i.e. 26 Jan 2007) to each competent authority in the EU where the respective products are authorised. The authority assesses the information and may update the label accordingly. Information exchange across member states is coordinated by the European Medicines Agency (EMA).

This provision applies to all authorised medicinal products without exception, i.e. to products authorised through mutual recognition, decentralised or purely national procedures as well as to medicines that are centrally authorised. A “paediatric study” is any study that involves patients less that 18 years old, even if there are adult patients in the study as well [52].

Data to be submitted includes clinical studies and trials (phase I to IV) and non-clinical studies that may be relevant but were not previously submitted, whether they were completed or discontinued, published or not, and regardless of the region where they were performed, the aim, outcome, population studied and indication [52].

Basically, the process itself is divided in three steps [52]:

1) Submission of the line listings for all authorised medicinal products
2) Upon request: submission of paediatric studies not yet submitted to the Rapporteur for assessment in the framework of the Worksharing procedure (for MRP/DCP and purely nationally authorised products; centrally authorised products will be assessed by the CHMP)
3) Formal variation procedure, if applicable.

The deadline for the submission of the information requested (provided as line listings) was 26 Jan 2008. Due to the number of products that need to be assessed, not all assessments can be done in parallel. Therefore, article 45 worksharing is organised in so-called “waves”: About once per quarter, a new list in published on the CMDh website [53] indicating which substances will be assessed next. For the decision which substances to include in the next wave, the priority list of off-patented products as well as unmet paediatric needs on a national level are taken into account [54]. As of July 2010, there had been eight waves including a total of 147 active substances [55].

Once a substance has appeared on the list, the procedure is as follows:

For MRP/DCP and purely nationally authorised products, the CMDh will appoint a rapporteur for the assessment of each substance, taking into consideration e.g. specific expertise or knowledge or experiences gains in a previous worksharing procedure. The rapporteur is not necessarily identical with the RMS for a medicine authorised via a mutual recognition or a decentralised procedure [54].

Then the EMA will inform the MAH which member state will act as rapporteur and share information such as timeframe and contact details for submission of the paediatric studies for assessment.
For a number of active substances, namely the off-patent ones, more than one MAH will be concerned. In such cases, the rapporteur will usually communicate with those MAHs that have submitted studies for the active substance in question [54].

MAHs concerned then have to submit the paediatric studies to the rapporteur within one month of request, in electronic format only. This submission should include:

- All data relevant for assessment (including published information, quality, non-clinical, and clinical)
- Critical expert overview clarifying relevance and context of the data
- A proposal to amend the SmPC/PIL or a justification that changes are not necessary
- Relevant PSUR data or reference to PSURs already submitted [54].

Data that has already been submitted does not have to be resubmitted; however, it should be briefly summarised in the overview of all available information on paediatric use.

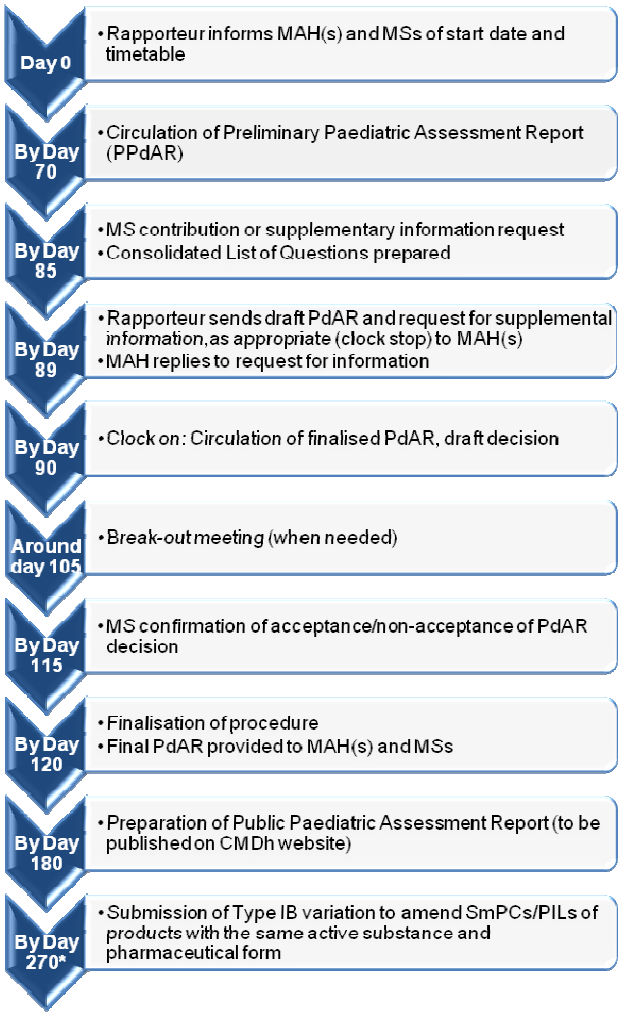


Fig. 1: Workflow of the Paediatric Assessment Procedure according to Best Practice Guide [54]

* for Art. 46 procedures: “By Day 240”

As a next step, the rapporteur starts the procedure. The assessment basically follows a 120-day timetable; however, if there are is no need for clarification or additional information, the procedure may even run smoothly without clock-stop and thus may be closed as early as Day 90 (see Fig. 1).

The rapporteur may ask for additional information in course of the procedure; however, a MAH cannot be requested to conduct further studies (although the rapporteur may want to encourage the MAH to do so, e.g. including an according statement in the PdAR recommendation part) [56].

Once the procedure is closed, the rapporteur has to prepare a public paediatric assessment report that will be published on CMDh website.

If an update of SmPC and PIL is required, a Type IB variation must be submitted within 90 days after the publication, in accordance with Section C.I.3 a) of the Variation Classification Guideline [57]]. This applies to all MAHs of an active substance, not just to those who were involved in the assessment procedure [54].

Article 46 Worksharing

MAH-sponsored paediatric studies involving authorised medicines that have been not completed by 26 Jan 2007 have to be submitted within six months after completion (Article 46 of EC/1901/2006), with a study being considered as completed when, according to the last protocol submitted to the authorities, the last visit of the last patient has occurred [36].

Again, a cover letter plus line listing will be sufficient; however, the paediatric data has to be available upon request [52].

While article 45 refers to any studies for an authorised product, article 46 only refers to studies sponsored by the MAH [52]. The obligation to submit a paediatric study does not depend on the MAH's intention to apply for a marketing authorisation for the paediatric indication studied. Compliance with an agreed PIP is not required; however, if the study was actually part of an agreed PIP, this fact should be indicated [58].

The start of a worksharing procedure according to Article 46 does not depend on "waves"; it should rather be started immediately after the MAH has submitted cover letter and line listing, provided there is no sound reason for a delay (e.g. the study is part of a PIP) [58].

By and large, the Article 46 assessment procedure follows the same timetable as mentioned above for the Article 45 assessment. Basically there is only a difference when it comes to the submission of the Type IB variation to amend SmPC and PIL: Following an Article 46 assessment, the MAH concerned by the procedure has only 30 days (instead of 90) to submit the variation application; other MAH, who are also required to update their product information to include e.g. important safety information, have to submit their Type IB variation within 60 days of PdAR publication [58].

If for a given product there are both studies completed before the cut-off date and studies that were completed afterwards, the respective Article 45 and Article 46 procedures may be combined into one mixed procedure [56].

3.1.3 Research incentives and funding

3.1.3.1 EU Framework Programme

Funding of studies into off-patent medicinal products may be provided through Community research programmes, namely the EU Framework Programmes, as set out in Recital 12 and Article 40 of the Paediatric Regulation.

The current edition of the EU Framework Programme is the "7th Framework Programme for Research and Technological Development" (FP7). FP7 is the EU's main instrument for funding research in Europe; it will run from 2007 to 2013. The EC budget for these seven years is € 50.5 billion, and there is an additional Euratom budget of € 2.7 billion [59]. The budget is to be spent on research grants hat are awarded on the basis of calls for proposals and a highly competitive peer review process. FP7 is open to participants from any country in the world. The **rules for participation** in the programme and for the procedures are laid down in Regulation EC/1906/2006 [60].

FP7 comprises four specific programmes, called "Cooperation", "Ideas", People", and "Capacities", plus a fifth specific programme on nuclear research [59]. Under every specific programme, there a several themes; one of the ten themes under the "Cooperation" programme is "Health". The Cooperation programme has a total budget of € 32 billion; for the Health theme, there are funds amounting to € 6 billion [59].

When there is a "call", there is a work programme published for every theme that provides details of the research topics and potential participants may submit proposals for research projects. So far, there have been five calls under FP7, and four of them had included a topic related to off-patent drug developments for children (see Table 4).

The work programme 2007-2008 was split into a first call (FP7-HEALTH-2007-A) and a second call (FP7-HEALTH-2007-B). The first one included topics in the field of paediatrics such as "Innovative approaches for the development of vaccines for young children" (HEALTH-2007-1.4-2) and "Paediatric formulations of drugs against HIV/AIDS, malaria and tuberculosis" (HEALTH-2007-2.3.2-5); the topic explicitly related to off-patent medicines for children, however, belonged to the latter.

The objective of topic "**HEALTH-2007-4.2-1**: **Adaption of off-patent medicines to the specific needs of paediatric populations**" was to support studies that are dedicated to provide evidence for specific paediatric use of off-patent medicines currently used off-label. Studies include the assessment of pharmacokinetics (as well as data analysis and extrapolation by means of *in silico* models), efficacy and safety, and/or the development of age-appropriate formulations. The Priority List for Off-Patent Medicines had to be considered [61]. Objectives for the following call for 2009, topic **HEALTH-2009-4.2-1**, were quite similar, with an additional statement that participation of third countries would be highly appreciated [62].

For topic "**HEALTH.2010.4.2-1: Off-patent medicines for children**" in the following call, it was emphasised that the research should aim to increase the availability of duly authorised products for children as well as to increase the information available on the paediatric use of off-patent drugs and that projects will need to develop and test new paediatric medicine as well as age-appropriate formulations of older, off-patent medicines. Active participation of SMEs was explicitly encouraged. In addition, the need for research into age-appropriate formulations, the needs of neonates and into new conditions such as rheumatology was emphasised [63]. For this call, the project selection process is ongoing; three projects have been proposed to be funded [64].

Other topics under the Health Theme 2010 related to paediatrics were "Vaccines for childhood bacterial diarrhoeal diseases" (HEALTH.2010.2.3.4-1), "Structuring clinical research in paediatric and adolescent oncology in Europe" (HEALTH.2010.2.4.1-3), and "International paediatric initiative" HEALTH.2010.4.2-2) [63].

Table 4: FP7 calls for the development of off-patent medicines for children.

FP7-HEALTH-2007-B	**[65]**
Pub. Date	2007-06-18
Total Health Budget	549 000 000€
Topic	HEALTH-2007-4.2-1
Title	**Adapting off-patent medicines to the specific needs of paediatric populations.**
Funding Scheme	Collaborative project (Small or medium-scale focused research project). Max. EU contribution of € 6 000 000 per project.
Expected Impact	Projects will provide evidence for a better use of off-patent medicinal products in paediatric populations. The acquired knowledge should aim at new Paediatric Use Marketing Authorisations (PUMA).
FP7-Health-2009-single stage	**[66]**
Pub. Date	2008-09-03
Total Health Budget	476 000 000€
Topic	HEALTH-2009-4.2-1
Title	**Adapting off-patent medicines to the specific needs of paediatric populations.**
Funding Scheme	Collaborative Project (Small or medium-scale focused research project). The requested European Community contribution in each project shall not exceed € 6 000 000.
Expected Impact	To provide evidence for a better use of off-patent medicinal products in paediatric populations. The acquired knowledge should aim at new Paediatric Use Marketing Authorisations (PUMAs).
FP7-Health-2010-single stage	**[67]**
Pub. Date	2009-07-30
Total Health Budget	333 500 000€
Topic	HEALTH.2010.4.2-1
Title	**Off-patent medicines for children.**
Funding Scheme	Collaborative Project (Small or medium-scale focused research project). EC contribution per project: max. € 6 000 000. One or more proposals can be selected.
Expected Impact	The expected result should be a Paediatric Use Marketing Authorisation (PUMA) application.
FP7-Health-2011-single stage	**[68]**
Pub. Date	2010-07-20
Total Health Budget	160 500 000€
Topic	HEALTH.2011.4.2-1
Title	**Investigator-driven clinical trials on off-patent medicines for children.**
Funding Scheme	Collaborative Project (small or medium scale focused research project). Requested EU contribution per project: Maximum € 6 000 000. One or more proposals can be selected.
Expected Impact	The expected result should lead either in whole or in part to a Paediatric Use Marketing Authorisation (PUMA) application.

