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THESE POUR LE DIPLOME D'ETAT DE DOCTEUR EN PHARMACIE

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Par Mr Clément DUBOS

American and European Paediatric Regulations:
After decades in the making, a worldwide concern addressed by uneven local regulations

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Réglementations pédiatriques Américaine and Européenne:
Après des décennies de développement, une problématique mondiale adressée par des législations inégales

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Abbreviations

BPCA	Best Pharmaceutical Children Act
CHMP	Committee for Human Medicinal Products
COMP	Committee for Orphan Medicinal Products
CRO	Clinical Research Organization
EC	European Commission
EEC	European Economic Commission
EMA	European Medicines Agency
EnprEMA	European network for paediatric research
EU	European Union
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act
FDAMA	Food and Drug Administration Modernization Act
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	Good Clinical Practice
ICH	International Conference for Harmonization
MA	Marketing Application
MAH	Marketing Authorization Holder
MRFG	Mutual Recognition Facilitation Group
MS	Member State
NCA	National Competent Authority
NME	New Molecular Entity
PIP	Paediatric Investigation Plan
PDCO	Paediatric Committee

PEG	Paediatric Expert Group
PeRC	Pediatric Review Committee
PPSR	Pediatric Plan Study Report
PREA	Pediatric Research Equity Act
PSP	Pediatric Study Plan
PUMA	Paediatric Use Marketing Authorization
RDP	Regulatory Data Protection
RfM	Request for Modification
SPC	Supplementary Protection certificate
US	United States
WHO	World Health Organization
WR	Written Request

Introduction

Il est indéniable aujourd'hui que les essais cliniques font partie intégrante de la médecine moderne. Toutefois le nombre de ces essais impliquant une population pédiatrique reste limité en comparaison du nombre d'essais cliniques effectués dans la population adulte. Cette analyse, déjà véridique dans les années 1990, s'explique par le manque de réglementation encadrant et permettant de promouvoir le développement dans une population segmentée par une physiologie évoluant au cours du temps.

A cause de cette absence de cadre règlementaire, l'utilisation hors-AMM était une pratique courante et fut une préoccupation majeure des autorités de sante européenne et américaine au fil des ans :

- *Dans l'Union Européenne, il s'avère que plus de 50% des médicaments utilisés en pédiatrie ont été évalués uniquement dans une population adulte et pour certains dans une indication différente de celle utilisée en pédiatrie.*
- *Aux Etats-Unis, une situation similaire pouvait être observée au début des années 1990, une période durant laquelle la recherche pédiatrique n'était pas encouragée. Seulement 38% des nouveaux médicaments développés et potentiellement utilisables en pédiatrie ont reçu une indication dans cette population.*

Il était alors pratique courante d'utiliser l'extrapolation des résultats de la population adulte afin de déterminer les doses pédiatriques. Toutefois la population pédiatrique ne peut être considérée comme des "petits adultes" et cette extrapolation de résultats peut alors s'avérer inappropriée voire même dangereuse.

A cause de ce manque de connaissances, tant sur l'efficacité que sur la sécurité d'utilisation des médicaments en pédiatrie, plusieurs tragédies liées à une utilisation hors-AMM virent le jour et obligèrent les autorités à se pencher sur ce manque de réglementation. Cela permettant par la suite la mise en place d'études spécifiquement réalisées dans le but d'obtenir des informations dans la population pédiatrique. Plusieurs décennies furent nécessaires pour réussir à développer les réglementations

actuelles dans l'optique d'assurer un meilleur encadrement de la population pédiatrique, toutefois de nombreux défis restent encore à relever avant d'arriver aux mêmes standards que la population adulte.

It is an undeniable fact that clinical trials are the backbone of modern evidence-based medicine. However, the volume of clinical trials involving children had been substantially lagging behind their adult counterparts in the early 1990's for a simple reason, the lack of a proper regulatory framework promoting such development in a very peculiar population representing a wide spectrum of different physiologies.

Due to the absence of proper regulations, the use of unlicensed and off-label medicines in children was widespread and had been a concern over the years for both the EMA and the FDA:

- In the European Union (EU), 50% or more of medicines used in children have actually only been studied in adults and never in this population, and not necessarily in the same indication (or the same disease).
- In the United States (US), a similar observation was made in the early 1990's, a time when the study of drugs in children was actually discouraged, only 38% of potentially useful new drugs in pediatrics were labeled for children when initially approved.

It was common practice to use extrapolation to simply deduce the necessary dosage to use in children. However, children are simply not "little adults" and extrapolating results from adult clinical trials to the treatment of children may be inappropriate and, possibly, harmful.

Sadly, because of a lack of knowledge on either the efficacy or the safety of the drugs in the paediatic population at the time, medicine-related tragedies occurred and prompted the authorities to reach a consensus on a much needed regulatory framework, allowing more studies to be initiated in order to obtain paediatric

information for medicines used in children. Decades were necessary to define the current regulations allowing a better development and standard of care for paediatrics, and hurdles still exist which hopefully will be tackled in the years to come in this ever-evolving field in order to finally reach the same standards of care as the ones observed in the adult population.

1 Yesterday: A lack of specific regulation *(5, 8, 11, 13, 31, 32, 33)*

The absence of treatments appropriately developed in the paediatric population had long been acknowledged by the scientific community, as shown in 1963 by Harry Shirkey who designated children as therapeutic orphans.

Children did not lack treatments per se since all approved drugs can be used in an off-label way. Thus, the use of off-label medicines for children has been common practice for decades; but this does not offer the same quality, safety and efficacy of medicines as it does in adults, which is a fact the physicians have to weigh in when trying to cure paediatric patients:

- No information available on effective and safe dosing regimens (dose range, frequency of administration and duration of therapy)
- An ethical dilemma exists as to the choice between using off-label medications when little or no information is available about their safety and efficacy or depriving the child of a possibly effective medicine, just because it happens to be off-label
- Parents and guardians being apprehensive that a medicine not tested in children, or not cleared for use in children, is being used to treat their child

This population lacks specific medications readily tested and not officially approved for use, which was not the case even for essential medicines. Children have specific therapeutic needs which cannot be met if medicines representing major therapeutic advances in adults are not tested and labelled for paediatric use.

Taking all of the above into account, it comes as no surprise that paediatric patients are more likely to be exposed to potentially dangerous medication errors than adult patients.

1.1 A dire need for a regulation steaming from tragic events

As early as 1901 and throughout the 20th century, several medicine related tragedies occurred in the paediatric population. Be it due to a lack of knowledge or pure ignorance regarding differences in pharmacotherapy in children, most of these

situations happened early in the paediatric development between in utero and neonatal period.

For instance, the earliest tragedy happened in 1901 with vaccines containing the diphtheria antitoxin. At the time, the antitoxin was obtained from the bottled blood serum of horses previously inoculated with concentrated doses of the bacteria. The potential for contamination was present a t all stages of the process which proved lethal to thirteen children in St. Louis who died after receiving diphtheria antitoxin contaminated with tetanus spores. It lead to the Biological Control Act setting up standards for the manufacturing process of vaccines but also required licensure for pharmaceutical firms making those vaccines.

In the 1930s the scientific community in the US widely acknowledged that the Food and Drugs Act of 1906 was obsolete but could not find an agreement on what its replacement should entail. In 1937 a new tragedy occurred costing the lives of more than a hundred patients. The medicine in question was called “Elixir Sulfinamide” used to treat streptococcal infections with great proven effectiveness in its original tablet and powder formulations. This elixir was a new sought liquid formulation containing diethylene glycol, usually used as an antifreeze agent, which had not been tested for toxicity since it was not required by law to do safety studies on new drugs. The following year the Federal Food, Drug, and Cosmetic Act was enacted and still today remains the basis for the FDA regulations and gave birth to a new system of drug control to ensure that all medicines placed upon the market shall be safe to use under the directions for use.

Another well-known worldwide pharmacological scandal in terms of physiological development concerned the in utero exposure to thalidomide leading to the birth of congenitally deformed infants. The drug first commercialized as a sedative was later used as a treatment for nausea and morning sickness in pregnant women. In the late 1950s, the use of medications during pregnancy was not strictly controlled, and drugs were not thoroughly tested for potential harm to the foetus. It turned out that the drug was teratogenic and contrary to the US where the drug was not approved and all distributed medicine directly to the physicians, even though it was not on the market,

was recalled only leading to 17 cases of children born with malformations, the drug was widespread in the EU leading in that case to thousands of children dying or being born with phocomelia. In the US albeit the drug did not manage to get on the market, a new legislation was passed in 1962 in the form of the Kefauver-Harris Drug Amendments Act which introduced amongst other changes the need to prove efficacy through clinical studies for new products, pharmacovigilance once they are on the market and even specific timelines for the evaluation of the dossier submitted to the FDA. In the EU, regulations also spawned following these events, specifically the first European pharmacological directive, Directive 65/65/EEC1 in 1965, introducing provisions for new products such as he need to have an authorization in at least one member state to be allowed on the marked and the need to provide results from pharmacological and toxicological tests alongside results from clinical trials.

Other instances must also be mentioned, first the use of sulfonamides in neonates which lead in turn to kernicterus (severe brain damage related to neonatal hyperbilirubinaemia), and also one must not forget the grey baby syndrome being a cardiovascular collapse, which was observed in newborns when using chloramphenicol.

These tragedies as shocking as they might have been at the time led to a much needed change in the mentality of the scientific community regarding the paediatric development of drugs.

Indeed, various health authorities requested the medicine manufacturers for much more extensive and thorough pre-marketing medicine investigations. At long last, efficacy and safety of the medicine were required to be investigated in the population for which it is aimed and marketed and at long last, specific paediatric development strategies were deemed necessary.

However, a large variety of hurdles had to be overcome to reach such a goal:

- Ethics and the difficulties of obtaining informed consent;
- Need for non-invasiveness;
- Need for microassays in such a fragile population (e.g. smaller blood samples);

- Stratification of patient population into at least five categories (premises of ICH E11);
- Difficulty in predicting long-term effects during the maturation process;
- Rare diseases (making patient recruitment difficult and small market size providing lower return on investment);
- Training of paediatricians to assess protocols for research;
- High regulatory requirements to be expected.

Should the regulators find a way to address all of the above, it would lead to the possibility of conducting ethial and scientifically valid paediatric clinical trials, those trial would help in providing new needed paeditric information in the drug label, and in turn it would allow the dissemination of proper treatment for the paediatric population.

1.2 Finding a proper definition of the paediatric population

1.2.1 International acknowledgement: ICH E11

The International Conference for Harmonization, an organisation working on the harmonisation of pharmaceutical regulatory requirements between the EU, Japan and the US, was the first joint paediatric regulatory action to have an Expert Working Group finalize a guidance for industry in July 2000, the ICH E11 on *Clinical Investigation of Medicinal Products in the Pediatric Population*.

The goals were to encourage and facilitate timely paediatric drug development internationally and to provide a needed outline of critical issues in paediatric drug development and approaches to ensure safe, efficient and ethical study of medicines in children.

The main points underlined by this guideline are the following:

- Pediatric patients should be given medicines that have been properly evaluated for their use in the intended population.
- Product development programs should include pediatric studies when pediatric use is anticipated.

- Development of product information in pediatric patients should be timely and, often requires the development of pediatric formulations.
- The rights of pediatric participants should be protected and they should be shielded from undue risk.
- Shared responsibility among companies, regulatory authorities, health professionals and society as a whole.

The ICH E11 guideline turned out to be a valuable instrument in designing paediatric clinical research worldwide; however, legally speaking the guideline is only a recommendation and as such is not considered a mandatory requirement. This meant that a great initiative had in the end a very limited if non-existent no effect on paediatric submissions in worldwide, indeed in 10 years less than 50% of the medicines authorised by the EMA had a potential paediatric use but no data was available for it.

1.2.2 Paediatrics: a fragmented population

It has been a long acknowledged fact that the paediatric population represents a spectrum of different physiologies, and children should not be treated as “miniature men and women”.

The population spectrum spreads from preterm newborn infants to adolescents, and the internationally and somewhat arbitrarily agreed classification of the paediatric population by the International Conference on Harmonisation (ICH) is as follows:

- preterm newborn infants
- term newborn infants (0 to 28 days)
- infants and toddlers (> 28 days to 23 months)
- children (2 to 11 years)
- adolescents (12 to 16 to 18 years, depending on the region).

The dynamic process of maturation taking place during human growth is one of the difference between the paediatric and the adult populations.

All the changes that can be observed before adulthood whether physiologically or pharmacologically have a great influence on the parameters used to define the clinical use of medicines, that is on efficacy, toxicity and dosing regimen.