Topic "**HEALTH.2011.4.2-1: Investigator-driven clinical trials on off-patent medicines for children**" was part of the most recent call. This time, there is a special focus is on medicines for neonates, for oncology in infants and for the treatment of paediatric epilepsy. It was made clear that outcomes must be relevant for patients and change clinical practice; pilot studies and systematic reviews will not be funded, Good Clinical Practice (GCP) as well as the relevant legislation and guidelines must be considered [69]. Another interesting topic in the field of paediatric medicine that was included in this call is titled "International paediatric initiative" (HEALTH.2010.4.2-2). This initiative aims at enhancing and accelerating the availability of medicines for children in Europe and in the US by integrating research efforts. Up to one proposal can be selected, and the project will be funded with up to € 12 million [63].

3.1.3.2 European Paediatric Research Network (EnprEMA)

Article 44 of the Paediatric Regulation sets out the legal basis for the development of a European network of existing national and European networks, investigators and centers with specific expertise in the performance of studies in the paediatric population (Article 44(1)). Funding is out of scope of this network; it rather aims at coordinating studies relating to paediatric medicines, building up scientific and administrative competences and avoiding unnecessary duplication of studies and testing in the paediatric population (Article 44(2)).

The EMA Management Board adopted the network implementation in January 2008 [70]. About 60 networks that might become a partner in the European Paediatric Research Network of were identified and an according list [71] was published on the EMA website in 2009. So far there have been two workshops (February 2009 and March 2010, respectively) to e.g. discuss recognition criteria for potential member networks and to elaborate structure for the operation of the European Paediatric network.

Membership in this "European Paediatric Research Network at the European Medicines Agency" (EnprEMA) is open to networks that fulfil the requirements laid down in a set of six recognition criteria. By means of a self-assessment, potential EnprEMA partners have to provide evidence of their research experience and their scientific competencies, their organisational structure and quality management processes, their training and education programme and the involvement of patients, parents and their organisations in their work [72]; the respective recognition criteria have been published on the EMA website [73].

The short and long term **goals** of the network encompass [70]:

- ***Collaboration***
  (e.g. to identify, co-ordinate and link together existing networks and ensure communication and exchange of information between networks inside and outside the EU)
- ***Building competences***
  e.g. define scientific and operational quality standards, provide training to network partners, organise and hold scientific meetings to discuss specific topics as identified by the Coordinating Group)
- ***Avoiding unnecessary studies***
  (e.g. avoid duplication of clinical trials in children by sharing information with European as well as international partners)
- ***Stimulating high quality research***
  (e.g. raise awareness on the need for clinical trials for children and increasing understanding of the purpose of research, contribute to GCP compliance)
- ***Strengthening the foundation of the European Research Area***
  (e.g. support development and research into off-patent medicines for children, including contribution to priority list of off-patent medicines)

The operational centre of EnprEMA is a **Coordinating Group** responsible for the long- and short-term strategy of the network. It will be composed of 20 members, representing as many types of networks as possible to take account of different therapeutic areas, age groups or specific activities such as European neonatal network, European paediatric pharmacists or pharmacovigilance. Two members of the PDCO and one member representing the European Commission will complete the group. Membership will last three years. Industry, although an important stakeholder, will not be represented in the group [72, 74].

The tasks of the EnprEMA Coordinating Group, amongst others, will be to facilitate access of pharmaceutical industry to paediatric clinical study centres and experts, to identify new networks, and to develop common educational tools for children and parents to increase their willingness to participate in clinical trials [72]. The Coordinating Group reports to the PDCO on a regular basis. The PDCO will act as the Scientific Committee of the network, and PDCO members are involved in the Coordinating Group to advise on scientific issues and on the future strategy of the network [70].

3.1.3.3 National rewards and incentives

As set out in Article 39(1) of the Paediatric Regulation, Member States (and Community) may provide additional incentives and rewards in order to support and stimulate paediatric drug development.

In accordance with Article 39(3) of the Paediatric Regulation, an inventory of Community and Member State rewards and incentives to support paediatric drug development was published in 2008, listing the measures in the individual Member States as communicated in accordance with Article 39(2) of the Paediatric Regulation [75].

In addition, there was a Report to the European Commission that, in accordance with Article 50(1) of the Paediatric Regulation, specified companies and products that have benefited from any of the rewards and incentives in the Paediatric Regulation. This report was published in on the Commission website in June 2010 and included information on incentives granted by Member States, based on a questionnaire that had been sent to the national competent authorities end of 2009 [64].

According to these documents, additional incentives offered by Member States include e.g.

- **Funding** into paediatric studies, either exclusively intended for paediatric research (e.g. in the Netherlands) or more general funding programmes (e.g. in Hungary, Italy (AIFA), Lithuania, Malta, Czech Republic).

- **Fee reductions or waivers** for paediatric clinical **trials** (e.g. in Portugal).

- **Fee reductions or waivers** for **scientific advice** from national competent authorities (e.g. in Portugal, or in the United Kingdom, where there is a fee waiver for products undergoing paediatric development that is however not applicable for mixed requests).

- **Fee reductions or waivers** for extension applications or marketing authorisations related to paediatric use (e.g. reductions in Slovenia; a fee waiver for products specifically developed for paediatric use in the United Kingdom).

- **Priority review** of applications related to paediatric use (e.g. in Slovenia or Belgium; as a general measure not exclusively applicable for paediatric applications in the United Kingdom)

- Establishing of **paediatric expert groups** (e.g. Austria) or p**aediatric working groups** as part of the national authority (e.g. in Italy).

- **National paediatric networks** (such as the Belgian Paediatric Research Network, the Medicines for Children Network (MCRN) in the Netherlands, the NIHR Medicines for Children Network in the United Kingdom

- Measures related to **reimbursement** of paediatric medicines (e.g. in Romania, where patients under 18 are reimbursed 100 percent of the reference price of medicines, with a full reimbursement for children under one year of age).

Some of the Member States are still in an evaluation phase for potential rewards and incentives for the future.

3.2 Current Situation in the US

3.2.1 US Regulatory Environment for Paediatric Medicines

US paediatric drug legislation began about three decades before the European Paediatric Regulation entered into force: In 1979, FDA issued a **rule on drug labelling** [76] in order to establish a paediatric use subsection in drug labels; this rule did not prove to be very successful as many drug labels continued to lack adequate information regarding paediatric use [77].

Table 5: US Paediatric Legislative Initiatives.

Year	Paediatric Legislation Initiative
1979	Rule on Drug Labeling
1994	Pediatric Rule of 1994
1997	Food and Drug Administration Modernization Act (FDAMA)
1998	Pediatric Rule of 1998
2002	Best Pharmaceuticals for Children Act (BPCA)
2003	Pediatric Research Equity Act (PREA)
2007	Food and Drug Administration Amendments Act (FDAAA)

So in 1994, FDA issued the so-called "**Pediatric Rule**" [78]. This time the extrapolation of adult data was proposed, with additional information such as data on paediatric pharmacokinetics or safety data, in order to support the use in children. So the main focus was on existing data to be reexamined, rather than the conduct of new clinical studies in children. Still, since paediatric labelling did not significantly improve, the effects of the rule were rather disappointing and did not meet expectations.

The **Food and Drug Administration Modernization Act of 1997** (**FDAMA**, [79]) took a different approach offering economic incentives by proposing a concept of paediatric exclusivity: In case the holder of an approved on-patent, non-biological medicinal product conducts clinical studies in children as requested by FDA, an additional 6-month exclusivity on the drug patent will be awarded. Prerequisite is a "**Written Request**" (**WR**) issued by the FDA; a WR outlines the clinical studies that have to be performed to gain the information needed, including details such as paediatric subsets, number of patients to be enrolled and a timeframe for the conduct of the studies. Accepting a WR is voluntary; the MAH may also decline the request. The patent extension that will be granted eventually applies to all medicines with the same active substance the respective MAH holds. It should be noted that the patent extension does not depend on a successful outcome of the studies conducted; as the paediatric exclusivity concept aims to increase paediatric information, it will also be granted in case a study shows e.g. that a given drug is ineffective or not safe in children.

FDAMA 1997 also mandated the publication of an annual list of approved medicines for which additional paediatric information might be beneficial.

One year later, the **Pediatric Rule 1998** [80] followed. While studies under FDAMA 1997 had been voluntary, now pharmaceutical companies were obliged to conduct paediatric studies for new drug applications as well as for already approved drugs should there be a therapeutic benefit for the paediatric population; biological products were no longer exempt. A system of waivers and deferrals as well as the requirement of developing age-appropriate formulations, where necessary, was foreseen. The rule became effective in 1999; however, in October 2002 it was overturned by a federal court as FDA was considered to be acting outside its authority in promulgating it. Congress later gave FDA that authority with the Pediatric Research Equity Act (PREA; [77]).

FDAMA 1997 had been enacted with a sunset provision and thus expired in September 2002. With the **Best Pharmaceuticals for Children Act 2002** (**BPCA**; [81]), the paediatric exclusivity programme was reauthorised for another five years.

While the overall Written Request process remained unchanged, some of the details were amended. For example, a mechanism was created for funding paediatric studies in case the MAH declines the Written Request issued by the FDA. Now these Written Requests could be referred to the **Foundation for the National Institutes of Health (FNIH)**, an independent non-profit organisation whose objective is to facilitate research in medical science [82], for possible funding of studies by grant mechanism [83]. Other provisions of BPCA 2002 were e.g. the establishment of an FDA Office of Pediatric Therapeutics responsible for coordination and facilitation of all activities related to paediatric issues or with a possible impact on paediatrics or the paediatric population, a mandate for the public dissemination of paediatric information, the definition of paediatric age groups to include neonates, and the requirement for a systematic review of adverse events for one years after paediatric exclusivity was granted.

BPCA 2002 was also the first time **off-patent** medicines were addressed, by adding a new section 409I (42 U.S.C. 284m) to the **Public Health Service Act** (**PHSA**). A process for studying off-patent drugs was introduced, and a research fund at the **National Institutes of Health (NIH)**, dedicated to research into off-patent medicines, was established; for the fiscal year 2002, $200 million were allocated [77].

The priority list that had been introduced with FDAMA 1997 was replaced with a list of drugs for which paediatric studies are needed, to be drawn up by NIH as part of the FDA-NIH collaboration BPCA 2002 established.

The **Pediatric Research Equity Act** (**PREA;** [84]]), enacted 2003, basically codifies the Pediatric Rule of 1998. Now FDA was authorised to mandate paediatric studies for new drug applications, new biologicals or for new indications, dosage forms, dosing regimens, or routes of administration for authorised medicinal products. Orphan drugs were exempt. This requirement applies to products where substantial paediatric use is anticipated (with a threshold of 50,000 children treated per year in the labelled indication) and/or if the medicinal product is considered to have a meaningful therapeutic benefit, i.e. to be a significant improvement in therapy for the respective condition, compared to products that are already available and adequately labelled. Deferrals or waivers could be granted, as appropriate [83].

PREA did not contain a sunset provision. As the mandatory “stick” PREA and the voluntary “carrot” BPCA were considered to be complementary approaches towards the same goal, i.e. achieving paediatric labelling, Congress authorized PREA to continue only as long as BPCA was in effect [77].

In addition to e.g. expanding the Prescription Drug User Fee Act (PDUFA) and enacting the Pediatric Medical Device Safety and Improvement Act of 2007, the **Food and Drug Administration Amendments Act of 2007** (**FDAAA,** [85]]), signed into law on 27 Sep 2007, reauthorised both PREA and BPCA. **FDAAA Title IV** continues PREA introducing some changes in order to strengthen the standards for e.g. required tests, labelling, and publicly accessible information [77].

One of the main changes affects both PREA and BPCA: FDAAA 2007 requires the FDA to establish an internal review committee, the **Pediatric Review Committee (PeRC)**. The tasks of PeRC include e.g. a review of all Written Requests before they are issued, of requests for waivers and deferrals as well as of study reports submitted in response to a Written Requests and to provide consultation within FDA as required [86].

Other new provisions include e.g. the establishment of a dispute resolution procedure which would allow the Commissioner, after specified steps, to deem a drug to be misbranded if a manufacturer refused to make a requested labeling change. Applicants who have been granted a deferral are now required to submit an annual deferral review that will be made public, and manufacturers that failed to develop an age-appropriate paediatric formulation have to submit a detailed explanation why the respective formulation cannot be developed. Criteria for applying PREA to products on the market change: PREA 2002 applied to products for which the absence of adequate labelling could be a risk for patients, whereas PREA 2007 employs a benefit instead of a risk approach and applies to products for which adequate labelling could confer a benefit on paediatric patients [77].

BPCA was reauthorised in **FDAAA Title V** with some changes for on- and/or off-patent drugs. An important change affecting the paediatric exclusivity part is the requirement that study reports have to be submitted to the FDA fifteen months before the existing exclusivity of the respective product expires; if this deadline is not met, the market exclusivity extension will not be granted. Along with the study reports, all reports about post marketing adverse events have to be submitted, and the applicant or marketing authorisation holder is required to propose paediatric labelling based on the study results [77].

If a Written Request for a on-patent drug is declined by the holder on whatever grounds, the FDA may decide that the drug nonetheless requires paediatric development. In case the Written Request cannot be referred to FNIH because of insufficient FNIH funds, the FDA may require the marketing authorisation holder to conduct paediatric studies under PREA [77].

The FDA may now ask for nonclinical studies in a Written Request and is also allowed to issue one study request capturing both on- and off-label drug uses. If a written request is declined because the marketing authorisation holder cannot develop an age-appropriate formulation, an explanation must be submitted to FDA. New formulations must be launched within one year of approval or else the name of the applicants will be made public [77].

There is a change of paradigm with regard to the annual list of drugs as it is replaced with a list of priority needs in pediatric therapeutics instead. This list may include drugs or indications and has to be revised every three years.

BPCA 2007 further encourages paediatric development of off-patent drugs. The research programme at the NIH was extended and expanded; the Written Request process is streamlined, now the NIH e.g. does not necessarily have to wait until a Written Request is referred by FDA, but may take the initiative and submit a **Proposed Paediatric Study Request** (**PPSR**), i.e. a kind of draft Written Request outlining the paediatric clinical trials that will be required for a given drug [87] (for a more detailed description of the process see section 3.2.2).

The 2007 provisions were enacted with a period to sunset on Oct 01, 2012 and thus will have to be reauthorised.

3.2.2 Chances for off-patent drugs: The Best Pharmaceuticals for Children Act

In the history of US Paediatric Legislation, the Best Pharmaceuticals for Children Act 2002 was the first initiative explicitly addressing medicines not covered by any kind of patent or marketing exclusivity. Providing a mechanism for studying off-patent drugs BPCA offers a chance for paediatric development of medicines that would otherwise be neglected and thus to improve paediatric labelling of these products.

Especially important in this context is FDA's collaboration with the National Institutes of Health (NIH), namely the **Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD)**, a part of the NIH that was put in charge for the implementation of the respective BPCA provisions. The NICHD, created in 1962, supports and conducts research related to the health of children, adults, families, and populations; it includes four research centers and two research divisions dedicated to research into specific health areas and it supports numerous clinical research networks [88]. Another example for collaboration of NICHD and FDA is e.g. the Newborn Drug Development Initiative (NDDI) that aims at stimulations the development of safe and effective medicines for term and preterm neonates.

NICHD's two main BPCA-related tasks are: to assess paediatric needs and publish a "Priority List of Needs in Pediatric Therapeutics" and to support the studying programme for off-patent drugs.

Paediatric Needs

The first list specifically addressing paediatric needs was mandated through FDAMA 1997. This "**List of Drugs for Which Additional Pediatric Information May Produce Health Benefits**" was compiled and published by FDA in consultation with experts in paediatrics [89]. BPCA 2002 replaced this list with an according document to be drawn up by NIH, in consultation with FDA and experts. Points to be considered when including drugs in the list were: the availability of information concerning the safe and effective paediatric use; the need for additional information; potential benefit for children arising from paediatric studies concerning the product and whether or not another formulation of the drug was necessary. Off-patent drugs were generally eligible for the list; on-patent drugs had to be referred for inclusion. The first "**List of Drugs for Which Pediatric Studies are Needed**" was published in January 2003 [90] and updated at least annually until BPCA was reauthorised in 2007.

With BPCA 2007 the provisions concerning the list were amended; a paradigm shift occurred: Now NIH is required to focus on therapeutic areas; the new points to consider are therapeutic gaps, particular paediatric diseases as well as the adequacy of necessary infrastructure to conduct paediatric research (including paediatric research networks and trained paediatric investigators).

Needs are prioritised in a **three-level approach**:

Level 1: ***Defining boundaries*** of therapeutics and therapeutic needs

Level 2: ***Needs assessment***:
a) Determining gaps in therapeutic areas and/or drugs from epidemiology studies and literature summaries
b) Determining gaps in therapeutic areas and/or drugs through consultation with experts in pediatric research (Global outreach and Therapeutic Area Expert Panels (BPCA-related working groups))
c) Determining labeling/study design gaps through FDA consultation

Level 3: ***Prioritisation***
a) Determining Priority Areas (priority categories: Affected Patient Population, Unmet Needs, and Scientific Importance)
b) Plan for prioritising interventions within therapeutics areas (evidence, impact, and feasibility Scores)
c) Final prioritisation

The final prioritisation is done by the Prioritization Steering Committee that will review the statements of the therapeutic area working groups, determine final priorities and is responsible for the dissemination of information on studies under the BPCA for public knowledge [91].

The first "**Best Pharmaceuticals for Children Act (BPCA) Priority List of Needs in Pediatric Therapeutics**" was published in the Federal Register in April 2009 [92]. Like the List of Drugs before, this priority list is the basis for the off-patent drug development programme.

Written Request Process for Off-Patent Drugs

The mechanism for studying off-patent drugs that the Best Pharmaceuticals for Children Act of 2002 introduced is laid down in Title IV, Part B, Section 409I of the Public Health Service Act (PHSA); the PHSA also contains provisions regarding the funding of the respective studies [93]. The whole procedure is coordinated by the FDA and the NICHD at the NIH; as amended by FDAAA 2007, the current process is as follows (Fig. 2):

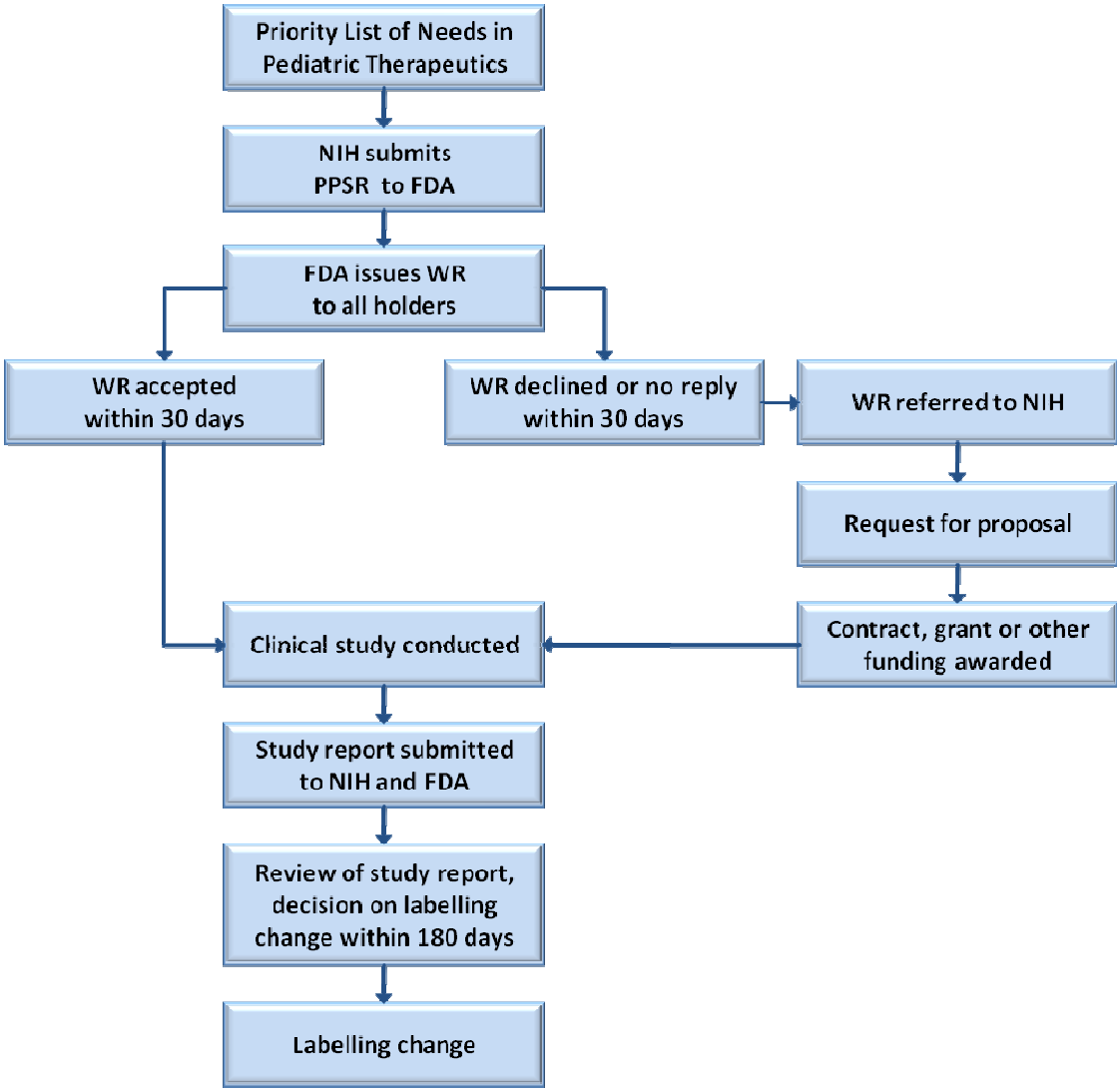


Fig. 2: Workflow for the Evaluation of Off-patent Drugs.

NIH: National Institutes of Health; PPSR: Proposed Pediatric Study Request; FDA: Federal Drug Administration; WR: Written Request.

In order to initiate the process, the NIH shall submit a **Proposed Pediatric Study Request** (**PPSR**) to FDA suggesting paediatric studies of an indication that is on the Priority List of Needs. A drug substance may be considered provided there is

- an approved generic (or an according marketing authorisation application),
- no patent protection or market exclusivity protection for at least one form of the drug, and
- a need for additional studies to assess the safety and efficacy of the drug in children.

A PPSR is a kind of draft Written Request outlining the clinical studies that will be required to obtain the information required to improve paediatric labelling of the drug in question [94] and allow for appropriate use in paediatric subsets [95].

Based on this PPSR, the FDA (in consultation with NIH) may issue a **Written Request** to all holders of an approved application for the drug (i.e. to originators as well as to holders of generics). The holders have 30 days to respond and either accept or decline; if none of the holders accepts the Written Request within 30 days or if there is no reply at all, the Written Request is referred to NIH.

The NIH will then develop and publish a **Request for Proposals** (**RFP**) to conduct the paediatric studies requested. The solicitation is published in Federal Business Opportunities [96] with a 30- to 90-day timeline [97]; marketing authorisation holders that have already been approached in the WR step are not allowed to respond. Resultant proposals are reviewed and then a contract, grant or another appropriate funding will be awarded to a selected recipient.

The clinical studies are then conducted as requested; upon completion, the **study report** has to be submitted to NIH and FDA. During the 180-day period after the submission of the study report, the FDA reviews the data and negotiates labelling changes with marketing authorisation holders of the studies drug, as appropriate. Study report and requested labelling changes are made public.

If the marketing authorisation holders do not agree to the labelling changes, there will be a referral procedure involving the Pediatric Advisory Committee (PAC); if after the procedure the holders still do not amend the labels as then requested, the drug may be deemed to be misbranded.

4 Where are we today?

The regulatory instruments described above aim at improving paediatric labelling and increasing the number of medicinal products appropriately studied for paediatric use. All of them have been in force for several years; now the question – and the focus of the second part of this thesis – is: What has been achieved so far? Have the efforts helped to expand the paediatric therapeutic armamentarium significantly or is there still room for improvement?

The following analyses are based on data obtained by a comprehensive search of information and documents publicly available on the following websites:

- ClinicalTrials.gov (http://clinicaltrials.gov);
- Community Research and Development Information Service, CORDIS (http://cordis.europa.eu);
- European Medicines Agency, EMA (http://www.ema.europa.eu);
- The Federal Register (http://www.gpoaccess.gov/fr/);
- Heads of Medicines Agencies, HMA (www.hma.eu);
- National Institute of Child Health & Human Development – Best Pharmaceuticals for Children Act (http://bpca.nichd.nih.gov);
- U.S. Food and Drug Administration, FDA (http://www.fda.gov).

Where required, current and obsolete German SmPCs were obtained from the publicly accessible part of AMIS database, ("Arzneimittelinformationssystem", via http://www.dimdi.de).

Cut-off date, unless otherwise indicated: 15 August 2010.

4.1 Achievements in the EU

4.1.1 Initial experiences with the Paediatric Use Marketing Authorisation

PIP applications for Paediatric Use Marketing Authorisations

The Paediatric Regulation mandates that applications for new marketing authorisations (Article 7), for new indications forms or routes of administration for already authorised on-patent medicines (Article 8) as well as applications for Paediatric Use Marketing Authorisations (Article 30) include paediatric data compliant with a Paediatric Investigation Plan (PIP) that had been agreed with the Paediatric Committee (PDCO)

This applies for all medicines except those exempt on grounds of Article 9 of the Paediatric Regulation or in cases where a waiver or deferral had been granted.

By PDCO's monthly meeting in August 2007, the first request related to a PIP for a PUMA had already been received [98].