Indeed a starting point of the differences observed could be how the proportions of body fat, protein and extracellular water content are shown to vary significantly during early childhood. For instance, newborns are known to experience a decrease of their body water from about 80% to 60% by the time they reach five months of age. Similarly, the percentage of body fat will double by four to five months, and this process will last throughout the second year of life until an increase of motor activity in children is observed and consequently the protein mass increase will be coupled with a compensatory reduction in fat.

Moreover, developmental changes in body composition and proportions also have a non-negligible impact on the distribution and elimination processes of the drugs. As an example, the liver and kidney size, relative to body weight, also changes during growth and development. Both these organs reach maximum relative weight in the one- and two-year-old child during the period of life when the capacity for drug metabolism and elimination is the greatest. Likewise, body surface area relative to body mass is greater in infants and young children than in older children and young adults.

Another important difference concerns the developmental changes in the gastrointestinal tract affecting oral absorption of drugs predominantly during the newborn period, infancy and early childhood.

These changes affect a large variety of parameters of the gastric system:

- Gastric acidity,
- Gastric emptying time,
- Gut motility,
- Gut surface area,
- Gastrointestinal medicine-metabolizing enzymes and transporters,
- Secretion of bile acids and pancreatic lipases,
- First-pass metabolism,
- Enterohepatic recirculation,
- Bacterial colonization of the gut,
- Diet at different ages and
- Diurnal variations.

As an example, when taking into account preterm and term infants, this specific part of the paediatric population has greatly reduced gastric acid secretion, while on the other hand it was observed that neonates show prolonged gastric emptying. It can be deduced that during the neonatal period, acid-labile medicines will be easily absorbed.

Another common factor impacting the absorption during the early stages of life would be the reflux of gastric contents retrograde into the oesophagus, and when excessive may very well result in regurgitation of medication and thus an unpredictable loss of orally administered medicines.

As mentioned above, absorption has been shown to be deeply impacted and dependent on the development of the paediatric population, and the same can be applied regarding the distribution of the drug in children, which is linked to the extracellular fluid volume, the total body water of any patient and fat content. For instance, the following differences can be observed in the different subsets:

- Newborn have a much higher extracellular fluid volume than any other population either paediatric or adult,
- Preterm babies have a higher extra-cellular fluid volume,
- Total body water is also much greater in neonates
- Fat content is lower in premature babies than in full-term neonates and infants.

As the distribution of drugs is either done in the extracellular water or as depot in the body fat based on the lipid-water partition coefficient, the changes observed in the paediatric population are bound to influence the distribution phase of the medicines in the different compartments of the body. It means that water-soluble compounds will need to be administered with larger initial doses in order to reach similar plasma concentrations to those in adults, while the lipid-soluble molecules will have larger distribution volumes in infants due to the increase in proportion of body fat occurring during the first year of life. Finally, the volume of distribution of many medicines may be impacted and show increased concentrations of unbound medicine as a result of a

lower plasma protein binding in neonates and premature babies than the one observed in adults.

The clearance of many medicines is primarily dependent on hepatic metabolism followed by excretion by the liver and kidneys. Once more there are significant differences which have an impact on those processes in the metabolism and elimination capacities of neonates, infants and children. The general observation is that the more premature the infant, the poorer the hepatic metabolizing and hepatic/renal excreting capacity. Thus, a longer plasma half-life and subsequently a longer time to reach steady-state are therefore observed for the medicines since either the liver and/or the kidneys are not fully functional yet in premature and newborns who, compared to older children and adults, require lower maintenance doses to avoid toxicity. Of note, in young children, the opposite situation takes place and the hepatic and renal elimination capacity for many drugs can even exceed what would be seen in adults, which in turn makes the administration of a higher maintenance dose a necessity.

Alongside quantitative differences in absorbing, distributing, metabolizing or even eliminating medicines in the paediatric population, there are also various qualitative differences impacting their metabolic pathways. An example is that of paracetamol, which in infants and children is primarily metabolized by sulfate conjugation whereas after for adolescents and adults glucuronidation becomes the primary pathway.

Although a great deal is known about pharmacokinetic changes during development, information regarding developmental changes in pharmacodynamics (medicine action and toxicity) is limited. There are few examples (f.i. clinically observed higher incidence of opioid-related respiratory depression and bradycardia associated with insufficient analgesia in newborns who receive opioids) that provide evidence for changes in the response to medicines during development independent of pharmacokinetic changes, however it is undeniable that medicine targets, such as receptors, transporters and channels, are also subjected to developmental processes (as are metabolizing enzymes). A clinically relevant example of such differences during development is the greater immunosuppressive response to ciclosporin seen in infants. The concentration

in infants at which 50% inhibition occurs in peripheral blood monocytes is only half that in older children and adults, nonetheless beyond this observation the exact molecular mechanism still needs to be further investigated.

Finally, it should be noted that paediatric-specific diseases occur in the growing and maturing organism. Examples include disorders in the postnatal adaptation period of the newborn, such as wet lung syndrome with respiratory stress and persistent fetal circulation with pulmonary hypertension or hormonal imbalances of the adolescent during puberty. Needless to say that such diseases being specific to these subsets of the population are not the primary target of the paediatric legislations due to the fact that any drug development would be directed at the children from the very start, but they also benefit from the regulation with the higher standards and scrutiny being placed on the paediatric clinical studies.

The main substantial changes observed in paediatrics and discussed above are summarized in the table 2-1 below:

Table 1-1 Summary of the major differences between adults and children

	Paediatrics
Body composition	Higher percentage of body water
	Higher percentage of body fat (limited motor activity)
	Lower percentage of protein mass
	Smaller liver and kidney size with lower capacity for drug metabolism and elimination
	Body surface area relative to body mass decreases
Absorption	Reduced gastric acid secretion (pre-term/infants)
	Prolonged gastric emptying (neonates)
	Higher rate of gastric content reflux
Distribution	Higher initial doses of water-soluble compounds
	Larger distribution volumes for lipid soluble molucules (infants)
	Lower plasma protein binding (neonates and prematures)
Elimination	Lower hepatic/renal excreting capacity
	Longer plasma half-life and time to reach steady-state
	Lower maintenance doses to avoid toxicity (prematures)
	Higher hepatic and renal elimination capacity (children)
PD	Higher immunosuppressive response (infants)
Specific diseases	Post-natal disorders, wet-lung syndrome, persistent fetal circulation, hormonal imbalances…

1.3 Résumé de la première partie

L'absence de traitements développés spécifiquement pour la population pédiatrique est un fait accepté de longue date par la communauté scientifique, comme le montre la définition la citation d'Harry Shirkey en 1963 qui définissait les enfants comme étant des orphelins thérapeutiques.

Il est important de souligner que cette population ne manquait pas, à proprement parler, de possibilités thérapeutiques lorsqu'un traitement devait être initié chez un patient, et ce grâce à la possibilité d'utilisation hors-AMM des médicaments autorisés dans la population adulte. Toutefois, même si cette pratique a été utilisée durant des décennies et continue à l'être aujourd'hui, cela n'offre pas les mêmes garanties d'efficacité et de sécurité d'utilisation, fait important que tout praticien doive prendre en compte lors de l'initiation d'un traitement dans de telles conditions.

Tout au long du 20e siècle, plusieurs tragédies liées à des médicaments non adaptés à l'utilisation pédiatrique eurent lieu. Que cela soit dû à un manque de connaissances ou par pure ignorance des procédés pharmacologiques dans cette population, la grande partie de ces évènements concerna les sous-groupes les plus fragiles, à savoir lors du développement in utero ou néonatal, et conduisit à la mise en place des prémices des réglementations pédiatriques actuelles.

En effet, de nombreuses autorités de santé demandèrent aux compagnies pharmaceutiques de mettre en place des procédés d'évaluations cliniques plus poussés avant de pouvoir mettre leurs produits sur le marché. L'évaluation de l'efficacité et de la sécurité des produits dans les populations ciblées devait enfin être réalisée et des stratégies de développement dans la population pédiatrique furent alors requises.

Le Conseil international d'harmonisation, structure internationale qui rassemble les autorités de réglementation et les représentants de l'industrie pharmaceutique d'Europe, du Japon et des États-Unis pour discuter des aspects scientifiques et techniques de l'enregistrement des médicaments, fut à l'origine de la première initiative commune visant à résoudre ce manque de cadre réglementaire pour la population

pédiatrique, initiative qui aboutit en juillet 2000 à la publication de l'ICH E11 « Investigations Cliniques des médicaments utilisés dans la population pédiatrique » et posa, entre autre, une définition des différents sous-groupes de cette population hétérogène. Cela fut une étape majeure, dû au fait que le processus de maturation physiologique prenant place dans le corps humain est un des points d'orgue dans l'évaluation des différences entre les populations pédiatrique et adulte, et de ce fait la détermination des différents paramètres utilisés en clinique, à savoir l'évaluation de l'efficacité, la sécurité et la toxicité.

2 Paediatric Regulations: Years in the making

Both the European Medicines Agency (EMA) in the European Union and the Food and Drug Administration (FDA) in the US perceived the need for legal obligations as well as incentives for pharmaceutical companies to perform pediatric studies to obtain pediatric information for medicines used in children and remedy the problem of usage of unauthorized medicinal products in the pediatric population.

2.1 EMA *(2, 6, 9, 10, 11, 12, 13, 14, 15)*

2.1.1 Changing minds by changing the GCP

As stated previously, the widespread use of unlicensed and off-label medicines in children has been an increasing concern over the last years. The evident lack of information and appropriate pharmaceutical formulations to support the administration of many medicines in children exposed the need for more studies to obtain paediatric information.

Based on this outcome, it was clear that there was a need for a legal obligation for pharmaceutical companies to perform studies if they intended to develop medicines for use in the paediatric population. However, the legislative process for a paediatric initiative in Europe, as important as it might have been for every party involved, turned out to be a long and arduous journey.

The need to include children in drug development had been long known to the regulator and implicitly included in the legislation, but none of the measures did provide the information needed for the majority of medicines.

It first started in 1997, when experts convened by the European Commission debated on paediatric medicines and one of the consensus at that time was that the need to strengthen the legislation in this field by introducing a specific system of incentives.

The following year at the International Conference on Harmonisation (ICH), the Commission supported the need for international discussion on the performance of clinical trials in children, leading to an ICH guideline being agreed on. The main goals

were to provide appropriate regulation regarding the facilitation of timely paediatric medicinal product development internationally, and agree on an outline of critical issues in paediatric drug development and approaches to the safe, efficient and ethical study of medicinal products which had been identified and considered since then of paramount importance.

Consequently, the aforementioned ICH guideline (ICH E11) became the European guideline presented as 'Note for guidance on clinical investigation of medicinal products in the paediatric population', which entered into force in July 2002.

Specific concerns about performing clinical trials in children, and in particular how to ensure patients' protection in said clinical trials were also implemented in the subsequent Directive (2001/20/EC) on Good Clinical Practice for Clinical Trials which was adopted in April 2001, and came fully into force in May 2004.

In addition, a draft document on 'Ethical considerations for clinical trials performed in children – Recommendations of the Ad Hoc Group for the development of implementing guidelines for Directive 2001/20/EC relating to good clinical practice in the conduct of clinical trials on medicinal products for human use' was released in October 2006 by the European Commission. The aim was to provide recommendations on aspects of paediatric clinical trials with the intention to contribute in strengthening their protection as participants of clinical trials as well as to facilitate a harmonised approach to clinical trials across the EU Member States, considering that the approval of clinical trials, including ethical approval, is primarily a national competence, thereby facilitating the conduct of clinical trials in the European Union.

2.1.2 7 years from a concept to an actual regulation

The above milestones paved the way for a proper legislative process for a paediatric initiative in Europe. On December 14th, 2000 a resolution was adopted by the Council of (Health) Ministers requesting the European Commission to draw up a proposal on this initiative, the first actual draft of a specific regulation, which was considered a public health priority.

Within 2 years, the European Commission published a consultation paper on 'Better medicines for children – proposed regulatory actions in paediatric medicinal products'. This paper represented, in February 2002, one of the first steps to address the problem of a lack of paediatric regulation, and a reflection paper followed, incorporating the comments received in June 2002.

The Commission's Better Regulation Action Plan (com(2002)278) led to the proposed Regulation on medicinal products for paediatric use being subjected to an extended impact assessment, necessary process aiming at analysing all economical, social and environmental consequences of any major regulation.

In March 2004, the European Commission consulted the Member States on a draft Regulation on medicinal products for paediatric use, and on 29 September 2004, the first proposal for a Regulation on medicinal products for paediatric use was finally released, together with an explanatory memorandum from the extended impact assessment, and a question-and-answer document, providing a glimmer of hope that paediatric patient would be soon recognized and protected as much as they should have been in the first place.

Following several votes, amendments and reviews, lasting from the second half of 2005 and the first of 2006, the Regulation was agreed on June 1st, 2006 by the European Parliament. On 27 December 2006 the Regulation, comprised of Regulation (EC) No 1901/2006 and the amending Regulation (EC) No 1902/2006, was published in the Official Journal of the European Union and entered into force on 26 January 2007.

The main objectives of the new E.U. regulation can be summarised as follows,

- Improve the quality and ethics of any research into medicines for children,
- Increase the availability of authorized medicines for children,
- Increase available information on medicines for children without unnecessary studies in children and without delaying authorization for adults.

In order to achieve these objectives, the E.U. pediatric regulation is based on the following 3 pillars:

1. The Paediatric Committee (PDCO)
2. The Paediatric Investigation Plan (PIP)
3. The Rewards and Incentives

2.1.3 The first pillar: The Paediatric Committee (PDCO)

Ahead of the finalization of the regulation and aware of the unmet medical needs of the paediatric population, the Committee for Medicinal Products for Human Use (CHMP) took the initiative of creating an ad hoc Expert Group on Paediatrics (PEG). With the implementation of Title IV of Regulation (EC) No 726/2004, the PEG was transformed into a temporary paediatric working party, which was constituted in 2005 under a new mandate.

The Paediatric Working Party comprised 14 experts representing the main areas of specific expertise (e.g. pharmaceutical formulations, pharmacokinetics, trials methodology, and several paediatric specialities such as neonatology, immunology, nephrology and adolescent medicine). In addition, several members ensured active links with other CHMP working parties (Safety, Efficacy, Pharmacovigilance, Quality) and with the Committee for Orphan Medicinal Products (COMP).

The mandate of the PEG was to coordinate the necessary actions and advise the EMEA and its scientific committees, the CHMP, the COMP and the Mutual Recognition Facilitation Group (MRFG) on all questions relating to the development and use of medicinal products in children. This concerned products already authorised, whether through the centralised or national mutual-recognition procedures, and those in development.

The PEG has now ceased its activities, and has been replaced, in accordance with the Paediatric Regulation, by a new scientific committee within the EMEA – the Paediatric Committee – which held its inaugural meeting on 4-5 July 2007.

The PDCO in the EU is the counterpart to the Pediatric Review Committee (PeRC) in the U.S. It is a committee composed of experts from the Committee for Medicinal Products for Human Use (CHMP), from each Member State (not represented via

CHMP membership), and members appointed by the European Commission representing healthcare professionals and patients' organizations. Those experts are chosen for their knowledge in development and assessment of all aspects of pediatric medicinal products with their main responsibility being to assess the content of submitted Pediatric Investigation Plans (PIP) and adopt opinions on them in accordance with the E.U. pediatric regulation. This includes the assessment of applications for a full or partial waiver and for deferrals. Other tasks of the PDCO also include assessing data generated in accordance with the PIP, advising and supporting the EMA on creation of a European pediatric network, and establishing and regularly updating an inventory of pediatric medicinal needs.

2.1.4 The second pillar: The Paediatric Investigation Plan

The development and authorization of a medicinal product for the pediatric population subsets is based on a specific plan called a Paediatric Investigation Plan or PIP. The plan has to be submitted at an early phase of development of a new compound for instance upon availability of adult PK studies after Phase 1.

Setting up a PIP entails an extensive preparation for the pharmaceutical companies even before knowing whether the drug being developed will obtain a marketing authorization for the adult population.

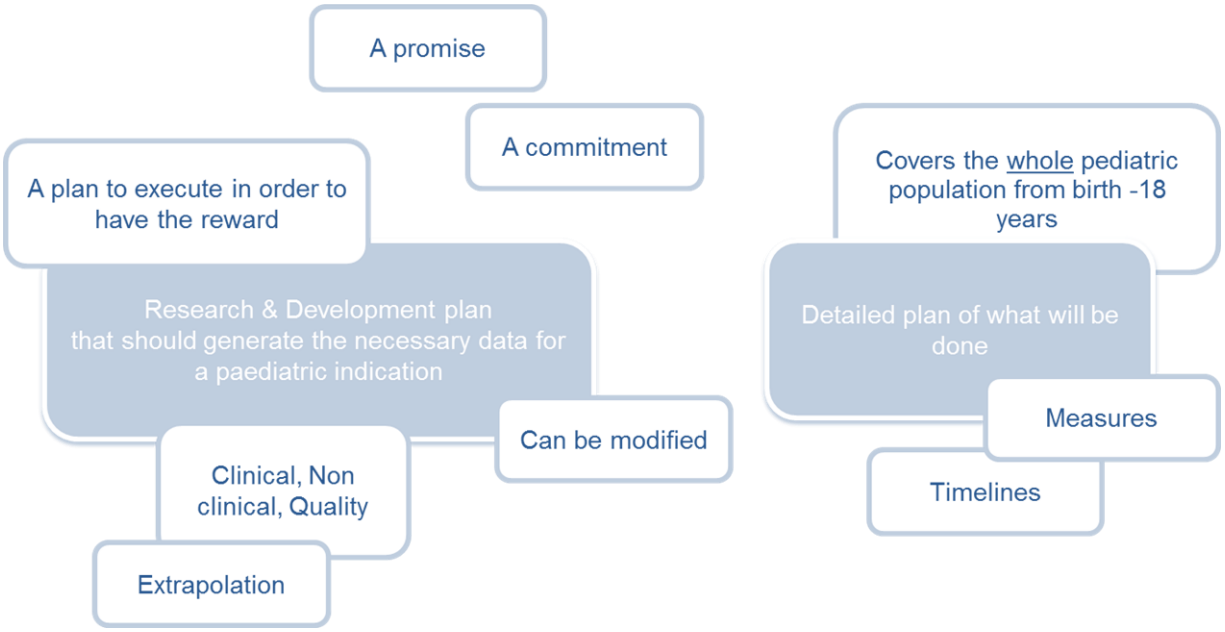

Figure 2-1 Simplified view of the goals and requirements of the PIP

The initial PIP dossier includes details of the timing and the measures (also known as key binding elements) proposed to demonstrate quality, safety, and efficacy in the pediatric population and should cover all ages from birth to adolescence, even if the subsets can still be defined and adapted according to the pathology being studied.

The plan is intended to reflect the development in clinical, non-clinical, and technical aspects including estimated timelines and covers all existing or planned indications and dosage forms which includes when determined necessary the specific pediatric formulations or routes of administration (i.e. liquid formulation or granules instead of tablets for children less than 6 years of age).

The scope of the intended PIP should be clearly defined and will be thoroughly discussed by the PDCO at the time of submission. Usually the indication in scope will be the same as for the adult population, however, the PDCO may request widening the proposed paediatric indication in order to avoid ignoring a potential paediatric use and unmet paediatric need based on the properties and mechanism of action of the drug being studied.

The timing of the studies in children relative to adults is also clearly defined, including deferrals until completion of studies in adults to ensure that studies in children are conducted only when it is safe and ethical to do so.

The PIP has to be agreed upon and/or amended by the PDCO and is binding for the company. Submitting a PIP for approval follows pre-defined milestones and timetables set in place by the EMA. The entire process is divided into three stages and can take more than a year to get a PIP approved by the PDCO.

The first phase starts with the letter of intent submitted by the applicant informing the PDCO of the upcoming PIP. This may be followed by a pre-submission meeting allowed by the committee to help ensure a smooth validation and overall procedure by answering all potential questions of the applicant. It is during this phase that the Paediatric Coordinator, Rapporteur and Peer Reviewer will be designated for the PIP evaluation.

After submission of the complete application and a 30-day validation period the second phase, namely the evaluation, will start and can be divided into 3 steps. The first two months may in the best case end up with the PDCO opinion and close the procedure, but in most cases due to the complexity of setting up paediatric studies the applicant will receive a list of questions to be addressed within the 3 months of clock-stop defined in the regulation, and finally the applicant will have another 2 months where the PDCO will examine and provide the possibility to the applicant to discuss the answers provided before issuing an opinion.

The third phase of the PIP process only concerns instances when the PDCO issues a negative opinion and the applicant can then request a re-examination which will last up to 2 months. This is an opportunity to have new Rapporteur and Peer Reviewer assigned and evaluate the proposed PIP based on the original information and scientific data provided.

At the end of the PIP application, the PDCO makes an opinion which when considered definitive is transferred to the EMA to reach a decision which will in turn be made public and mark the end of the process.

However binding a PIP may be, should new information become available during the development, the regulation still allows the company to submit a request for modification (RfM) of the agreed-upon PIP to the PDCO relying on a sound scientific rationale and data supporting each claim for change.

Similarly to the initial dossier, the request for modifications need to be submitted to the PDCO following a procedure spanning over 5 months from the letter of intent to the final PDCO Opinion. The main differences from an initial submission are the absence of clock-stop phase during the process and the fact that only new elements which significantly alter the key binding elements will be assessed.

Under certain pre-specified conditions, a company can apply for a partial or complete waiver for the paediatric plan. It can only be granted if the drug is likely to be ineffective or unsafe in part or all of the pediatric population, if it is intended for conditions that occur only in adult populations (e.g., Alzheimer's disease), if it does not represent a significant therapeutic benefit over existing treatments for pediatric patients, or in certain cases when the indication is part of a published list of conditions exempt by the agency from the requirement of a PIP.

Should the applicant be able to provide the PDCO with strong scientific and technical justifications or grounds related to public health which would substantiate the fact that waiving the PIP requirement would not end up in a loss of opportunity for the paediatric population, the waiver will be granted but it is interesting to point out that any waiver can be revoked should new information on the condition become available and paediatric studies therefore needed to cover a new unmet need. In those special cases, the PDCO will grant the applicant 36 months to allow time for PIP to be agreed/paediatric studies to be initiated before marketing authorization application submission.

Deferrals are another toll provided to the pharmaceutical industry to help ease the burden and difficulties encountered when doing paediatric development. A deferral allows postponing the initiation or the completion of the measures in the PIP, often

doing so until the studies in adults have been conducted, in order not to delay the MA in adults and to perform studies in children when it is proven safe to do so.

If deferral on a PIP has been granted, the applicant has an obligation to submit to the EMA Annual Reports to provide an update on progress with paediatric studies after the marketing authorization has been granted. Hence, once a year and until the final opinion on the compliance with the agreed PIP is adopted a report needs to be submitted lest the applicant wants to be subject to an infringement procedure facing financial penalties.

2.1.5 The third pillar: The Rewards and Incentives

When looking at it from a pharmaceutical company's point of view, developing a paediatric drug is huge investment with low chance of making a benefit like one would see from any other drug in the adult population (exception made of the orphan drugs). With this in mind the regulators set in the new legislation a system of incentives and rewards when doing paediatric research in the hopes that it would help stimulate the research.

There are different incentives created with the new Regulation to compensate the financial burden of the development:

- The possibility for the MAH to apply and get a Paediatric Scientific Advice to better plan and coordinate the development steps of the drug with the PDCO free of charge.
- Similarly, no fees will be requested for all applications related to the PIP, be it initial submission, request for waiver, deferral or modification and the annual Compliance Checks and final Compliance Check when submitting the results of the completed PIP in order to receive the long-awaited rewards.
- The Paediatric Use Marketing Authorisation (PUMA) application is also a possibility when a CP product is concerned by the development, giving the possibility, amongst other points, of having to pay reduced fees for the examination of the application and the maintenance of the MA.

- As for nationally authorised products, the regulators allowed the MAH in specific cases, through the procedure of Article 29, to ask for a centralized review by the EMA using the referral procedure & timetable and then having the implementation of the line extension (extension of indication, new formulation or new route) in all MSs. This optional procedure is only possible if the below elements are met:
    a. The medicinal product must be protected by a SPC or a patent which qualifies for an SPC.
    b. The application must be accompanied by results of studies and information in compliance with an agreed PIP.
    c. The procedure is limited to the evaluation of the paediatric data.

After completing the studies defined in the PIP, the MAH needs to follow pre-determined steps in order to be entitled to the different rewards depending on the medicine being studied. The main prerequisite for getting any reward and consequently to receive marketing authorization in the indication is a compliance check with the agreed PIP.

The Timing of the Compliance Check is crucial to the process, it needs to be done at the request of the applicant at every relevant regulatory submission (either marketing authorisation, or new indication, or route/pharmaceutical form) and prior to said-submission, or at the validation but will be inducing a delay and holding the validation process since the applicant is not authorised to submit the application until the PDCO has adopted its opinion, and a copy can be annexed to the application.