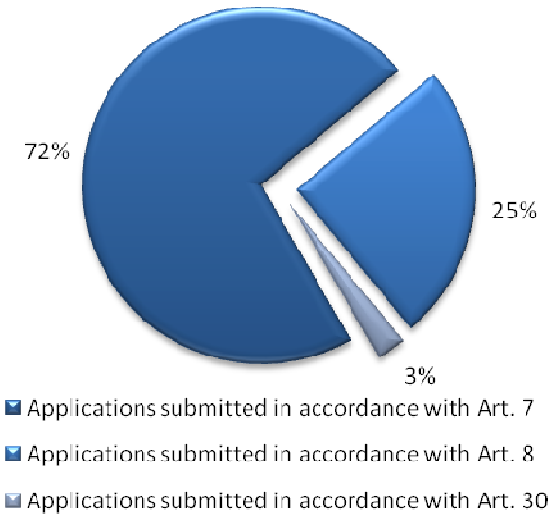
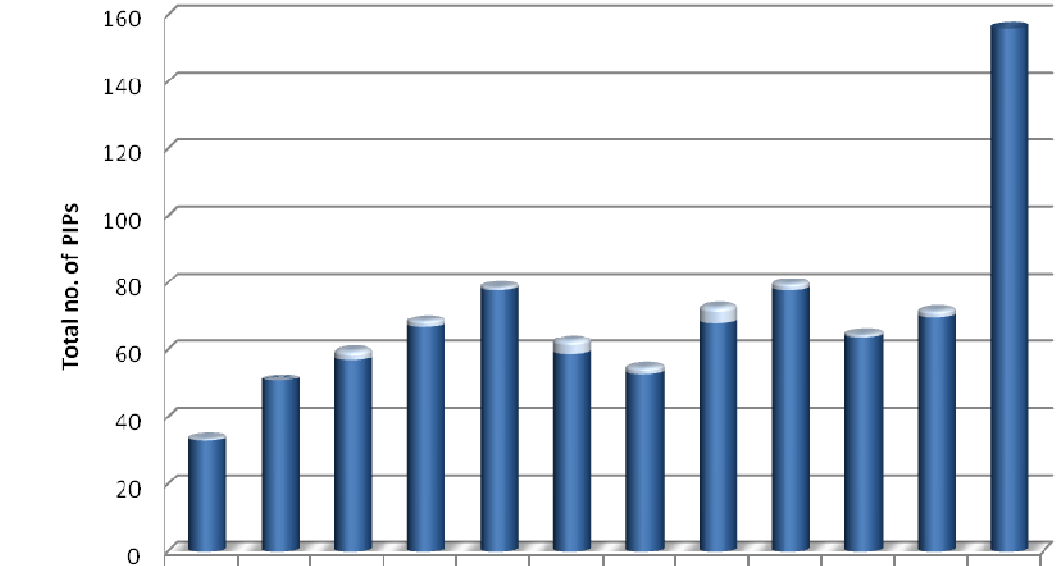


Fig. 3: Percentage of PIP-applications per article.

As of August 2010, only 3% of all PIP requests were related to intended PUMA applications. Information derived from PDCO meeting highlights August 2010 [99].

As of August 2010, as indicated in PDCO's meeting highlights from the August 2010 meeting, there have been 23 PIP requests in accordance with Article 30 altogether [99], equalling 3% of the total number of PIP or waiver requests received during these three years (Fig. 3).

The next step was an evaluation of the number of PIP submissions to PDCO per time span, in order to find out if there is a trend such as constantly increasing numbers of PIP requests for PUMAs over the time. For this purpose, the statistics parts of all PDCO meeting highlights issued so far were consulted; based on the cumulative numbers of applications given in each of these documents, the number of applications per quarter was calculated (Fig. 4).



	Q3 2007	Q4 2007	Q1 2008	Q2 2008	Q3 2008	Q4 2008	Q1 2009	Q2 2009	Q3 2009	Q4 2009	Q1 2010	Q2 2010
PIPs (Art. 30)	1	0	3	2	1	4	2	5	2	1	2	0
PIPs (Art. 7/8)	33	51	57	67	78	59	53	68	78	64	70	156

Fig. 4: Number of PIP/waiver requests submitted per quarter, stratified by applications in accordance with Articles 7 or 8 and Article 30, respectively.

Based on information indicated in PDCOs monthly meeting highlights, the numbers of PIP applications per quarter were calculated. A trend towards increasing numbers or shares of PIP applications for PUMAs did not emerge.
Note: Quarters are based on PDCO meeting dates, e.g. Q4/2008 would mean the time span between the September 2008 and the December 2008 meeting. For months with two meeting, e.g. April 2009, the second meeting in the respective month was considered**.**

Looking at the result, a trend towards increasing numbers of PIP requests related to PUMAs over time could not be identified; numbers peaked in Q2/2009 when five applications were received but by and large numbers remained constant; e.g. in 2008 and 2009, ten requests were submitted each. It however seems notable that in Q2/2010, the total number of submitted PIP requests more than doubled as compared to previous quarters, but there was not a single application for a PIP related to a PUMA.

There is no evidence that a PUMA has yet been authorised; end of 2009, it was published that until then no companies had benefited from the marketing protection periods granted by PUMA (either centrally authorised or in any of the Member States) [64] and as of July 2010, no marketing authorisation procedure for a PUMA has been started at the EMA [100].

Analysis of ongoing FP7 Projects that might lead to PUMA applications

Article 40 of the Paediatric Regulation provides for funding of research into paediatric development of off-patent drugs through EU Framework Programmes, namely FP7. These projects are expected to lead to a PUMA application for the drugs and indications studied, provided the drugs prove to be adequately safe and effective for paediatric use.

So far there have been four calls under FP7 relating to paediatric development of off-patent drugs. As of August 2010 there are projects funded from the 2007 and 2009 calls; projects to be funded that were proposed after the 2010 call are still under evaluation, and the latest call is still open for the submission of research proposals.

Each research proposal is carefully evaluated before funding is granted. For the 2007 call, 15 proposals were received, six of them were supported; the 2009 call was answered with 12 proposals of which 3 succeeded. So at present there are nine research projects ongoing (see Table 6).

Table 6: Proposals related to paediatric development of off-patent drugs (2007 and 2009 calls) [101]

List of conducted calls: Total number of conducted calls (selection process completed)					
Call	**Call identifier**	**Number of submitted proposals**	**Number of supported proposals**	**EU contribution [€]**	**Call Specific Success**
2nd	FP7-HEALTH-2007-4.2-1	15	6	22 000 000	40%
3rd	FP7-HEALTH-2009-4.2-1	12	3	18 000 000	25%

To identify these research projects, the drugs, indications and paediatric subsets under study, the website of the Community Research and Development Information Service (**CORDIS**) was consulted. Details regarding the individual projects including research objectives are provided in Annex 1.

Active substances and paediatric subsets studied in these projects as well as information related to the development of new, age-appropriate formulations was compiled (Table 7):

Table 7: Active substances and paediatric subsets studied in FP7 projects.

Active substance	Project	Paediatric Age Group	New Formulation
6-Mercaptopurine	LOULLA & PHILLA	not specified	Yes (oral liquid)
Budesonide	NEUROSIS	very preterm neonates (born between 23 and 27 weeks gestational age)	No
Bumetanide	NEMO	neonates	Yes
Ciprofloxacine	TINN	preterm and term neonates	Yes
Cyclophosphamide	03K	infants, young children	Yes (oral liquid)
Doxorubicin	EPOC	Children < 3 years	No
Fentanyl	NEOOPIOID	very preterm and term neonates	Yes
Fluconazole	TINN	preterm and term neonates	Yes
Meropenem	NEOMERO	neonates and infants aged < 3 months	No
Methotrexate	LOULLA & PHILLA	not specified	Yes (oral liquid)
Morphine	NEOOPIOID	very preterm and term neonates	Yes
Risperidone	PERS	children and adolescents	No
Temozolomide	03K	infants, young children	Yes (oral liquid)

In nine projects, a total of 13 off-patent active substances are studied; the vast majority either belongs to the field of paediatric oncology or is intended to treat an infection (Fig. 5).

Regarding **paediatric age groups**, most projects focus on very young paediatric populations, i.e. very preterm, preterm or term neonates; only the risperidone study involves children and adolescents. This however corresponds with paediatric needs as described in the needs lists that had to be considered when designing a project to be funded under FP7.

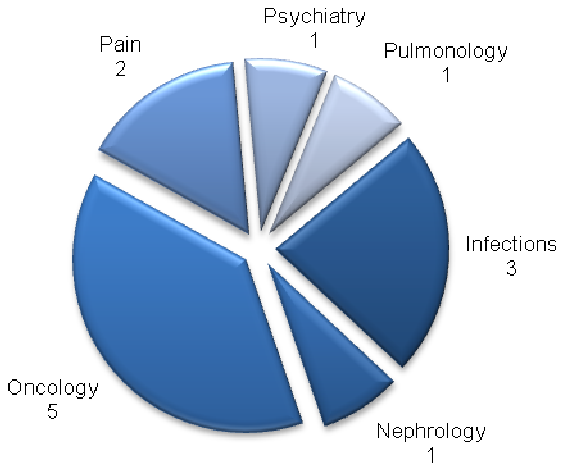


Fig. 5 Off-patent substances studied under FP7 by Therapeutic Area

Most of the drugs studied are intended for the treatment of paediatric cancer or infectious diseases.
Assigment of therapeutic area is based on WHO ATC codes (second level) and indication under study, if necessary.

In order to achieve a PUMA, it is necessary to develop an age-appropriate **formulation** if the formulations that are already available do not suit paediatric needs. For most of the drugs substances under evaluation, a new formulation is being developed; this will be an oral liquid for those substances where the nature of the new formulation has already been described.

4.1.2 Results of EU Paediatric Worksharing

According to Article 45(1) of the Paediatric Regulation, MAHs were obliged to send all available paediatric studies that had been completed before 26 Jan 2007 to their competent authority for assessment. MAH-sponsored studies involving an authorised medicinal product not completed by then have to be submitted within six months of completion (Article 46(1)). The assessment is organised as a worksharing, i.e. for each substance there is a rapporteur that will take care of the assessment on behalf of the other Member States.

Depending on the outcome of the assessment the competent authority may then decide on an update of SmPC and PIL and a variation of the respective marketing authorisation, as applicable. This approach aims at improving paediatric information in SmPC and PIL. The provisions basically apply to both on- and off-patent drugs, but especially for the latter the Paediatric Worksharing might be a valuable instrument that allows to increase the safety of paediatric use of older drugs and it is even thinkable that for some of the substances used off-label before, a paediatric indication might be added, based on the data received from MAHs.

Paediatric Worksharing according to Article 45

The „List of active substances for which data has been submitted in accordance with Article 45" specifies almost 1000 submissions for chemical active substances (including combinations), around 460 for what may be best described as natural product, as this group subsumes e.g. herbal preparations and homeopathics, almost 200 vaccines and about 75 radiopharmaceuticals [102]. Even if there may be some repetition regarding active substances on said list, these submissions add up to a huge amount of data that needs to be assessed.

In August 2010, most of these substances are still waiting to be actually included in a worksharing procedure as in the first eight waves only included 147 active substances (or combinations thereof) [103]. As of 15 Aug 2010, 31 procedures have been finalised and the respective public paediatric assessment reports have been published on the CMDh website (Fig. 6):

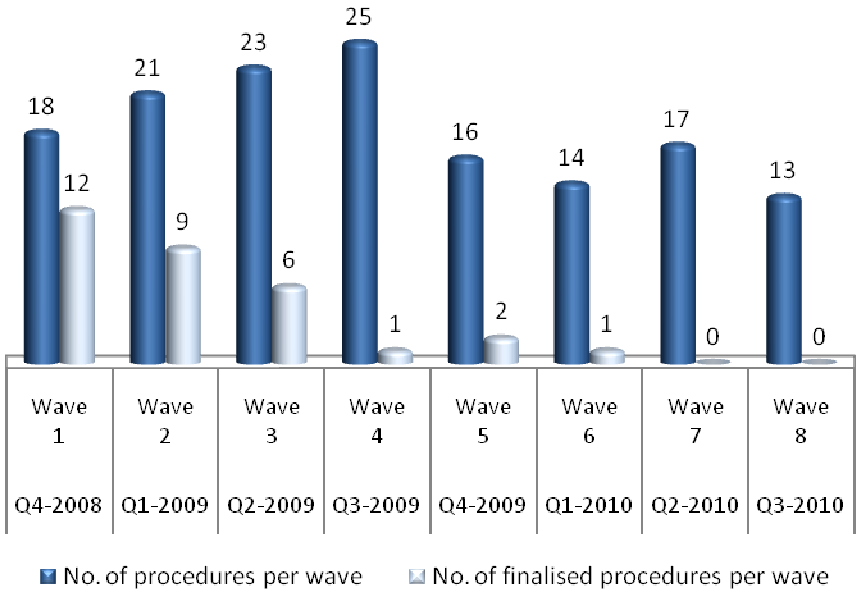


Fig. 6: Number of worksharing procedures started and finalised as of Aug. 2010, per wave.
The total number of active substances (including combinations) for which a work sharing procedure has been started before August 2010 adds up to 147; as of 15 August 2010, PdARs for 31 active substances had been published.

Except for Cyprus and Finland, all Member States have assumed rapporteurship in one or more procedures so far. However, workload is not spread evenly over Member States; the United Kingdom (UK, 22 procedures), Germany (DE, 19 procedures), and the Netherlands (NL, 15 procedures) are clearly above average here (Fig. 7).

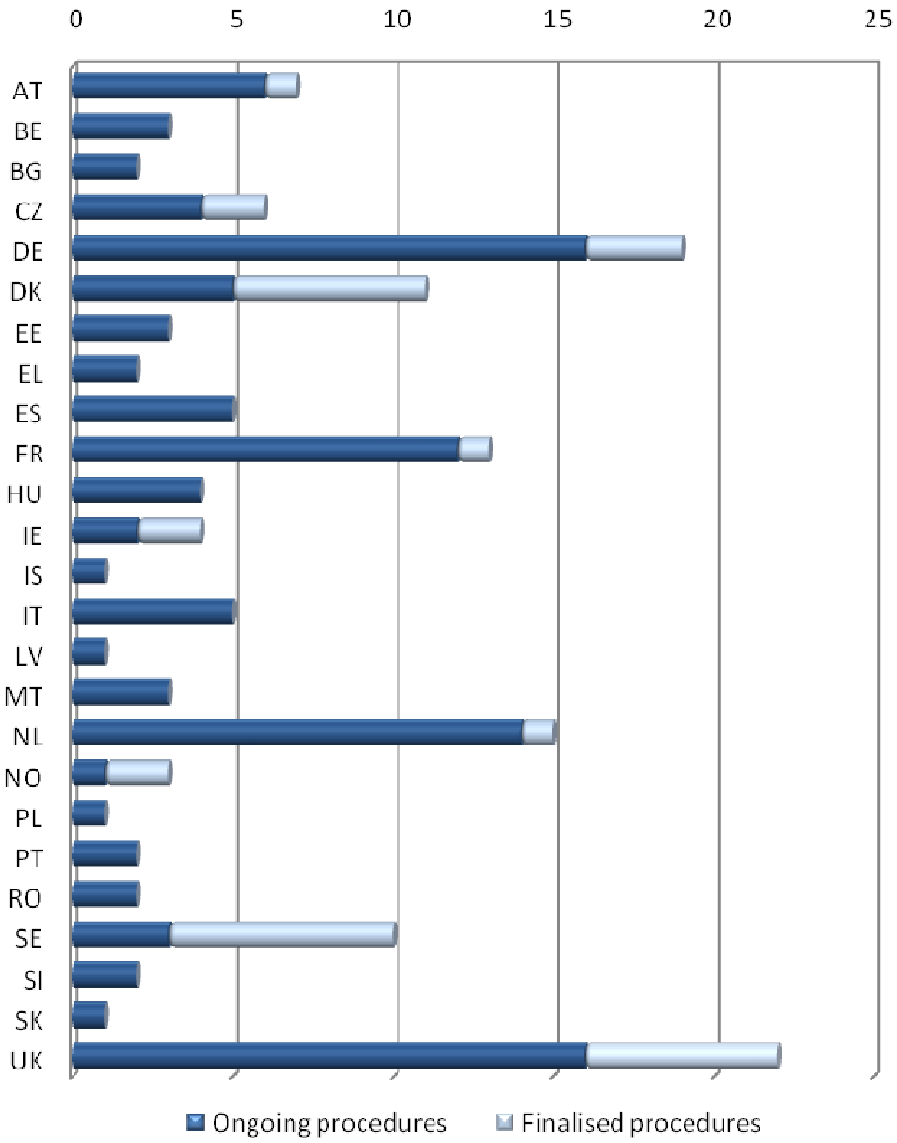


Fig. 7: Number of worksharing procedures started and finalised as of Aug. 2010, per Member State.
Only Cyprus and Finland have not assumed rapporteurship for a paediatric worksharing procedure so far. (Country codes according to EU Interinstitutional Style Guide [104].)

As the focus of this thesis is on off-patent drugs, the next step was to evaluate how many of the drugs already assessed are actually off-patent. For the purpose of this evaluation, active substances for which generic products could be identified, for example by checking German AMIS database [105] or that have been registered in the EU for about twenty years or more (keeping in mind the maximum term of European patents) were considered to be off-patent.

Using this approach, less than a tenth of the 147 substances included in the procedure so far could not be classified as off-patent; of the 31 procedures that have already been finalised, only one substance fell in the patented category.

According to the flow-chart detailed in the Best Practice Guide (see 3.1.2.2) an assessment procedure will normally be finalised by Day 120. In some cases, when there is no request for supplementary information and no need for a clock stop, it may even be completed as early as Day 90. However, the actual **time** it takes until a procedure is finalised depends e.g. on the length of the clock stop period required and is highly variable. Based on the data indicated in the public paediatric assessment reports of the off-patent drugs already assessed, it was calculated how long the individual procedures lasted, it became obvious that but however, about half of the procedures (14/27) for which both start and finalisation date were given in the assessment report, took 9.5 months or longer (Fig. 8).

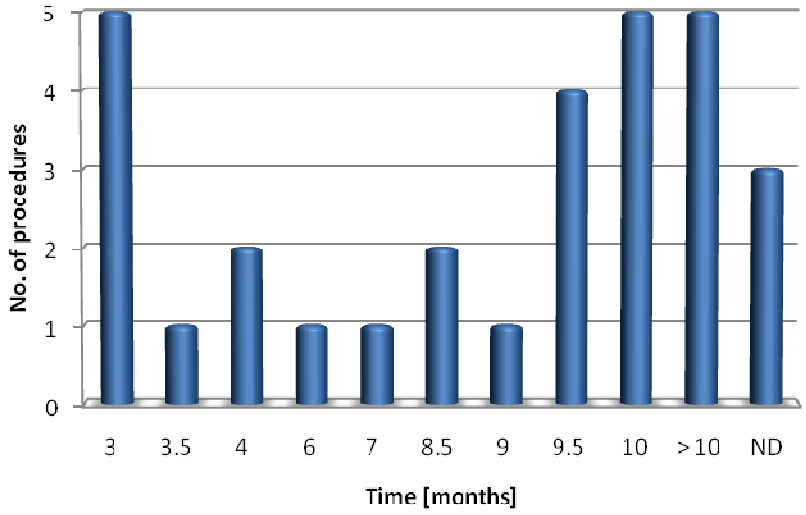


Fig. 8: Time from start of worksharing procedure to finalisation.
Values are derived from information given in PdARs and rounded to half months.
ND: not documented; PdARs do not specify start dates.

Based on ATC codes (second levels, according to WHO ATC index [106]), the off-patent substances already assessed belong to twelve different **therapeutic areas**, with a focus on cardiovascular drugs (20%) (Fig. 9):

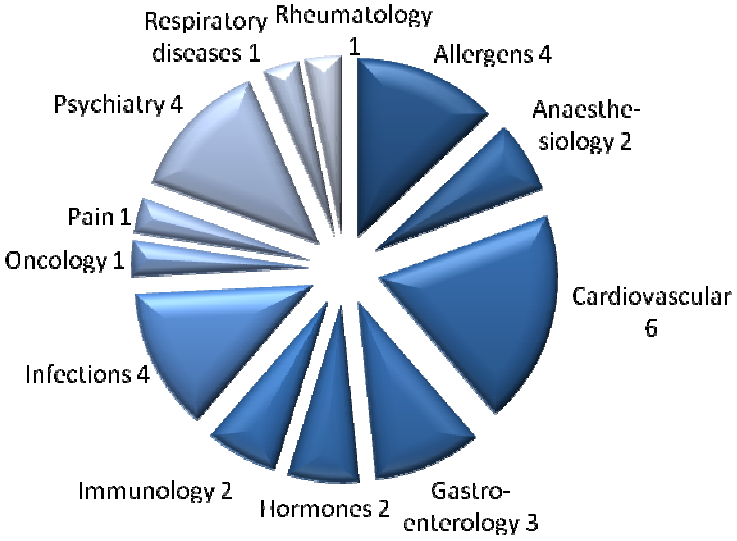


Fig. 9: Finalised worksharing procedures by Therapeutic Area.
Note: Fentanyl was allocated to both “Pain” (N01) and “Anaesthesiology” (N02) as the respective PdAR refers to both transdermal patches used for pain management and Fentanyl injection used in anesthesiology [107].)

Outcomes of the worksharing assessment of off-patent drugs under Article 45

EU Paediatric Worksharing provisions apply to medicines with and without existing paediatric indications in the label, i.e. it basically is not relevant whether children are mentioned in section 4.1 or dosing recommendations are provided in section 4.2 of the SmPC or not.

All available information in respect of the paediatric population is assessed; subsequent regulatory action depends on the outcome of the assessment, and the rapporteur's recommendation may range from "no regulatory action required" to an extensive SmPC revision (see Table 8):

Table 8: Possible outcomes of EU Paediatric Worksharing assessment and resulting recommendations for SmPC amendment [108].

Medicinal Products with existing Paediatric Indication	
Outcome of Worksharing Assessment	**Recommendations for SmPC**
No new safety or efficacy information	No change or recommendation to revise SmPC in line with SmPC guidance
New efficacy information not leading to a change in indication or dose recommendations for children	Amendment of section 5.1 (additional study information)
New efficacy information leading to a change in indication or dose recommendations for children	Amendment of sections 4.1 indication, 4.2 dosing, and 5.1 (corresponding information from clinical studies).
New safety information not affecting risk-benefit-ratio	Amendment of sections 4.3 to 4.9, as appropriate
New safety information which affects risk-benefit-ratio	Amendment of sections 4.1 to 4.9, as appropriate
Medicinal Products without existing Paediatric Indication	
Outcome of Worksharing Procedure	**Recommendations for SmPC**
Efficacy information insufficient No adverse safety information	Amendment of sections 4.2 (recommendation not to use in children) and 5.1 (corresponding study information).
Efficacy information shows lack of therapeutic benefit Adverse safety information	Amendment of sections 4.2 (recommendation not to use in children) and 5.1 (corresponding study information); additional contraindications or warnings in sections 4.3 and 4.4, as appropriate.
New efficacy information regarding leading to updated indication and dose recommendations for children	Amendment of sections 4.1 indication, 4.2 dosing, and 5.1 (corresponding information from clinical studies).

In order to assess the impact of the worksharing assessment on SmPC wording, the published PdARs were analysed. As previously stated, there have been PdARs for 30 off-patent drug substances so far. For the purpose of the following analysis, however, each of the three fentanyl formulations, i.e. injection, patches, and lozenges, had to be counted separately, as these formulations differed in terms of paediatric use from the beginning, and the PdAR gave different recommendations for each of them [107].

For nine of the then 32 medicinal products (28%), no regulatory action was deemed necessary by the rapporteur. For the remaining products, a total of 57 changes was recommended; for most of them, this included the posology section 4.2. Amendments of the sections related to pharmacokinetics (5.1), pharmacodynamics (5.2), and warnings and precautions (4.4) were also more common than others (Fig. 10).

It should however be noted that, although the worksharing procedure is not primarily intended to harmonise labels in the Member States, the rapporteur's quite often took the opportunity to recommend harmonised wording, e.g. there are some products for which changes to the posology section are recommended, but these amendments do not introduce new dosing information but rather propose a harmonisation of the existing wording.

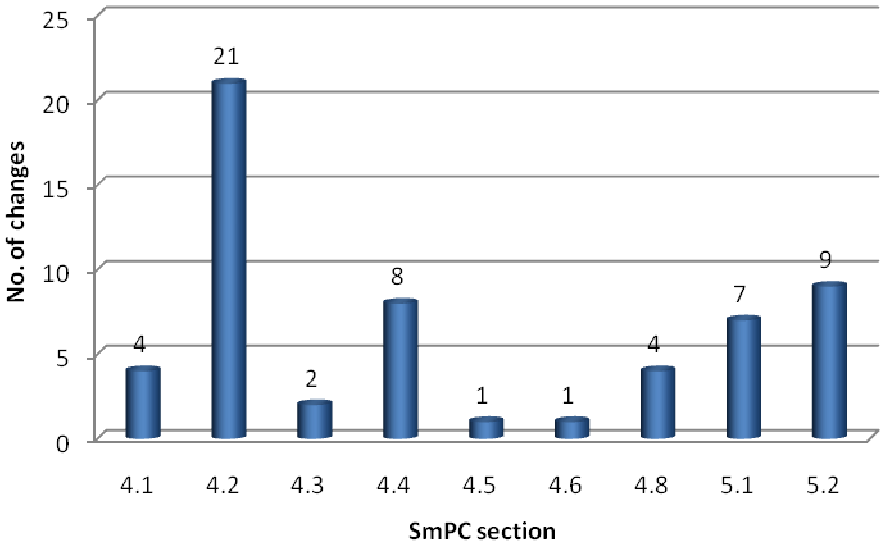


Fig. 10: Total number of SmPC changes for off-patent drugs as recommended in PdAR, stratified by SmPC section.

SmPC changes were recommended for 23 medicinal products (please note that fentanyl injection, patches, and lozenges were counted as separate products as the PdAR made specific change recommendations for each of them); the section amended most frequently was the dosing section, 4.2.