The purpose of the compliance check is to verify that all measures and studies agreed in the PIP have been conducted in accordance with it.

It is nonetheless possible to do a partial compliance check on an agreed PIP which has been partially completed when deferrals on the initiation or completion have been granted for several measures of the PIP. The partial compliance check therefore covers measures within the condition covered by the regulatory application, for which initiation or completion have not been deferred, as well as measures which are deferred

but due to be initiated or completed before or at the time of submission of the application. Furthermore, if the results of a deferred study or measure included in the PIP are submitted in the regulatory application as a full study report, the compliance check will be done even if it is not due yet.

Once again the applicant needs to properly plan ahead for this 60-day process which purpose in itself is to compare the study reports submitted to the PIP information and thus verify that the pharmaceutical company has complied with all the key binding elements set by the PDCO Decision in the PIP.

This process entails that all binding measures and timelines have been respected and that the final clinical study report is submitted within 6 months of the studies' completion, defined as last patient last visit, to comply with the provisions set forth by the Article 46 of the Paediatric Regulation.

This major step in the PIP process can only be avoided when the applicant is granted a full waiver (be it product-specific or class-related) or when granted a deferral with no measures to be completed by the date of submission of the regulatory application. If no such situation occurs, the compliance check determines whether the manufacturer will be granted the rewards for successfully completing a PIP. Nonetheless, should the applicant be found non-compliant at the time of the validation of the compliance check, there is still room for the submission of a request for modification to the PDCO which will be the last opportunity given to negotiate the key binding elements that the applicant has not been able to fulfil before the end of the study.

A full compliance check positive outcome leads to the application being validated as well as to the grant of the "compliance statement" which is a pre-requisite for the PIP rewards, however it doesn't necessarily mean that an initially positive outcome will not be overturned during the assessment of the application. It can be compared to a two-step process where the initial compliance check is done at the validation by the PDCO, and then the CHMP analyses the data and discovers major violations of the key binding elements not described in the clinical study report, which ultimately will lead to the non-

issuance of the “compliance statement” by the Competent Authority and this will prevent the applicant from obtaining the rewards.

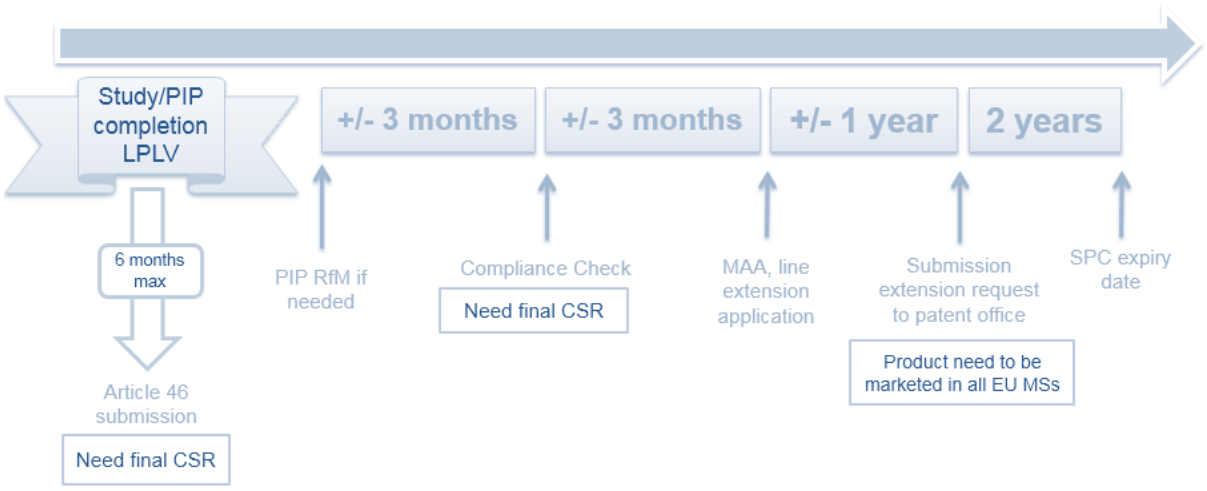

Figure 2-2 Overview of the timelines for compliance check

The rewards for completing a PIP differ depending on the product concerned and have been created by the regulators in order to compensate the paediatric burden of such research through the use of financial rewards.

A new medicinal product (also known as new molecular entity) is eligible to a 6-month extension of the SPC, orphan-designated medicinal products are subject to the same requirements and benefit afterwards from an additional two years of market exclusivity to the 10-year exclusivity rewarded under their specific Orphan Regulation but for a medicinal product with multiple orphan indications in different conditions: reward granted for each entirely separate orphan designated indication for which a PIP has been completed and complied with, and when off-patent medicines are concerned the applicant can ask for the paediatric data to benefit from two years of data and market protection.

Also according to the provisions from the Article 8 of the Regulation which leads to the authorisation of a new paediatric indication, the applicant will have to choose between the SPC extension or the RDP extension since the reward shall not apply if the applicant applies for, and obtains, a one-year extension of the period of marketing

protection for the medicinal product concerned, on the grounds that this new paediatric indication brings a significant clinical benefit in comparison with existing therapies.

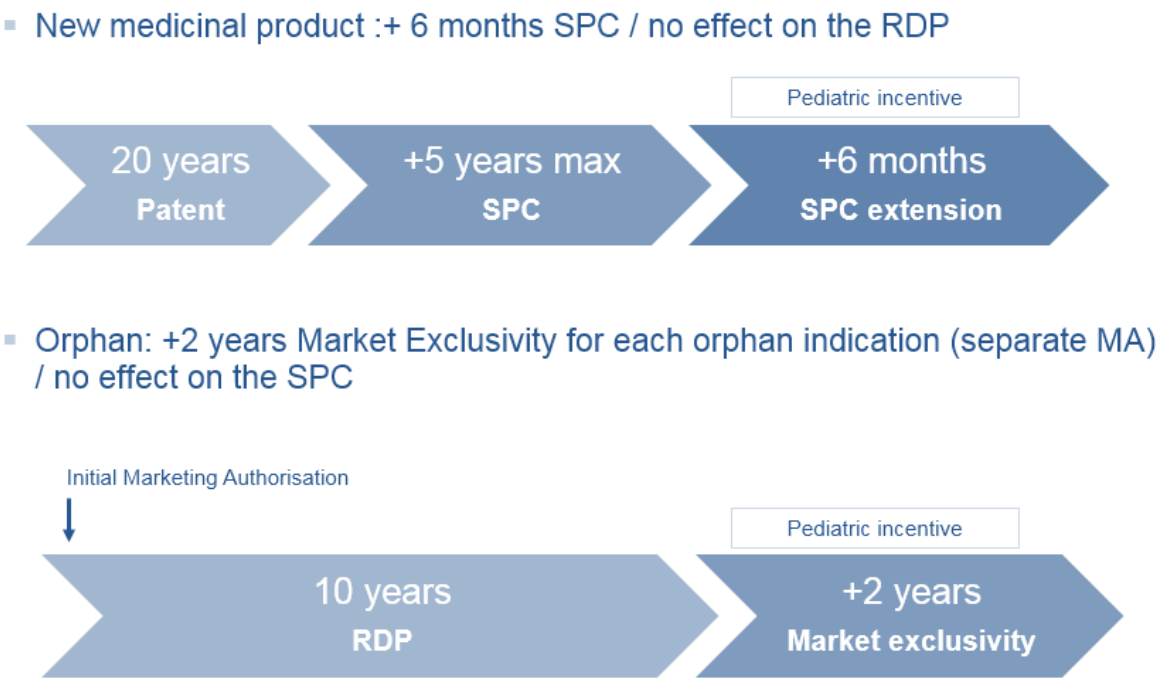

Figure 2-3 Overview of the rewards granted when compliant with an agreed PIP

In the specific case of a NME with an existing SPC or valid patent qualifying for a SPC and in order to be able to claim the SPC reward, the applicant needs to fulfil three conditions:

1. The results of the PIP studies must be reflected in the SmPC and the patient leaflet as necessary to ensure that the research will improve the information available on the use of medicinal products in the paediatric population.
2. Product marketed in all EU Member States (exception made of PUMA).
3. Compliance statement in MA issued by the NCA/EC if development compliant with agreed PIP/all the measures included in the agreed PIP are complied with and if the SmPC reflects the results of studies conducted.

Once the authorization is obtained in all MS and study results are included in the product information, notwithstanding whether the results from the paediatric studies are negative and fail to lead to a paediatric indication, the reward for conducting studies

in the paediatric population and not for demonstrating that a product is safe and effective in the paediatric population can be granted.

The applicant can then submit individual applications to national patent offices in the EU since no European patent as of yet, and this step is once more subject to ample preparation on the applicant's part as the process to grant national extensions will need to be submitted 2 years before SPC expiry date and has to be taken into consideration by adding an average window of 3.5 years between completion of the PIP and the reward.

2.1.6 Supplementary tools to incentivize the paediatric development in the EU.

Other tools have also been created in order to help stimulating the research and improve the information available for medicines used in children:

- The possibility of merging separate PIPs (for 2 conditions) because the regulatory submission encompasses both conditions or splitting PIPs becoming necessary from the manufacturer's standpoint when in a single PIP with several conditions needs to be split due to the development of one condition coming to a stop or being substantially delayed. Merging may be a compulsory measure from the PDCO and entails that completion of all measures of both decisions is necessary to consider that the PIP is completed which in turn could prove detrimental by inducing delay or complications for the pharmaceutical companies. However the process of splitting a PIP into two separate ones is done on a voluntary basis and while it might very well on the one hand reduce the scope of PIP decisions it can allow in return an earlier completion of a PIP, hence an earlier reward and, provided that the results of the studies show a clinical benefit for the paediatric population, help securing a new indication for the product faster.
- An inventory listing the different therapeutic areas where a dire need of paediatric research and development has been identified.

- As a transparency measure established to ensure that all pediatric clinical studies performed in the E.U. are registered within the E.U. database on clinical trials (EudraCT), including all worldwide studies in children if the study is part of a PIP.
- Alongside the transparency measure on EudraCT, the EMA makes available all details of the results of pediatric clinical trials even if terminated prematurely.
- The creation in 2011 of an umbrella network of 39 national and international stakeholder networks (Pharmaceutical Industry, CRO's, Patients, parents and patient organisations, National Competent Authorities, Ethics Committees) recognized for their paediatric research experience named the European Pediatric Research Network (EnprEMA) which goal is to foster high quality ethical research through efficient inter-network and stakeholder collaboration as well as facilitate the conduct of clinical studies on medicinal products to be used in children.

2.1.7 Penalties for not complying with the Regulation.

As counterpart to these incentives, the EMA also established a set of penalties should the manufacturers not comply with the requirements newly set by the Paediatric Regulation. These are financial penalties and a public "denunciation" by the EC that the manufacturer is infringing the Paediatric Regulation.

The penalties will apply should the pharmaceutical company decide not to comply with the following obligations:

- Obligation to comply with the time limits for initiating or completing measures specified in the Agency's decision on deferral following the initial MA
- Obligation to place the medicinal product on the market within two years of the date on which the paediatric indication is authorized
- Obligation to transfer the MA or to allow a third party to use documentation contained in the MA dossier
- Obligation to submit paediatric studies to the Agency, including the obligation to enter information into the European database on third country clinical trials
- Obligation to submit an annual report to the Agency

In such cases, the EMA will consider that the MAH has committed, intentionally or negligently, an infringement and set a fine not exceeding 5 % of the holder's Community turnover in the preceding business year. In addition, the EMA will also set up a secondary fine as long as the MAH has not terminated the infringement, fine being equivalent to periodic penalty payments per day not exceeding 2,5 % of the holder's average daily Community turnover in the preceding business year. Periodic penalty payments may be imposed for a period running from the date of notification of that decision until the infringement has been brought to an end.

2.2 FDA *(2, 3, 6, 18, 19, 21, 22, 23, 24, 25, 26)*

The paediatric knowledge gap in the US was historically similar to what had been observed in the EU, with drugs being used in children without the same level of evidence as what was the norm in clinical studies for adult patients. Indeed, in surveys conducted in 1973 and 1991 it was recorded that around 80% of listed medication labels disclaimed usage or lacked dosing information for children. Moreover, two supplementary surveys conducted between 1984 and 1989 and then between 1991 and 2001 (done as a repeat survey) reported that only 20-30 % of drugs approved by the FDA in the 80's were labeled for pediatric use, and later computed data on new drugs showed that in the early 1990's, only 38% of those new drugs which could prove to be potentially useful in pediatrics were labeled for children when initially approved.