Full title of SmPC sections: 4.1 Therapeutic indications; 4.2 Posology and method of administration, 4.3 Contraindications; 4.4 Special warnings and precautions for use; 4.5 Interaction with other medicinal products and other forms of interaction; 4.6 Fertility, pregnancy and lactation; 4.8 Undesirable effects; 5.1 Pharmacodynamic properties; 5.2 Pharmacokinetic properties. For SmPC sections not included, there were no change recommendations.

The following step focused on the existence of paediatric indications in the label of a given medicine before and after the worksharing assessment.

Not for all medicinal products SmPCs, indications, and dosing recommendations are necessarily harmonised throughout Europe, which is particularly true for older off-patents that have been used for many years. Therefore, where required, the German SmPC as available in the public part of the AMIS database [105], was used as a basis for the before-after comparison.

This analysis revealed that “before”, 21 out of 32 medicinal products (66%) had a paediatric indication, i.e. paediatric dosing recommendations for one or more paediatric subsets were given in the posology section of the respective SmPC while eleven had not. This number actually rose to 25 after the respective worksharing procedures, i.e. four products previously not recommended for use in paediatric patients (mostly on the grounds that safety and efficacy had not been established in children) actually obtained a paediatric indication (Fig. 11).

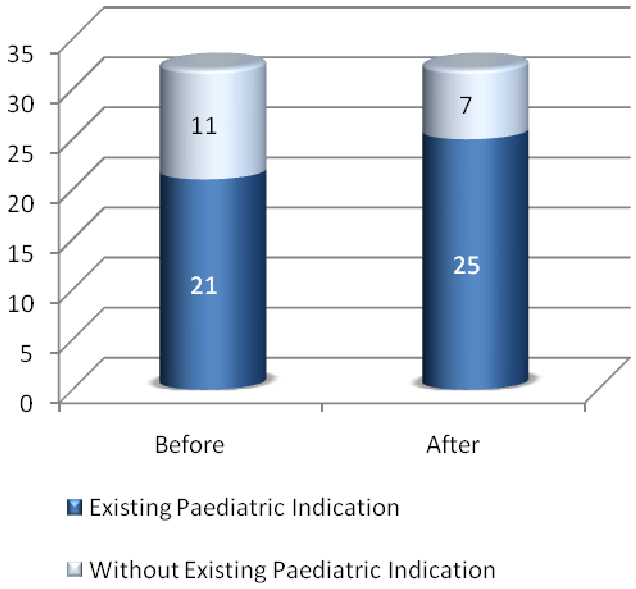


Fig. 11: Number of Medicines with and without Paediatric Indication before and after Worksharing.

The number of medicinal products with a paediatric indication rose from 21 before to 25 after the respective worksharing procedures (please note that fentanyl injection, patches, and lozenges were counted as separate products as the PdAR made specific change recommendations for each of them).

The medicines that obtained a new paediatric indication were mostly cardiovascular drugs, two of them intended to treat hypertension (Table 9). Three of these drugs were to be found on the respective list of paediatric needs for either cardiovascular products [109] or pain [41]; yet the respective paediatric needs described is these documents are not fully met, as e.g. amlodipine is not indicated for all age groups but for children aged six years and above, and similarly the fentanyl product, although available in an oromucosal formulation, is only indicated for a rather small subset instead of all age groups, as the fentanyl lozenges were considered suitable for adolescents 16 years of age and above only.

Table 9: Medicines with new Paediatric Indication after Worksharing

Active Substance	Therapeutic Area	Indication	Age Group
Amlodipine	Cardiovascular	hypertension	6 to 17 years
Fentanyl (lozenges)	Pain	breakthrough pain in patients already receiving maintenance opioid therapy for chronic cancer pain	16 years and above
Lisinopril	Cardiovascular	hypertension	6 to 16 years
Simvastatin	Cardiovascular	heterozygous familial hypercholesterolaemia	10 to 17 years

Paediatric Worksharing according to Article 46

End of 2009, submissions under Article 46 had been received for 70 medicinal products authorised via MRP, DCP or purely national procedures [64]; as of 15 August 2010, PdARs for a total of six active substances, four of them off-patent, had been finalised and published on the CMDh website [53].

Of the four off-patent drugs in the Article 46 group, two belong to the therapeutic area of gastroenterology, one to immunology and one is an antiviral drug. Data for these products was assessed under the rapporteurship of Ireland (one procedure, taking four months), the United Kingdom (one procedure, taking 6.5 months) and Germany (two procedures, taking 10 and 13 months, respectively).

The outcome of the assessments was as follows: Two medicines had a paediatric indication before. For one of them, no regulatory action was required; for the second one, SmPC amendments affecting sections 4.4 Warnings and precautions, 4.5 Interactions, and 4.8 Undesirable effects were recommended. For one of the two medicines without paediatric indication, an amendment of section 4.2 Posology was recommended in order to make clear that there is a non-recommendation for the paediatric use of this drug.

The last of the substances, famciclovir, is also subject to an ongoing worksharing procedure under Article 45; therefore there is no final decision or a final wording recommendation for the SmPC yet and the outcome of the Article 45 assessment will have to be awaited.

Paediatric Worksharing for centrally authorised medicinal products

Both Article 45 and Article 46 of the Paediatric Regulation apply to all authorised medicinal products, regardless of the authorisation procedure; centrally authorised products are not exempt.

The EMA had been provided with data on approximately 60 centrally authorised products under Article 45; as of end of 2009, SmPC updates had been required for four of them [64]. Article 46 submissions for 24 centrally authorised products lead to SmPC updates for only two of them [64]. As, based on lacking generic competition, none of the substances was classified off-patent, they were out of scope and hence not considered for this evaluation.

4.2 Achievements in the US

As described in chapter 3.2.2, in the US studying paediatric indications of off-patent priority list drugs is triggered by a Written Request issued by the FDA; under BPCA 2007, this step is preceded by an NIH-issued PPSR.

The first step in the evaluation of achievements of the off-patent drug research programme and the current status of the projects was to find out about the actual number of Written Requests issued so far for off-patent drugs:

As published on the FDA website, there have been Written Requests for a total of 19 off-patent priority list drugs so far [110]. As expected, they had all been on the Priority List of Drugs; in fact, about half of these drugs had already been on the first “List of Drugs for Which Pediatric Studies are Needed” published in 2003 [111] (Fig. 12).

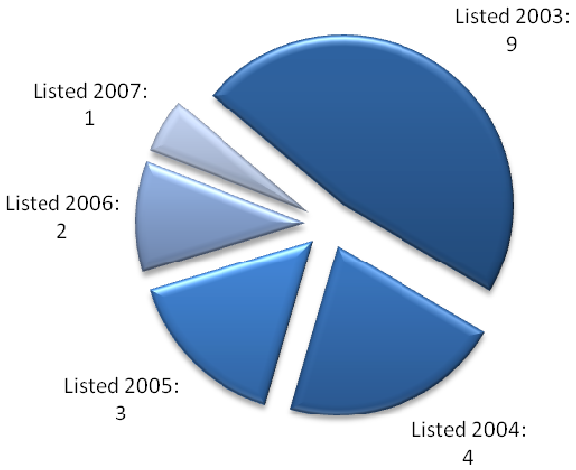


Fig. 12: Year of Inclusion in Priority List of Drugs.

The mere number of drugs does not necessarily equal the number of Written Requests as in case there is more than one indication a given drug substance needs to be studied for, FDA will issue individual Written Requests for each indication.

As a consequence, for three of these 19 substances actually two Written Requests each could be retrieved, namely for azithromycin, lorazepam, rifampin; thus the total number of Written Requests adds up to 22.

Initially Written Requests are issued to all holders of an approved application of the drug who are free to accept or decline the request. However, only one of the Written Requests issued for an off-patent drug was actually accepted by a marketing authorisation holder: **Lindane**, intended for second line treatment of scabies [112]. All Written Requests related to the remaining 18 substances were declined by industry and, as a consequence, had to be referred to NIH for further consideration.

In a following step the ranges of indications and therapeutic areas covered by the remaining 21 Written Requests were determined. The finding: They belong to a total of nine different therapeutic areas, with a focus on medicines intended for the treatment of infectious diseases (6 WRs, i.e. 29%) and paediatric cancer (5 WRs; i.e. 24%) (Fig. 13):

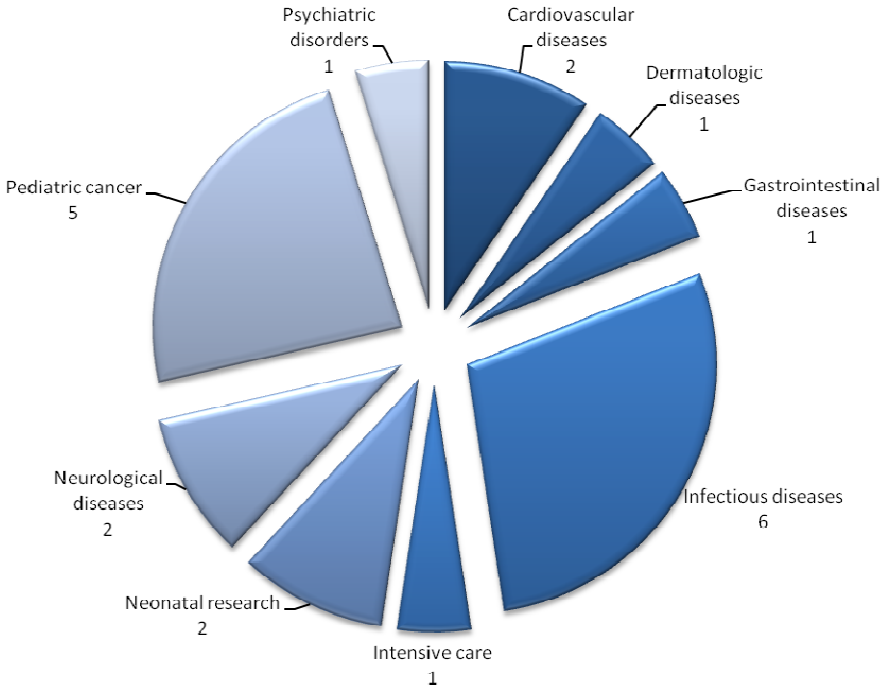


Fig. 13: Number of Written Requests issued for Off-patent drugs, by Therapeutic Area.

Written requests were issued for drugs coming from nine different therapeutic areas, with a focus on anti-infectives and cancer medicines.
Classification based on indication and current "Priority List of Needs in Paediatric Therapeutics" as published on the BPCA website [113].

The usual course of action after a Written Request has been referred includes a Request for Proposals leading to a cooperation with a third-party investigator who will conduct the studies whose findings will finally result in a labelling change.

Starting point for an analysis of the current status of individual programmes and WR-triggered clinical studies was the "Priority List of Needs in Paediatric Therapeutics" published on the BPCA website [113], current as of 01 Sep 2009, that indicates plans and progress for each drug and priority, respectively. Further to that, the information below is based on the details about grants, contracts, and interagency agreements for studies given on the BPCA website [114] and on trial-related information as provided in the ClinicalTrials.gov register [115].

The results of this inquiry are summarised below (Fig. 14; Table 10; for a more detailed table including status on clinical trials as last retrieved, if applicable, please refer to Annex 2).

As already stated, one of a total of 22 Written Requests was accepted by the marketing authorisation holder; however no progress in terms of clinical trials or labelling changes could be detected. Two Written Requests were issued, but later on the projects were not pursued any longer. This applies to **rifampin** for the "treatment of methacillin-resistant S. aureus endocarditis", as in the BPCA Scientific Prioritization Meeting 2008 there was a recommendation to remove rifampin from the list for this indication [116]; as a result, rifampin is not included in current Priority List of Therapeutic Needs as published on BPCA website any more [113]. One of the **azithromycin** projects, intended to study the use of azithromycin to treat chlamydia trachomatis infections, was cancelled due to feasibility issues related to the conduct of the studies and lack of response to Request for Proposals [117].

One of the caveats in the off-patent studying mechanism is a possible change in exclusivity status, i.e. a drug that was off-patent may become a on-patent drug again. This was the case for two substances that were off-patent when the respective Written Requests were issued, but turned on-patent later: **hydrocortisone valerate** and **metoclopramide**. Thus these requests were, after being declined by the marketing authorisation holders, referred to the Foundation of the NIH (FNIH), as foreseen for on-patent drugs.

For four of the Written Requests referred to NIH, no information about ongoing clinical trials or the like could be retrieved; in these cases the most recent information says that NIH received a Written Request from the FDA and (pre-) clinical studies are being considered or developed. For 13 Written Requests (about 60%), information about clinical trials, either ongoing or already completed, was available. For some programmes, e.g. the one related to lithium, one clinical study has already been completed. As however a study programme based on a Written Request may consist of several studies, in all of these cases results from at least one more study are required and thus even for these drugs a labelling change is not likely to happen in the near future; for example in some cases, pharmacokinetic study has been completed while efficacy studies have not yet begun or are just on the way.