It should be noted that this situation can be explained by a simple fact, being that at the time, the study of drugs in children was actually discouraged due to concerns from the scientific community over potential ethical issues, the fear of harming children when testing a new drug, or even the increased liability of the investigators and pharmaceutical companies for involving children in a clinical trial.

The scientific belief was that dosing could be simply determined by extrapolation of the body weight with once more a common agreement that children could simply be defined physiologically as "little adults" and scientists faced the inherent difficulties of limited populations for certain diseases or a lack of infrastructure (facilities, equipment, laboratories) and technical expertise in conducting paediatric trials. And finally, like in

the EU, there was a lack of pediatric regulation/legislation to incentivize or require drug companies to conduct pediatric trials.

Such hurdles ended up with a paediatric knowledge gap that had a non-negligible impact on the standard of care of the children overall:

- Indeed, children did not receive potentially lifesaving or otherwise beneficial therapeutics because they were not approved for use in children.
- Children received unapproved therapeutics (off-label use) based on adult studies with no or limited pediatric experience, sometimes with disastrous results.

2.2.1 The Pediatric Labeling Rule vs the Pediatric Rule

In 1977, in order to tackle these horrendous problems for the paediatric development, the American Academy of Pediatrics Committee on Drugs put forth statement highlighting that "*it is unethical to adhere to a system which forces physicians to use therapeutic agents in an uncontrolled experimental situation virtually every time they prescribe for children*". This was the turning point marking the premises of a legislation in the US with preset previsions on the dire need that controlled studies in the paediatric population be done for every drugs so as to ensure that the benefits of therapeutic advances will become available to all who need them.

Over the past decades, the FDA has thrived to evolve from an outdated view of "little adults" who should be protected from research to one where children are protected children through research.

The first steps towards a paediatric legislation in the US were taken in 1994 with the issue of the Pediatric Labeling Rule which role was to force the pharmaceutical companies to review existing data and determine whether they had sufficient input in the paediatric setting to support an additional claim for pediatric use in the drug's labeling. When such situation was met, the manufacturer had to file for a modification of the drug label through the use of a supplemental New Drug Application (sNDA) and seek FDA approval on the label change. Even though this new regulatory tool showed great potential by allowing the labeling update of drugs in this specific population

through extrapolation of the efficacy data observed in adults alongside additional pharmacokinetics, pharmacodynamics, and safety studies in pediatric patients, provided the disease and the response to the drug were known to be similar in children compared to adults, only a limited number of drugs benefited from subsequent well-designed and well-conducted studies.

The major flaw in the Pediatric Labeling Rule was that it was entirely voluntary-based and because of this failed to substantially increase the amount of drugs with adequate paediatric labeling. To remedy this issue, the FDA decided in the following years, first in 1997 and then 1998, to revise and finalise a new tool, the Pediatric Rule.

The design of this new regulatory process was to avoid the loss of opportunity for any drug which could either be likely to be commonly used in a paediatric context or would present a significant therapeutic benefit over existing approved paediatric treatments. This would in turn enable the MAH to have drugs which would present at approval or soon after an appropriate paediatric labeling for the approved indication. From this moment on any drug manufacturer would be required to provide safety and efficacy data in the relevant paediatric age groups relevant to the claimed indication. Nonetheless the rule left some leeway in such cases where obtaining the necessary information would prove difficult if not impossible. In these situations, the manufacturers could either ask for a deferral should the collection and filling delay the availability of a drug with a significant therapeutic advantage for adults, or seek a partial or complete waiver for products which paediatric data would not prove to have any meaningful therapeutic benefit over existing treatment or would even be unsafe or ineffective in pediatric patients.

Further to the Paediatric Rule development, the FDA developed a process which would help in creating a specific list for drugs where additional paediatric information would prove beneficial, this was the Food and Drug Administration Modernization Act (FDAMA). This new addition to the CFR gave supplementary powers to the FDA regarding the paeditric studies process, indeed, the pharmaceutical companies would have to seek approval from the agency on which studies were necessary to collect sufficient data in children and then receive a binding Written Request from the FDA

summarizing the milestones previously agreed upon and setting a timeframe to reach said goals.

In order to balance these newly defined requirements, the FDA set in place incentives for the companies to do their utmost when developing medicines in children. Thus, a manufacturer would be allowed thanks to the FDAMA to claim six additional months of marketing exclusivity when submitting studies according to the requirements set by the WR. Data later showed that as a result of this incentive, many drugs received paediatric labeling claims making the FDAMA the first actual successful step in the US legislation toward paediatric drug development.

2.2.2 The Best Pharmaceutical Children Act and the Pediatric Equity Research Act

However the US Congress, through the FDA report, identified drawbacks in 2001 resulting from the application of the incentives provided by the FDAMA, such as the fact that only a small portion of the drugs being on the market would be eligible to those provisions. In the spirit of righting some wrongs, the Best Pharmaceuticals for Children Act (BPCA) in 2002 entered into force and renewed the abovementioned incentives but this time for both drugs still protected by a patent but also off-patent molecules, with new provisions of government mandated contracts and an obligation to disclose study results in the public domain.

The BPCA provides for voluntary pediatric drug studies via a Written Request (WR) and its inception reflects the need for clinical information that may produce health benefits in the paediatric population. The BPCA while not being mandatory authorizes the FDA to request paediatric studies of either approved or unapproved indications if used by the pharmaceutical companies. When using the BPCA, the process requires the sponsor to submit a Proposed Pediatric Study Plan (PPSR) comprised of three main components, the rationale for studies and study design, a detailed study design and appropriate formulations for each age group, in order for the FDA to review and issue a WR and make the sponsor eligible to receive the pediatric exclusivity reward for conducting and fulfilling a WR.

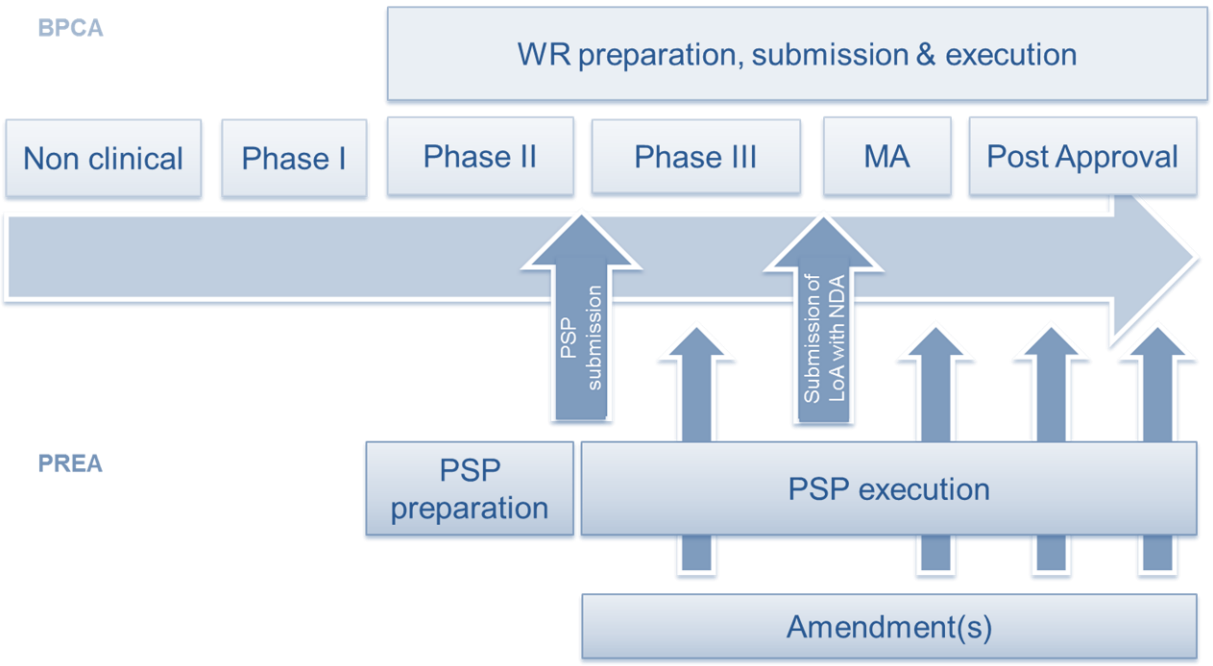

Figure 2-4 Comparison of timelines preparation steps of the PREA and the BPCA

Following the BPCA, another initiative was enacted in 2003, the Pediatric Research Equity Act (PREA). Finally the components set by the PR were acted in the US legislation and forced the companies to assess the paediatric use of their drugs, follow a paediatric plan and develop when necessary age-appropriate formulation, unless waived or deferred beforehand by the FDA.

Contrary to the studies done under the BPCA, the ones realised in order to fulfil the requirements under the PREA are mandatory but limited to the indication(s) approved in adults while products intended for pediatric-specific indications will be subject to the requirements of PREA only if they are initially developed for a subset of the relevant pediatric population. The submission of an initial Pediatric Study Plan (iPSP) is a requirement for any product subject to PREA.

The purpose of the PSP is to identify early in the development phase where an unmet need can be tackled by pediatric studies and subsequently begin planning for said studies. Under the requirements of the PREA, an agreed initial PSP must be submitted as part of any marketing application subject to PREA. Although a PSP is only required if subject to PREA, the FDA still encourages the pharmaceutical companies to include

in the PSP all potential pediatric development plans for the product, including those that may be studied under BPCA (f.i. other than adult indication or even orphans) and form the basis of a PPSR that can be submitted in order to obtain a WR. This path when taken can allow a product to concomitantly have both a PSP and a WR, both mandatory and voluntary studies, hence potentially benefiting from the incentives of BPCA if compliant with the studies contained in the WR.

An important note must be made in this specific case of trying to comply with both BPCA and PREA, the sponsor cannot use the PSP intended for PREA as the PPSR that will be the basis of the BPCA. It all means incentive-wise that the exclusivity reward if sought after by the applicant will only be obtained after a WR has been issued and complied with and not under the PREA. Hence, the WR should be obtained from the FDA before submitting the pediatric studies to satisfy the requirements of the PREA because the pediatric exclusivity will only be granted after issuance of the WR.

Under the PREA, the sponsor who intends to submit an application for a drug or biological product that includes a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration is required to submit an initial PSP within 60 calendar days after the date of the end-of-Phase 2 meeting if no other date has been previously agreed upon with the FDA.

Due to this requirement ample preparation is needed from the industry's perspective. In order to provide assistance and ease the process, the FDA encourages the applicant to request early consultations and discussions through pre-IND meeting as early as end of phase I to properly identify whether pediatric studies will be required under PREA and if there is a need to submit before or defer until after approval. In the case of diseases that are life-threatening or severely debilitating in the paediatric population and where a dire need of treatment has been identified, the studies might be initiated could earlier despite the potential lack of information regarding both safety and effectiveness.

The content of an initial PSP is defined by the Food Drug & Cosmetic Act (FD&C Act). The Act states that the plan must include an outline of the pediatric study or studies

that the applicant plans to conduct (including, to the extent practicable, study objectives and design, age groups, relevant endpoints, and statistical approach) as well as any request for a deferral, a partial or complete waiver if applicable, along with any supporting documentation.

An example of how an initial PSP can be organized is included below:

1. Overview of the disease in the pediatric population:

   Brief summary on the available information on the pathophysiology, incidence and prevalence of the disease, methods of diagnosis, and currently available treatments and/or prevention strategies in the pediatric population, including neonates, and available information on key differences between adults and the pediatric population.

2. Overview of the drug or biological product:

   Proposed mechanism of action of the drug and possible therapeutic uses of the drug in children beyond the disease or indication being sought in adults which could serve as the basis for a Written Request (under section 505A of the FD&C Act (21 U.S.C. 355a)). Discussion can be sought on the potential therapeutic benefits and unmet needs in the pediatric population beyond the indication(s) for which pediatric assessments will be required under PREA, and should be included in the overview of a PPSR asking the FDA to issue a Written Request. In the case of studies that could be conducted under a pediatric Written Request, in addition to those required under PREA and included in the iPSP, the sponsor will have to submit a separate PPSR.

3. Overview of planned extrapolation to specific pediatric populations:

   Addressing whether extrapolation is planned in the PSP in case the disease and effects of the drug are sufficiently similar between adults and paediatric patients (e.g. disease pathogenesis, criteria for disease definition, clinical classification, measures of disease progression, pathophysiologic, histopathologic, and pathobiological characteristics of the disease). Appropriate justification on the extrpoliation of the effectiveness of the drug should be added (supportive data betweena adults and children or between age groups). Should the extrapolation of

the data be unfeasible (lack of data) at the time of the iPSP, the applicant has to include a plan to establish pediatric effectiveness in the iPSP. If new information becomes available at a later stage and allow for extrapolation, an amendment to the iPSP can then be submitted.