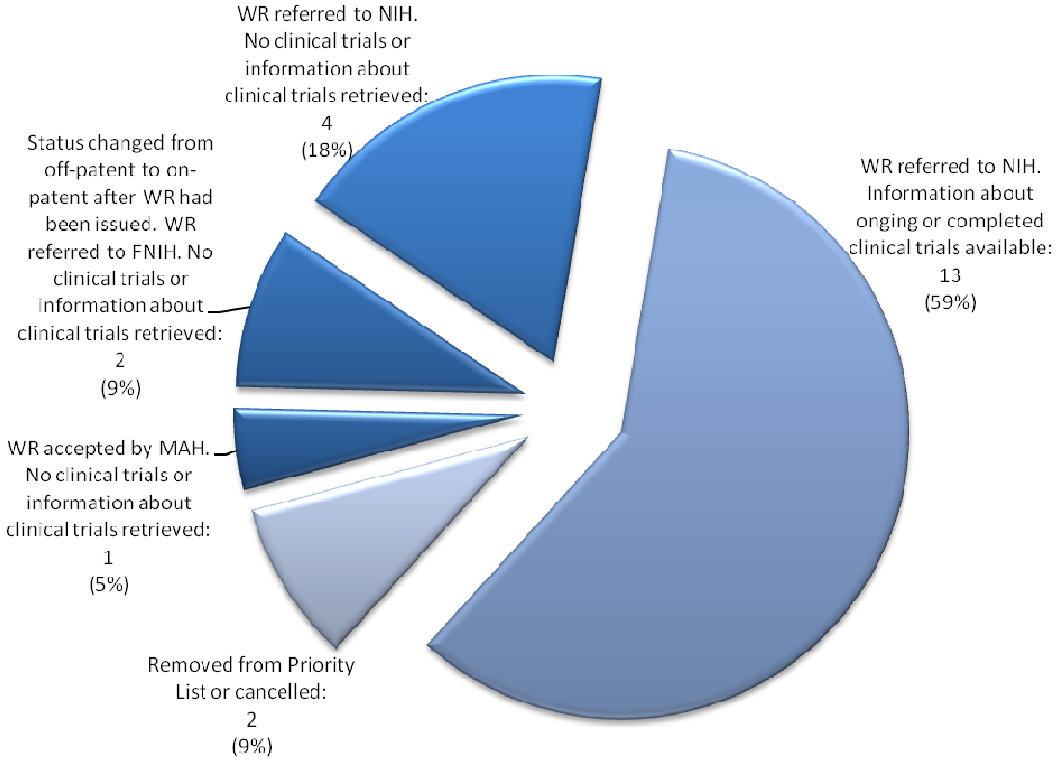


Fig. 14: Status of projects in Response to Written Requests for Off-Patent Drugs

Table 10: Drug substances and indications Written Request have been issued for, by status of projects.

1. WR referred to NIH. Information about ongoing or completed clinical trials available.	
Azithromycin	Treatment of Ureaplasma urealyticum
Baclofen	Spasticity/cerebral palsy
Dactinomycin	Paediatric cancer
Daunomycin	Paediatric cancer
Isotretinoin	Neuroblastoma
Lithium	Children with acute mania and bipolar disorder
Lorazepam	Sedation in the intensive care unit for children on respirators
Meropenem	Complicated intra-abdominal infections
Methotrexate	Paediatric cancer
Morphine	Analgesia
Sodium Nitroprusside	Hypertension
Vincristine	Paediatric cancer
2. WR referred to NIH. No clinical trials or information about clinical trials retrieved.	
Ampicillin	Neonatal sepsis and/or meningitis
Griseofulvin	Tinea capitis
Hydrochlorothiazide	Hypertension
Rifampin	Cerebrospinal fluid shunt infection
3. Removed from Priority List or cancelled.	
Azithromycin	Treatment of Chlamydia trachomatis
Rifampin	Treatment of methacillin-resistant S. aureus endocarditis
4. WR accepted by MAH. No clinical trials or information about clinical trials retrieved.	
Lindane	Second line treatment of scabies
5. Status changed from off-patent to on-patent after WR had been issued. WR referred to FNIH. No clinical trials or information about clinical trials retrieved.	
Hydrocortisone valerate	Atopic Dermatitis
Metoclopramide	Gastro-esophageal reflux

These findings along with an examination of “Table of Medicines with New Pediatric Information”, current as of September 08, 2010 [118] and in combination with a cursory check of relevant drug labels published in FDA’s “Drugs@FDA” database [119] finally led to the overall conclusion that despite a number of ongoing projects there have been no labelling changes so far for any of the off-patent drugs mentioned above.

5 Discussion

Off-patent medicines exclusively for children: PUMA

The Paediatric Regulation's Paediatric Use Marketing Authorisation (PUMA) approach aims at increasing the number of available off-patent medicines appropriately tested in children. Incentives are provided in order to make paediatric development of these older drugs sufficiently attractive to either bigger pharmaceutical companies already holding corresponding marketing authorisations for adult use or to small- or medium-sized enterprises interested in developing a niche market.

For a PUMA marketing authorisation application, results from clinical studies conducted in accordance with an agreed PIP are required; the number of according PIP request thus indicates the maximum number of PUMA applications that may be submitted in the foreseeable future.

In the first three years of its existence, PDCO received a total of 23 PIP applications under Article 30 of the Paediatric Regulation, i.e. PIP applications related to a PUMA, equalling 3% of all submitted PIPs [99]. This percentage has proven fairly stable over time and has no tendency to increase; actually it rather trends to decrease as the number of PIP requests under Article 30 is falling: There had been ten applications per year in 2008 and 2009, respectively, but only been two in 2010 so far; in the second quarter of 2010, while PIP applications under Articles 7 and 8, respectively, more than doubled, there was not a single PIP request related to a future PUMA.

According to the information provided by the Member states end of 2009/beginning of 2010 [64] and the current CHMP statistics [100], there has been no marketing authorisation application in order to obtain a PUMA so far. This is significantly less than some estimations that had been made before the Paediatric Regulation came into force; for example in 2004, the legislative financial statement related to the forthcoming Paediatric Regulation included estimations that for a period of six years starting 2007, there would be around 30 PUMA applications submitted per year; a stable number was not estimated but a figure of 15 procedures per year was assumed [120].

Both clinical studies and marketing authorisation procedures are rather time-consuming processes which is why it may not be too surprising that no PUMAs have been granted yet. The reluctance with regard to the submission of PUMA-PIPs (and, depending on outcomes of clinical trials, not every PIP may actually lead to a PUMA) however suggests that the PUMA incentive may actually be not sufficiently attractive to encourage paediatric development of off-patent medicines.

This had already been a concern in an Impact Assessment of the draft Paediatric Regulation in 2004 when there were considerations that the ten-year data protection period incentive granted for paediatric data might be too weak to stimulate research in the off-patent field [121].

There might be just too many imponderables: To begin with, there is only an incentive in case the efforts actually result in a PUMA; unlike the situation for medicines still under patent, there is no reward in case the investigations fail to prove safety and efficacy of paediatric use. And even if there is a PUMA and the main incentive, ten years of data exclusivity for paediatric data, is granted – data protection does not necessarily mean marketing exclusivity; competitors may apply for corresponding based on their own research, and although the intention is not to involve children in clinical trials if this is not necessary, there is no indication that e.g. PDCO would reject an according PIP based on this intention. Furthermore the existence of a medicinal product exclusively intended for use in children does not necessarily prevent off-label use of adult medicines containing the same active substance and coming in an appropriate formulation (e.g. scored tablets), based on e.g. economic considerations and reimbursement situation.

This suggests that despite recent improvements market forces alone might still not be sufficient to really advance the development of off-patent drugs for paediatric use. So public funding of research might be a more promising approach in order to the expand paediatrician's therapeutic arsenal.

Public funding is provided through the EU Framework Programme, FP7 for the period 2007-2013. At present, there are nine ongoing projects based on two off-patent related calls for proposals in 2007 and 2009, respectively. As the priority list of needs as provided by PDCO is a basis for these projects, they are likely to actually meet a paediatric need rather than being driven by commercial interests. There is a focus on oncology, where off-label and unlicensed use are even more widespread than in other therapeutic areas, and most medicines will be developed for younger paediatric subsets, i.e. preterm and term newborns and infants, which are also age groups that are both extremely vulnerable and exposed to off-label and unlicensed drug use above average. But however, funds and thus the number of projects are limited; and as complex clinical studies are required in order to obtain the necessary data (the projects currently funded typically run over three to five years), this instrument is likely to improve paediatric drug therapy only in the long run and it will take some time until the priority list will be worked off.

EU Paediatric Worksharing

EU Paediatric Worksharing aims to improve paediatric labelling of authorised medicinal products, regardless of their patent status. The intention, namely of worksharing according to Article 45, is to gather all pieces of information available related to safety and efficacy of the use of a drug in the paediatric population. Information may come e.g. from old clinical trials involving children that have never been submitted to a competent authority or from post-marketing studies. This instrument does not require conducting additional clinical studies in children, which is why it offers a chance to improve paediatric information of older medicines whose marketing authorisation holders normally are rather reluctant when it comes to investing in further paediatric investigations. In order to assess drugs with higher need first, the priority list of off-patent drugs is considered when prioritising drug substances for inclusion in worksharing [54].

Through combination of information provided by, in case of generics, several holders of marketing authorisations for a drug substance, there is a chance that an assessment may lead to the conclusion that there is enough evidence to support a paediatric indication for a product formerly not authorised for use in children.

The examination of the assessment reports published as of August 2010 showed that, based on approval dates and existence of generic competition, only one out of 31 was not to be considered **off-patent**. There was a focus on cardiovascular drugs, 20% of the substances already assessed belong to that field, but by and large the selection of drugs was not too one-sided as the 30 off-patent drug substances came from twelve different **therapeutic areas**.

Almost all Member States, except for Cyprus and Finland, have assumed **rapporteurship** so far, although to varying extent, with the bigger national competent authorities, like the authorities of the United Kingdom, Germany, the Netherlands, and France, taking lead, as expected.

Looking at the **timelines** it became obvious that only few of the worksharing procedures go off without a hitch and are completed within the minimum time of 90 days. Most procedures are rather longsome; due to clock-stop periods required to provide responses and supplementary information, about half of the procedures so far have taken 9.5 months or longer, and this is only for the procedures that have already been closed. It should also be noted that even from the first wave, started in 2008, a third of procedures is still ongoing; in Q3/2009, the fourth wave included 25 substances and now, one year later, only one of these procedures has been closed. It is assumed that the individual procedures are started albeit with some delay yet within feasible time, so this suggests that the average time from start to finalisation of procedures will increase.

Time-consuming procedures might slow down the whole process a little bit, block capacities and thus delaying the initiation of procedures for other drugs; this may be an explanation why the number of substances included in the individual waves has been declining and was only 13 for the most recent wave. Should the worksharing process keep advancing at a rate of about 70 drug substances per year that are selected for inclusion in a procedure, it may take around 25 years to assess all products for which there have been submissions under Article 45 of the Paediatric Regulation.

Considering the **outcomes** of the assessments; for the purpose of this evaluation, fentanyl patches, injection, and lozenges had to be counted as three medicinal products as they were all included in one assessment report, but with different paediatric indications both at the beginning and at the end of the procedure, and three different formulation-specific recommendations for SmPC updates.

So with 30 off-patent drugs and fentanyl counting a three products, there was a total of 32 medicinal products under evaluation. No regulatory action was required for nine of them; SmPC changes were recommended for 23 medicinal products; the section amended most frequently, for 21 products, was 4.2, the posology section. It should however be noted that these changes do not necessarily mean that new information in terms of paediatric dosing recommendations were introduced; in several cases the rapporteur recommended a harmonisation of wording.

Before the respective worksharing procedure, 21 of the 32 products under evaluation had a paediatric indication, eleven had not. None of these 21 lost its paediatric indication. As a result of the assessment of the remaining eleven products, four of them actually obtained a paediatric indication, as the information available supported paediatric use of these products. Age subsets affected were six years and above in two, ten years and above in one case; one of the products, fentanyl lozenges, was considered suitable for adolescents aged 16 years and above only; three of the medicines were cardiovascular drugs.

This results show that EU Paediatric Worksharing actually does offer a chance for off-patent medicines to obtain a paediatric indication based on existing data, without need for additional investigations. So far it has led to sound paediatric dosing recommendations for four off-patent drug substances that were not recommended for use in children before worksharing, and introducing relevant information in e.g. in the warning and precautions section or the sections dedicated to pharmacokinetics and pharmacodynamics it improved information and as a result safe use of several other medicines.

The US experience – the BPCA study programme for off-patent drugs

The BPCA study programme for off-patent medicines was introduced in with the Best Pharmaceuticals for Children Act in 2002 in order to foster the paediatric development of drugs that .

In the past eight years, FDA issued 19 **Written Requests** for drugs that were on the “Priority List of Drugs for Which Paediatric Studies are needed”, with nine of the drugs being included in the very first version of this list issued in 2003 and the rest being subsequently added with the annual updates.

If there is a paediatric need for the study of a drug substance for e.g. two indications, separate Written Request will be issued to cover these indications. This was the case for three off-patents on the FDA list; from the information given on FDA and BPCA websites, a total of 22 Written Requests could be identified for 19 different substances.

Half of these Written Requests were for drugs intended to treat paediatric cancer or infectious diseases; these two therapeutic areas are commonly known to be areas where off-label use, especially in very young children, is fairly common and thus the need for appropriate labelling rather urgent.

Only one out of 22 Written Requests was accepted by the holder of the respective marketing authorisation, the others were declined. This was to expected, as under BPCA 2007 no incentives are provided for studying off-patent drugs which is why accepting such a request in not attractive for pharmaceutical companies. So far, the one that was accepted has not led to a labelling change; results are still pending and so this has not led to a label change yet.

For rifampin, two Written Requests were issued; one of them was not pursued and in 2008 there was a recommendation to remove rifampin from the priority list in the respective indication. The Written Request for the investigation of azithromycin treatment of neonatal sepsis and/or meningitis was not studied due to feasibility issues and lack of response for the request for proposals. Another two Written Requests were not pursued by NIH as they were issued when the respective drugs were off-patent; however, metoclopramide and hydrocortisone valerate both changed status to on-patent after issuance and thus were referred to the Foundation for the NIH (FNIH).

For four Written Requests referred to NIH, no clinical trials could be retrieved and the most recent information of progress of the project was in these cases that clinical trials are considered or being developed. For the remaining 13 Written Requests, clinical trials in various stages of completion could be retrieved. But even if some studies have already been completed: This does not necessarily mean that labelling changes are likely to happen on short notice; for some products e.g. the pharmacokinetic study has been completed, but the efficacy studies are still ongoing or have not even started yet.

So, as a result, there has been some progress since the BPCA study programme for off-patent drugs was established, but overall progress is rather slow. Despite all efforts and resources invested, there have not been any paediatric labelling changes for off-patent drugs resulting from the BPCA programme so far. This finding is consistent with a February 2010 statement by Dianne Murphy, Director of the FDA Office of Pediatric Therapeutics, that “despite a number of ongoing studies, the “off-patent” programme has not yet completed a paediatric study that has resulted in a label change for a generic or off-patent drug” [122].

A Comparison of EU and US Approaches

The BPCA does not foresee a procedure that is comparable to the EU Paediatric Worksharing; however, although worksharing has proven that it may result in improved paediatric labelling of off-patent medicines and even led to new paediatric indications for some products, it is not specific for off-patent drugs, as this provision applies to all authorise medicines regardless of their patent status.

The instruments specifically established in order to stimulate research into off-patent drugs and have several aspects in common, yet there are some important differences (Table 11):

Table 11: Specific regulatory instruments for studying off-patent medicines for children in Europe and the US (based on [123], modified and expanded).

	EU	US
Legal basis	Regulation (EC) No. 1901/2006	BPCA 2007
Sunset	No	October 2012
Instrument	Paediatric Use Marketing Authorisation (PUMA)	BPCA paediatric study programme
Intended for	Medicinal products developed exclusively for use in the paediatric population	Authorised medicinal products without paediatric indication
Eligible	All off-patent medicinal products (for FP7 funding: based on priority list)	All off-patent medicinal products, based on priority list
Definition "off-patent"	Not covered by SPC or patent that qualifies for an SPC.	Not covered by patent or marketing exclusivity. Caveat: Status may change from off-patent to on-patent again.
Conduct of paediatric studies	Voluntary	Voluntary
Tool	PIP	WR
What needs to be done	Paediatric studies and age-appropriate formulation, if required	Paediatric studies and age-appropriate formulation, if required
Incentives	Ten years data protection, brand name retention, free scientific advice, fee reductions, eligibility for centralised procedure	None
Funding (other than industry)	EU Framework Programme (FP7)	Public funds (NIH)

One of these differences is **authority**: Basically in the EU a pharmaceutical company, whether big pharma or of the small-and-medium enterprise type, is free to study any off-patent drug in order to achieve a PUMA. The European priority list is the basis for proposals in response to calls under the FP7 Framework Programme, but it is not necessarily relevant for an industry decision whether or not to develop a particular drug. Thus, even if there will be a rising number of PUMAs in the future, there it is likely that industry will rather focus on therapeutic areas that seem most profitable rather than those where new paediatric therapies are needed most [124]. The PDCO does not have the authority to enforce development of a particular off-patent drug substance for paediatric use, no matter how urgent the need. That is different in the US, where the NIH prepares the list of paediatric needs and, by means of submitting a PPSR, may directly influence which drugs are to be studied next.

Another difference is **money**, in terms of incentives and study funds. If an industry sponsor agrees to study an off-patent drug under BPCA, there will be no reward or incentive; therefore it is not surprising that Written Requests issued for off-patent drugs are usually declined. PUMA incentives may not be too attractive, but any incentive is better than no incentives at all, and although the European instrument may lag behind expectations, the number of PIP applications related to a PUMA submitted within three years is significantly higher than the number of US Written Requests accepted by a marketing authorisation holder within eight.

The study fund part is more attractive in the US, where there is a provision included in the legislative text that specifies appropriations intended to support research into off-patent medicines. The EU Paediatric Regulation provides funding through the EU Framework Programmes, but this programme is not specifically intended for paediatric drug development, but this is only one topic among many others that have to share available research funds. Moreover, calls for research proposals are announced annually in the EU whereas in the US, drug-specific requests for proposals are published as appropriate. Originally it had been planned to install a study funds for paediatric research into off-patent medicines in the EU, modelled after the US funds. Because of concerns that without an appropriate funding programme the Paediatric Regulation might only stimulate the paediatric development of new and authorised on-patent medicinal products, it was suggested to include provisions establishing a special financial instrument to provide sufficient funds for off-patent development to cover all or at least a large part of development costs [125]; these provisions were still included in the legislative text in the first reading of the Paediatric Regulation [126], but were later removed and in the final regulation only reference to community framework programmes was made. The funds, called “Medicines Investigation for the Children of Europe” (**MICE**), has never been realised.

Neither of the approaches has so far led to significant results in terms of off-patents medicines that are now available for in-label use in children, be it a medicine exclusively for children (EU) or an adult product with a new paediatric indication added (US). Projects are on the way in both regions, but it may take some more time until they actually take effect.

Maybe a combination of efforts, both in terms of authority collaboration and in combination of procedures, might lead to more success. The importance of **EU-US cooperation** has been recognised from the beginning, and as a consequence, a paediatric cluster between FDA’s Office of Pediatric Therapeutics and EMA’s PDCO was established: In order to facilitate communication and regular exchange of information on paediatric drug development in Europe and the US, a framework has been agreed that aims at global paediatric development plans that are compatible for both EMA and FDA. Amongst others, this framework proposes: information exchange on PIPs, Written Requests, deferrals, and waivers as well as on safety issues and adverse drug reactions in children; exchange of staff and mutual attendance of meetings, e.g. FDA staff may attend PDCO meetings, and EMA staff the FDA’s Pediatric Implementation Team meetings; monthly teleconferences; monthly line-listings on e.g. PIPs, PPSRs, Written Requests, waivers, and deferrals; ad-hoc exchange on general issues as appropriate [127]. Cooperation might result in e.g. making EU PIPs ans US Written Requests more compatible in order to avoid unnecessary paediatric studies and make paediatric research more effective and efficient [128]. This is of particular importances as in the past, FDA and EMA occasionally had divergent opinions about the same clinical studies [124].

In addition to cooperation, maybe a **combination** of EU and US instruments might be more promising than the individual instruments alone, for example having a PUMA-like instrument in place in order to allow pharmaceutical companies to e.g. broaden their portfolio adding a paediatric version to an existing brand line of products or to capture niche markets and complement this approach with a study programme mirroring the BPCA one (including a specific funding programme), intended for medicines for which there is an urgent paediatric need while their development is not attractive for industry.

6 Conclusion and outlook

Rising awareness for the special needs children have when it comes to drug therapy have led to various legislative initiatives in both the US and, with some delay, in Europe. These initiatives acknowledge that children have a right to be treated with appropriate medicines; they aim to improve children's health by fostering paediatric development of off-patent drugs and thus improve paediatric labelling of medicinal products in order to allow safe and effective paediatric drug therapy.

Regulatory instruments established include the BPCA study programme for off-patent drugs in the US, in place since 2002, and the Paediatric Use Marketing Authorisation (PUMA) in Europe (2007). In addition to the PUMA, the Paediatric Regulation has also established the EU Paediatric Worksharing procedure, which is not solely intended for off-patent but also for authorised on-patent medicinal products. Nevertheless experience has shown that older medicines may also benefit from it as worksharing so far has resulted in improved labelling or even a new paediatric indication for some off-patent products.

While within the on-patent sector paediatric initiatives are considered to be rather successful – for example, current FDA statistics list a total of 390 paediatric labelling changes resulting from PREA, BPCA or combinations thereof [129] – progress for off-patent medicines is rather slow. Although there have been some PIP application related to a future PUMA, this number is lagging behind expectations, most likely because of the imponderables associated with it and the relatively weak incentive of 10 years data protection. Funding is crucial, and increased appropriations that allow to support more projects might be able to expedite processes in both Europe and the US.

Research projects in order to study off-patent drugs for use in the paediatric population are on their way and, depending on the outcome of the studies, may lead to more paediatric medicines in the future. But as all of these projects include clinical trials in children and in several cases also the development of a new, age-appropriate formulation, projects are generally rather complex and will take their time to be completed. Because of this, neither the BPCA study programme nor the PUMA have so far led to paediatric labelling changes or the authorisation of a medicinal product exclusively developed for children.

All things considered it will take some more time until the initiatives will take effect and the first paediatric labelling change for an off-patent drug resulting from the BPCA study programme and the first PUMA, respectively, will be granted. There are many off-patent drugs relevant for paediatric drug therapy and many indications to be studied, and for only a few of them the process has already started. So there is still a long way to go before off-label and unlicensed use of adult medicines in children will be history:

"There's still a big ocean of unstudied drugs that we have to sail across before we complete them all"
Richard L. Gorman (2007) [130].

7 Summary

For many medicinal products, safety and efficacy for paediatric use have never been properly established. In the past, pharmaceutical companies often refrained from testing their products in the paediatric population because of ethical concerns, high complexity of clinical trials and financial considerations.

Because of a significant lack of both paediatric labeling information and age-appropriate formulations, off-label or unlicensed use is common in paediatric drug therapy. Paediatric doses are often extrapolated from adult data, and this approach may involve an increased risk for inefficacy and/or unpredictable adverse reactions; the paediatric organism is still developing and thus a child's drug response may differ from that of an adult. The lack of paediatric information in drug labels has been a rising concern and consensus has developed that children also should have access to safe and effective medicines. This includes off-patent medicines, where paediatric development is even less attractive than within the on-patent sector, mainly due to expected low return on investment because of a combination of high costs for clinical development, small markets, and generic competition.

To remedy this situation in respect of off-patent medicines, regulatory instruments have been established in both the EU and US that aim at improving paediatric labelling of medicines and increasing number and availability of off-patent medicines, preferably in age-appropriate formulations, appropriately tested in children. In the US, a Written Request mechanism to initiate study programmes for studies into off-patent drugs was introduced with the Best Pharmaceuticals for Children Act (BPCA) in 2002. Europe followed in 2006, when the Paediatric Regulation established the Paediatric Use Marketing Authorisation (PUMA) intended for medicinal products for exclusive use in children, and EU Paediatric Worksharing, a tool that is not limited to off-patent medicines, but nevertheless offers chances for an improvement of paediatric labelling of off-patents, based on e.g. previously unpublished study results.

All these regulatory instruments have been in place for several years now – but what has actually been achieved so far? An analysis based on data made publicly available by EU and US authorities, respectively, shows that as of August 2010, despite a number of ongoing projects, overall progress is slow in both regions. While EU Paediatric Worksharing, despite not being the primary tool for increasing the availability of off-patent drugs for children, has led to improved paediatric labelling for a number of off-patent medicines and even to new paediatric indications for some of them, the more specific instruments have not yet led to more medicinal products authorised for children. So far, no PUMA has been granted, and to date only three percent of all PIP applications submitted to EMA were for clinical studies that may eventually lead to a PUMA. At present, there is a total of nine projects funded under FP7; as these projects typically take several years to be completed, paediatric marketing authorisations based on results from the respective studies are not to be expected in the near future. The situation is similar in the US, where at present, there are several NIH/NICHD funded clinical studies into off-patent drugs ongoing; however, these efforts have not led to a paediatric labelling change so far.

The analyses led to the overall conclusion that the instruments in place have not proven too effective so far; the final breakthrough has yet to happen. The projects that have been started do not cover too many off-patent drug substances and indications where there is paediatric need, thus being only a drop in the ocean of medicines that had to be studied in order to meet all paediatric therapeutic needs, and even these projects will take significantly more time until they may actually show results. Maybe combined EU and US efforts, in terms of cooperation or even combined instruments, might eventually lead to more success in finally meeting children's needs and significantly improving paediatric drug therapy by expanding the therapeutic armamentarium with medicines adequately developed and tested for paediatric use.

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