4. Planned request for drug- specific waiver:
    a. A full waiver can be granted by the FDA if one of three conditions is met, the necessary studies are impossible or highly impracticable (f.i. incidence too low, geographic dispersion of the patients), or there is strong evidence that the product would be ineffective or unsafe in all age groups; or the product does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients.
    b. A partial waiver can also be granted for a specific age group if one of the above condition is met and also should the applicant be able to show that attempts at creating pediatric formulation necessary for that age group have failed.
5. Plan to request deferral of pediatric studies:

    Similarly to the plan for a waiver request, the applicant can build a dossier justifying the need to defer the submission of the paeditric assessment after the submission of the application. The following reasons can be the basis of the FDA agreeing on a deferral:
    a. The drug or biological product is ready for approval for use in adults before pediatric studies are complete.
    b. Pediatric studies should be delayed until additional safety or effectiveness data have been collected.
    c. There is another appropriate reason for deferral (e.g.development of a pediatric formulation is not complete).
6. Tabular summary of planned nonclinical and clinical studies:
7. Age-appropriate formulation development:

Summary of the formulation development plans for all age groups and details of measures taken to ensure appropriate design of a drug, including to the extent practicable the design of delivery systems (f.i. capsules, tablets, infusions, devices).

8. Nonclinical studies:

   Information must be provided to support the maximum dose and duration of treatment to be used in pediatric studies. If the data from the non-clinical studies is insufficient, the sponsor needs to add a description of the future studies to be intiated.

9. Clinical data to support design and/or initiation of studies in children:

   Overview of current information in a summary of available data in adult or pediatric patients who have received treatment with the drug for the proposed indication, for other conditions, or in earlier studies.

10. Planned pediatric clinical studies:
    a. Pediatric pharmacokinetic studies
    b. Clinical effectiveness and safety studies planned

11. Timeline of the pediatric development plan:

    General timelines for each of the planned studies (non-clinical and clinical) based on current projections of the development program of the product.

12. Agreements for pediatric studies with other regulatory authorities:

    Summary of the latest agreed paediatric investigation plan with other health authorities, such as the EMA, and highlight or comment on the observed differences between the two plans in order to discuss if feasible an alignment in pediatric development plans across regulatory authorities.

The total length for review of an iPSP by the FDA is 210 days and is divided in four stages. The first step is the submission of a complete PSP by the sponsor to the FDA which will then assess the submitted plan within 90 days. After this period, the sponsor will receive comments for which a new 90-day period is granted to assess and answer the queries received from the FDA and finally submit a new version of the PSP. The last stage will be the evaluation of the “agreed” PSP by the FDA within 30 days after

which the Agency will issue a statement confirming whether the agreement on the PSP stands. If a sponsor receives a letter of non-agreement, the FDA will make every effort to work with the sponsor and resolve the area(s) of disagreement as quickly as possible; however, there is no statutory timeline attached to this process. If the sponsor disagrees with the FDA's recommendations, it can request a meeting with the FDA to discuss any disagreement. After the sponsor and the FDA have resolved any disagreement, the sponsor should submit the proposed agreed iPSP or proposed agreed amended iPSP for FDA review.

The sponsor should postpone submitting a marketing application until an agreement has been reached on the iPSP with the FDA. Furthermore as mentioned in the description of the content of the iPSP, the sponsor will receive feedback at the time of the review of the iPSP on the plan to request a waiver and/or deferral upon submission of the marketing application, and such feedback may include recommendations on the timing of pediatric drug development with the aim of including pediatric data in the initial marketing application, rather than needing a deferral and the formal decision by the FDA about granting a waiver and/or deferral of required pediatric assessments will only be made after approval of the marketing application.

At the time of submission of the application, the sponsor needs to submit the pediatric assessment containing data gathered from the PSP, meaning from the agreed upon pediatric studies using appropriate formulations for each age group for which the assessment is required, and other data that are adequate to assess the safety and effectiveness of the drug or the biological product for the claimed indications in all relevant pediatric subpopulations and support dosing and administration for each pediatric subpopulation for which the drug or the biological product has been assessed to be safe and effective. Under PREA, a pediatric assessment must be submitted at the time an application for a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration is submitted to the FDA, unless the requirement for the assessment has been deferred or waived.

The pediatric assessment is a cornerstone of the application since failure to submit it or a request for approval of a pediatric formulation in accordance with the statutory

requirements of the PREA, the product may be considered misbranded and subject to relevant enforcement action. Such scenario is not the basis for withdrawing approval of a product however, the FDA could bring an injunction or a seizure of proceedings.

All in all the US legislative framework for paediatric studies consists of two separate regulations, one defining the requirements of such development with the PREA, and a second focusing on how to properly define the incentives and rewards with the BPCA. In addition of having a different purpose, they also differ in their scope. The PREA relates to both the medicines and biologics as well as the mandatory studies on the indication under review (exception made of orphan indications), while the BPCA covers only medicines and the studies in such cases are realised on a voluntary basis and might end up in extending the approved indication (including orphan indications).

Both “Acts” are clearly designed to encourage pediatric research and the expansion of development of pediatric medicines, and thus logically require that the data collected in the studies be presented publicly and added appropriately in the labels.

	US PREA	US BPCA
Paediatric development	Mandatory	Optional
Name of the pediatric plan	Paediatric Study Plan (PSP)	Proposed Pediatric Study Request (PPSR) Written Request (WR)
Timing	No later than 60 days after EoP2 meeting	Any time
Reward	No reward	6-month exclusivity
Biologicals	Included	Included
Orphan	Exempted	Included
Scope of pediatric development	Adult indication	Not limited to adult indication
Labelling	Studies must be labeled	Studies must be labeled

Figure 2-5 Comparative overview of the PREA and BPCA

2.2.3 The Food and Drug Administration Amendments Act and the Food and Drug Administration Safety and Innovation Act

In an effort to continue on this path, it is understandable that the FDA, within the scope of the 2007 Food and Drug Administration Amendments Act (FDAAA), confirmed those two frameworks at the time of their sunset period and renewed them for 5 years. Aware of the importance of continued legislative evolution in this field, the FDA introduced as part of the 2007 “Act” the Pediatric Review Committee (PeRC) composed of FDA members recognized for their expertise in paediatric related scientific subjects, be it clinical pharmacology, statistics, chemistry, legal issues, ethics, oe even appropriate expertise pertaining to the product under review as well as other designated individuals, with one goal in mind, to help ensure quality and consistency of the paediatric development in the US.

The latest addition to the list of legislation bringing focus to the paediatric research is the Food and Drug Administration Safety and Innovation Act (FDASIA) signed into law on July 9, 2012. The purpose of FDASIA is to both renew and strengthen three essential laws to improve the safety and effectiveness of pediatric drugs, biological products, and medical devices used in children: the BPCA, the PREA, and the Pediatric Medical Device Safety and Improvement Act.

The most important measure brought forth by the new legislation is to make BPCA and PREA permanent. Previously, both Acts were subject to sunset periods, a way to evaluate the need and results from enacting them. By making BPCA and PREA no longer subject to reauthorization every five years, FDASIA ensures acknowledgement by drug developers that pediatric product development programs must be considered during overall product development and that children will have a permanent place on the agenda for drug research and development in the US. Furthermore, FDASIA requires earlier pediatric study plan submission by drug manufacturers subject to PREA and gives FDA new authority to help ensure PREA requirements are addressed

in a more timely fashion. These improvements will help spur pediatric drug development and speed pediatric drug information to patients and providers.

From a pharmaceutical company perspective, the permanent reauthorizations eased concerns that drug developers may have felt in initiating pediatric studies conducted under BPCA or PREA. In addition, it provided assurance the program would continue, and decisions on timing of this aspect of product development could be designed with confidence in the program's future availability. Additionally, Title IX, section 908, amends the FD&C Act (21 USC 360aa et seq.) to establish a priority review voucher program to encourage treatments for rare pediatric diseases.

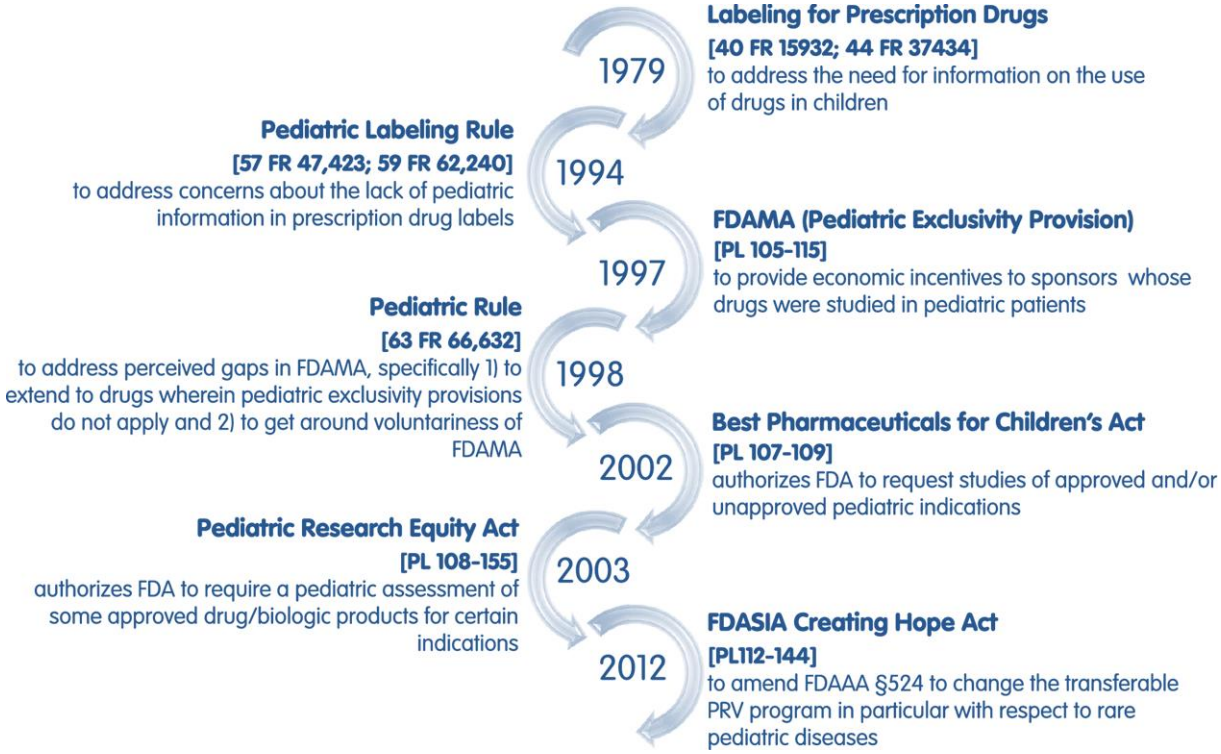

Figure 2-6 History of U.S. Pediatric Regulation

2.2.4 Incentives for conducting and completing paediatric research in the US

In the US and contrary to Europe where all paediatric development would be eligible for rewards when a completing a PIP, only one of the acts created, namely the BPCA,

provides incentives and rewards for paeditric drug development while the PREA makes it mandatory.

Under the BPCA, when the terms of the WR have been met and studies were conducted using good scientific principles, the company is awarded an additional 6 months of exclusivity. The exclusivity awarded after review by the FDA Pediatric Exclusivity Board attaches to all existing marketing exclusivities and patents for the drug moiety and similar to the EU the paediatric exclusivity does not require positive pediatric studies.

Even if technically reward can only be claimed through the BPCA, if a mandatory PSP is made under PREA, the sponsor may become eligible for the reward (ie, 6 months exclusivity) by proposing studies in a BPCA WR (PPSR) procedure.

An incentive also available for paediatric development is the voucher program set up in 2007 by the US Congress. Although its use is limited to rare diseases, it is undoubtedly an interesting tool to consider in such cases for the three-dimensional impact it has on the commercial value of a product, first on the competitiveness, second being the time-value and last the exclusivity.

At first the program did have provisions regarding paediatric drugs, however in 2012, through the enactment of the FDASIA which included Section 908 the "Rare Pediatric Disease Priority Review Voucher Incentive Program" it was extended to rare pediatric diseases.

To be eligible for a pediatric voucher, the drug must check the below requirements:

- Be considered novel which is determined if it contains no active ingredient that has been previously approved by FDA and qualifies for priority review (in addition to the bonus priority review), and
- Allows treatment of a rare pediatric disease by relying on clinical data from studies examining a pediatric population and dosages of the drug intended for that population and not seek approval for an adult indication in the original rare pediatric disease product application.

The program allows that following approval by the FDA of a treatment for a neglected or rare pediatric disease the developer then receives a voucher for priority review for a different drug. Two drugs receive priority review for each voucher: the drug winning a voucher for a neglected or rare pediatric disease, and the drug using a voucher for another indication. One of the commercial incentives of the program is from the fact that a voucher may be sold from one company to another (e.g. a small company winning a voucher for developing a drug for a neglected disease sells it to a large company for use on a commercial disease). Priority review means that the FDA aims to render a decision in 6 months. In contrast, the FDA aims to complete a standard review in about 10 months. The voucher program is intended to reduce two types of inefficiency, its primary purpose is to motivate more treatments for neglected and rare diseases and at the same time allows speedy approval of potential new therapies in the US.

		Tropical	Rare Paediatric Disease
	Legislation	FDAAA (2007)	FDASIA (2012)
Voucher winner	Program Expiration	None	October 2020
	Eligibility	List of neglected diseases defined by the FDAAA	Rare paediatric diseases (advice can be sought from the FDA to know whether it qualifies)
	Obligations for voucher winner	None	Winner must market drug within a year and report to FDA about use of drug within five years
Voucher user	Notification	90 days prior to voucher redemption	
	Transferability	Unlimited	
	Additional user fee	$2,457,140 in fiscal year 2019	
	Voucher expiration date	None	

Figure 2-7 Overview of the Voucher Program Incentive

Another incentive is related to medical devices and the efforts made by the FDA to optimize and foster paediatric medical device development since few medical devices are indicated and labeled for a pediatric population when compared to the offer observed for adults. With increasing numbers of novel devices approved for adults, the number of devices approved for pediatrics has also increased. However, despite legislative and regulatory changes designed to incentivize pediatric device development with the PMDSIA enacted alongside the FDAAA in 2007, the percentage of novel devices approved for use in pediatric populations over the past decade has been relatively stagnant. It turns out that the problems observed for drugs are indeed the same when it comes to the use of medical devices in paediatrics, a lack of devices designed, evaluated, and approved for this populaiton, which leads to off-label use of devices. Even if some products are specifically-designed for paediatrics, designing pediatric medical devices can be as challenging as developing drugs for this populaiton: children are often smaller and more active than adults, body structures and functions evolve throughout childhood, and children may be long-term device users bringing new concerns about device longevity and long-term exposure to implanted materials. Therefore the FDA set up in 2007 a program facilitating the development, production, and distribution of pediatric medical devices through funding of nonprofit consortia responsible for mentoring, supporting, and providing regulatory and marketing consultation to pediatric medical device developers. This initiative is still active and was renewed in 2012 with the FDASIA alongside other measures which might prove beneficial to the development of medical devices (f.i. Least Burdensome Standard, review of the 510k guidance, Humanitarian Device Exemptions).

2.3 Résumé de la deuxième partie

Les autorités de santé que sont l'EMA et la FDA ont toutes deux reconnues le besoin de développer des obligations légales, ainsi qu'un système récompensant les entreprises pharmaceutiques mettant en place des études pédiatriques dans l'optique

de pouvoir enfin collecter des informations sur l'impact des traitements dans la population pédiatrique et tenter de remédier au problème de l'utilisation hors-AMM.

Malgré la volonté des autorités de santé de développer un cadre réglementaire promouvant le développement pédiatrique, le processus législatif dans les deux régions fut long et difficile avant d'arriver à la publication de réglementations américaines et européennes efficaces.

En Europe, ce besoin reconnu de longue date par les autorités était implicitement inclus dans les réglementations mais aucune mesure n'était mise en place afin de permettre la collecte d'information pédiatrique. Les prémices d'une réglementation européenne arrivèrent en 1997 lorsque des experts conviés par la Commission Européennes parvinrent à débattre du défaut d'information observé pour les médicaments pédiatriques et réussirent à arriver au consensus sur la nécessité d'introduire un système de récompenses spécifique au développement pédiatrique. Après plusieurs années de développement, et poussé par l'impulsion donnée par la publication de l'ICH E11, le Parlement Européen publia le 1er juin 2006 la réglementation pédiatrique 1901/2006 qui entra en vigueur début 2007. Les principaux objectifs de cette réglementation sont au nombre de trois : améliorer la qualité et l'éthique de la recherche pédiatrique, augmenter le nombre de médicaments disponibles pour cette population, et enfin faire grandir la connaissance médicale sur l'utilisation des médicaments pédiatriques en s'assurant d'éviter la mise en place d'études injustifiées. Pour se faire la réglementation repose sur trois piliers, le Comité Pédiatrique (PDCO), le Plan d'Investigation Pédiatrique (PIP), et le tant espéré système spécifique d'obligations et récompenses.

Ce manque d'information observé en Europe était aussi présent aux Etats-Unis entraînant également dans cette région une utilisation non contrôlée et hors-AMM des médicaments initialement approuvés dans la population adulte. Dans ce contexte, la FDA a mis en place de nombreuses initiatives durant la dernière décennie afin de faire évoluer la vision dépassée qu'était celle d'enfants considérés comme de « petits adultes », à celle de patients distincts qui ont tout autant besoin d'être protégés par des recherches poussées sur les médicaments utilisés dans cette population.

Plusieurs « Actes », le dernier en date étant le Food and Drug Administration Safety and Innovation Act (FDASIA), amendant la législation américaine virent ainsi le jour et introduisirent, tout comme ce fut le cas en Europe, un système d'obligations et récompenses afin de motiver la recherche dans ce domaine. Ce système repose sur deux « Actes » introduits en 2002 et 2003 et sont respectivement le Best Pharmaceuticals for Children Act (BPCA) et le Pediatric Research Equity Act (PREA), le premier se basant sur le volontariat permettant aux entreprises d'espérer bénéficier d'une période de protection supplémentaire lorsque des études pédiatriques sont réalisées, alors que le second introduisit des obligations de conduire certaines études pédiatriques dans l'indication autorisée chez les adultes.

Deux régions, deux systèmes, mais un but commun qui après plusieurs années d'exécution commence à porter ses fruits.

3 Today: Two Authorities, two regulations, one result?

3.1 EMA *(2, 13, 15, 16, 17, 33)*

As stated above, the European Legislation came into force in January 2007, which is applicable across the all EU Member States with respect to medicinal products for paediatric use. This legislation aims to enhance the safety of medicines for children by increasing research, development and authorization of medicines based on specific paediatric experience, without subjecting the paediatric population to unnecessary clinical trials.

Furthermore, this legislation set specific requirements for the pharmaceutical industry regarding the development of medicines for paediatric use, as well as providing incentives to the industry for undertaking such developments. Since the implementation of the Regulation, from 2007 until 2016, 267 new medicines for use in children and 43 new pharmaceutical forms appropriate for children were authorised in the EU.

As drug development is a lengthy process, it was expected that no immediate impact would be seen after the entry into force of the Regulation. However given time, more and more paediatric development took place and after a few years the number of new medicines/indications receiving authorisation for use in children had more than doubled with 68 drugs in the three years preceding the Regulation compared to 31 in the 2012-2014 timeframe.

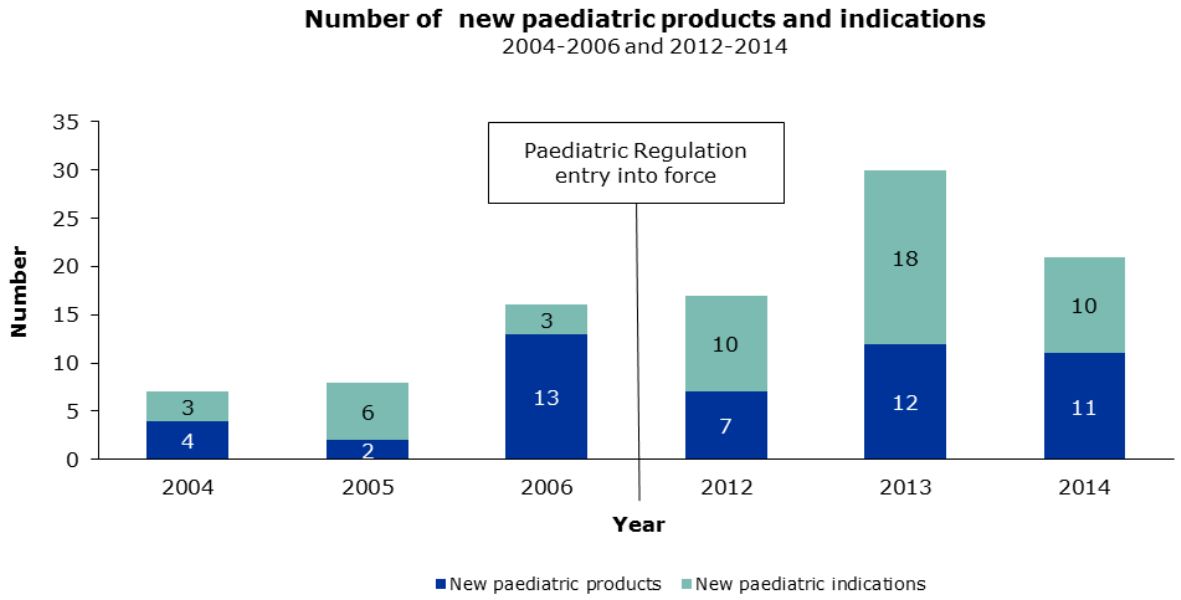

Figure 3-1 Number of centrally authorised medicines for children in 2004-2006 and 2012-2014 (new initial marketing authorisations, new paediatric indications)

All the data collected so far, thanks to the measures set by the Regulation and the studies conducted by the pharmaceutical companies, has been of tremendous help in improving the knowledge of both the drugs and the children as well as the treatment of this specific population (new indications, safety information, warnings, and contraindications).

Before 2007, around 19,000 reports had never submitted to a regulatory agency on completed paediatric studies. As mandated by Article 45, these were provided after 2007 by pharmaceutical companies to the EMA or to the national competent authorities depending on the authorisaiton process used for the concerned drugs. Within 8 years, 62 Article 45 assessments of centrally authorised medicines and 2219 for nationally authorised medicines were completed, which resulted in approximately 140 updates of the product information and 16 new paediatric indications including in areas where no paediatric medicines were approved. This clearly represents a significant outcome based on data that would have not otherwise been used.

In the first ten years since the entry into force of the regulation, paediatric trials discussed by the PDCO and then included in PIPs increased to about 80 per year

which can be counted as a significant increase since it represents almost 30% of all paediatric trials as recorded in the EU Clinical Trials database, with an overall increase from 9.3% in 2006 to 12.4% in 2016 of clinical trials involving children per year compared to all clinical trials per year when taking into account the remainder of the trials being deferred for lack of sufficient data to initiate them safely.

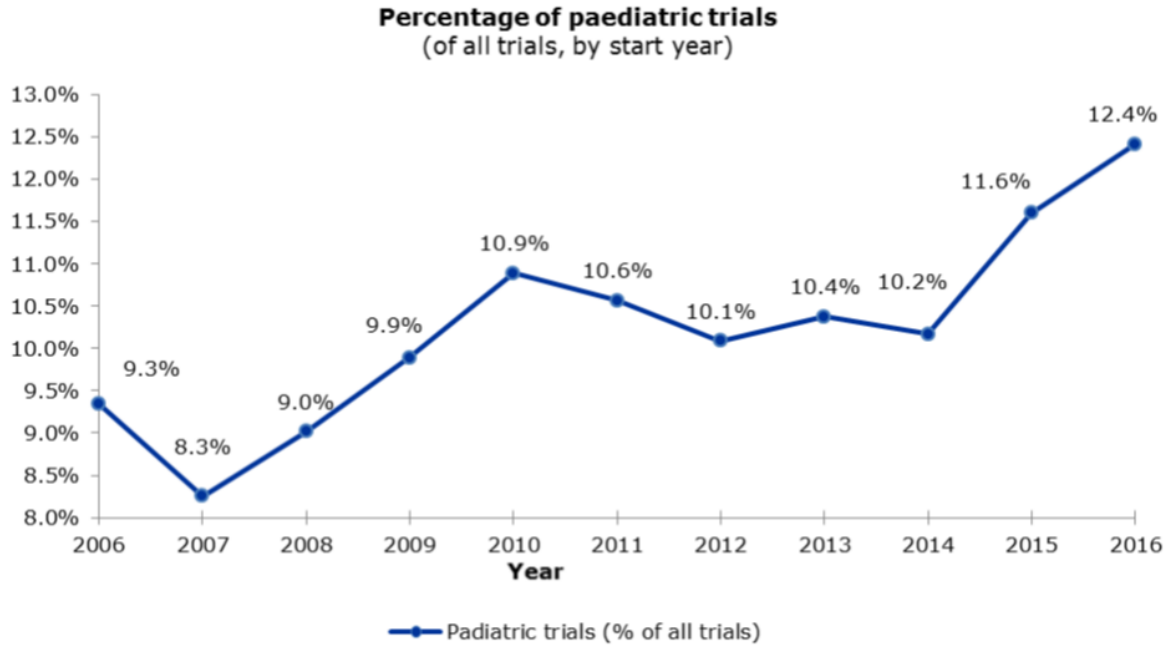

Figure 3-2 Proportion of clinical trials that include children

Nonetheless, it is important to note as well that regarding paediatric trials which are expected to contribute data for regulatory submissions in the scope of the Paediatric Regulation, the number of studies conducted in Europe almost doubled from 96 in 2007-2009 to 164 in 2014-2016, giving high hopes that children will be able to enjoy better care and personalised treatment.

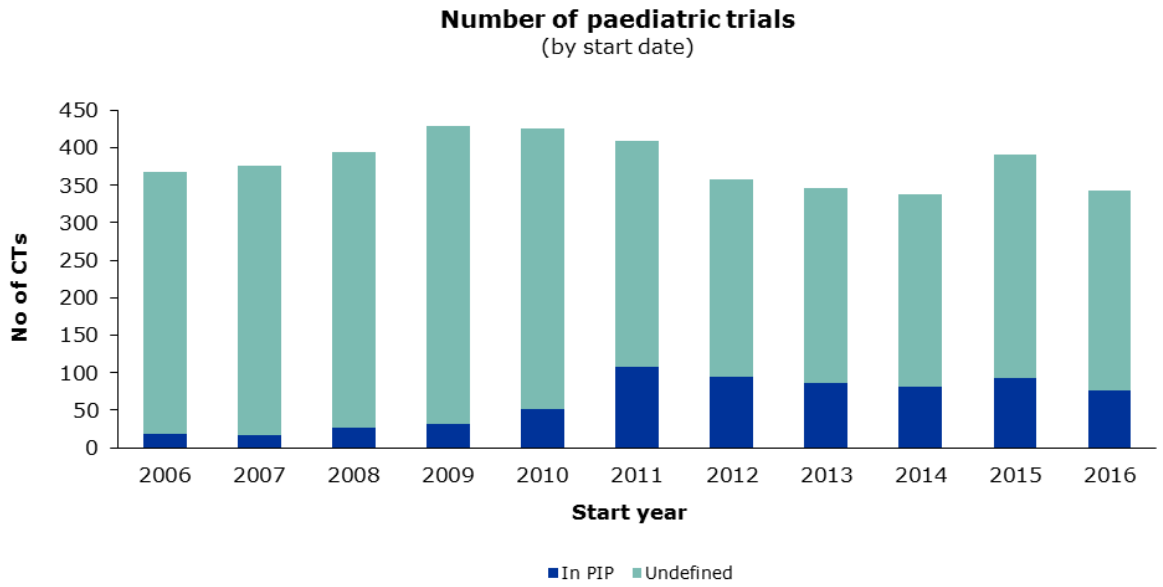

Figure 3-3 Absolute number of authorised paediatric clinical trials by start date

PIP being the main tool introduced by this regulation to help meet the medical need in children, it is interesting to see that they have also been used for a substantial proportion of medicines previously used off-label as well as for medicines that have additionally received orphan designation. Also the information on ongoing and completed PIPs has become public knowledge through publication of EMA decisions and of information on paediatric clinical trials, both measures providing guidance for new drug developments and assisting in the prevention of duplications in paediatric development.

To put it into perspective, from 2007 to 2016 the PDCO issued agreement for 950 PIPs, with a quarter including neonates, while also granting 475 waivers in specific cases for one or more indications. Moreover, both the EMA and the Member States stood fast in enforcing the incentives and helped the manufacturers by granting scientific advice for almost 800 and 350 product developments respectively.

During the same period, a substantial number of modifications to the agreed PIPs were submitted to the PDCO and resulted in a median of 1.5 years delay in the planned completion of modified PIPs. The most common modifications were related to the timelines for completion of the PIP where sponsors required delays to strive for a timely

completion, as well as the reduction of the sample size needed in the age groups participating in the studies. It was believed to be the result of the observation of other modifications in different studies and the need to further adapt the design of the agreed studies to ensure the possibility of submission of the trials data as early as possible.

As mentioned above, once a PIP is completed the applicant in order to be able to pass the validation of applications for either marketing authorisation (Article 7) or variation/line extensions (Article 8) must request the PDCO to do a compliance check as per the provisions of Article 23 of the Paediatric Regulation. Over the years the number of opinions from the PDCO on Compliance checks have steadily increased, and in 2016 it was reported that the Committee had issued positive compliance checks for 131 agreed PIPs, implying the completion as per the requirements set by the PIP of the full paediatric programme.

Similarly to what had been observed for data under Article 45 of the paediatric regulation, data for 360 active substances have been submitted since 2008 under Article 46, and led to over 80 recommendations to update the summary of product characteristics for both nationally and centrally-approved medicines.

The Paediatric Regulation also introduced a system of obligations and rewards which has proven to be effective in stimulating paediatric development of medicines as demonstrated by the high number of agreed PIPs, paediatric clinical trials, and new medicines for children. However, those incentives alone have also shown their limits as it is obviously shown by the lack of interest for the PUMA incentive and related reward only for the paedaiatric indication, created to stimulate voluntary paediatric research into off-patent medicines which are of interest to children, for which only two instances of products using it have been authorised in 9 years.

Overall in the EU, the Paediatric Regulation has had a very positive impact on paediatric drug development, as shown by the data collected during the first nine years after entering into force. The implementation of the regulation by the European regulatory network during this period has proven to be a complex process. The regulation has led to successful changes in the development and authorisation process

of medicines and brought about a major increase in awareness of paediatric needs in regulatory interactions. Paediatric considerations have now become an integral part of any pharmaceutical development across the EU and are taken into account from the outset of the life-cycle of each medicine.

Other initiatives introduced at the time, such as Enpr-EMA, have brought a new spirit of collaboration and open exchange between all actors. In turn it has facilitated systematic paediatric medicine development as set out in PIPs, and contributed to the involvement in both paediatric research and development by all stakeholders of this field, which as hoped allowed for more paediatric medicines and more information on paediatric use of medicines to become available.

The Paediatric Regulation has undoubtedly led to the development of many medicines for the treatment of paediatric diseases, however, challenges remain and sometimes it appears that the development of paediatric medicines is not necessarily driven by paediatric needs but rather by medicine development for the adult market. This can be illustrated for instance by a the high number of completed PIPs in areas such as HIV infection where research and development are flourishing, while other areas such as paediatric oncology and neonatology are being neglected by the industry, a problem which was also brought forward regarding the discrepancy between disease burden and the number of agreed PIPs is seen in various therapeutic areas.

It is still necessary to address challenges, difficulties and consequences in order to achieve the objectives more efficiently, and to progress regulatory science on paediatric medicine development. Challenges in carrying out paediatric research, including the rarity of many childhood diseases, heterogeneity of the population and issues regarding consent, mean that efforts are needed to obtain good evidence with as few subjects as possible and prevent unnecessary clinical trials. In that regard, new approaches that have been agreed include in particular extrapolation in more than 50 PIPs as of 2016. In addition, innovative trial designs, as well as explicit integration of modelling and simulation into the development, allowed paediatric developments even in areas with historically very limited or no paediatric research.

The new regulation allowed a culture shift that promotes awareness and the generation of quality data in paediatric clinical research. The changes due to the new requirements have led to a substantial increase in the proportion of clinical trials including children in the past ten years. This has already begun to translate into new authorised medicines and improved paediatric information. Since the publication of the 5-year Report in 2011 to the European Commission, several process improvements have been implemented by the EMA, such as less detailed PIP opinions to allow flexibility and to accommodate changes based on emerging data during the medicine development. Furthermore, to encourage discussions on the paediatric needs that could be addressed with a specific medicine so called early paediatric interaction meetings have been introduced. Those changes, albeit only the first steps of many to perfect the regulation at hand, are expected to further improve the positive impact of the Paediatric Regulation and make even more medicines available to children with appropriate information in the years to ome.

3.2 FDA *(2, 24, 27, 28, 29)*

In 2002 and 2003 respectively, the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA) entered into force, providing an incentives such as six months of marketing exclusivity for products studied in response to a WR for paediatric studies from the FDA when doing paediatric development.

Thanks to those changes, it was observed that between July 1998 and September 2011, 90% of the FDA approved labeling changes were related to studies requested under BPCA or required under PREA. However in 2007 another review of the progress of paediatric studies required under the PREA legislation showed that delays could be observed for the studies in place. It was sadly seen that almost 80% of drug studies and 60% of studies on biological products were either not completed or were finished late.

Figures from the FDA were also publishes as part of the “Pediatric Exclusivity Statistics” which as the name states are related to the implementation of pediatric exclusivity and pediatric studies. These statistics showed that as of August 2010, the

FDA received 610 PPSRs and issued 394 WR (320 with PPSR and 74 without PPSR), and at the same time the FDA granted pediatric exclusivity for 173 approved drugs. Furthermore between September 2007 and June 2010, 273 studies (efficacy and safety studies as well as PK and safety studies for the most part) were completed under the BPCA and/or the PREA as following the implementation of the FDAAA. The total number of products under BPCA and PREA amended by FDAAA was 38 and 65, respectively as of August 2010 which showed the interest of the paharmaceutical industry for the new BPCA incentives.

The Pediatric legislation in the United States was most recently updated in 2012 with the Safety and Innovation Act, which includes among its provisions that the two previously introduced acts being the PREA and the BPCA, become permanent.

This major change comes from the fact that the BPCA and the PREA have shown to be effective tools to answer the need of paediatric information. It is the FDA's belief that the FDASIA has allowed to strengthen these two important laws. The successful completion of pediatric studies either voluntary or mandatory under BPCA and PREA respectively has led to the addition of new pediatric information on labeling for over 600 products since the enactment of these acts in the early 2000's with 149 having occurred between 2012 and 2016 after the passage into law of the FDASIA.

Another additional important upside resulting from the framework provided by the two acts is the acquisition of a better understanding of the differences between the paediatric and adult population and their impact on the drug development alongside the significant progress made in study design for this population (f.i. endpoints, biomarkers, exposure-response). This was particularly of importance for the neonate population, with several products approved since 2012. Neonates which are known to be a difficult population to study frst due to the lack of data to identify appropriate endpoints and the inability to extrapolate efficacy from adults but also because trials are sparse due to multiple scientific, regulatory, and ethical challenges.

Continuous efforts have been made by the FDA since 2002 (enactment of the BPCA and the PREA) to increase the number of trials in this less than well-defined population.

In that regards, the FDA established following the FDASIA a Neonatal Subcommittee of the PAC whose purpose was to address the challenges regarding study design, study implementation, and ethics encountered whenever facing drug development in this population.

In order to tackle the recurring critical need for reporting of adverse events in the pediatric population, the FDA has also put in place a pediatric-focused postmarket surveillance with safety reviews presented to the Pediatric advisory committee which provide much needed information on the paediatric population (e.g. safety information, unexpected adverse events). One of the benefits of the pediatric postmarket surveillance and public reporting to the PAC comes from the fact that it is triggered by the pediatric information from paediatric trials that results in new labeling. Those trials are recognized to be difficult to set up and that is why even findings from a negative trial for pediatric studies are included in the labeling. The importance of this fact comes from the potential off-label use of drugs available for adults in paediatrics. An 18 month post-labeling activity has been created in that regard to provide an estimate on “real world” use of these products in children and has been of great help in gaining insight as to the use of drugs in the paediatric population. In the three years following the enactment of the FDASIA, the PAC was presented 87 products for review which allowed the identification of important safety signals. This led to a Boxed Warning (being the FDA’s strongest warning) for a product, and the manufacturers were required to develop safety strategies to protect children.

From the FDA’s standpoint, the implementation of pediatric-focused provisions under the FDASIA could be considered successful. However the agency did agree that even though both the BPCA and the PREA amended by the FDASIA have been instrumental in improving pediatric labeling and drug research, some future modifications may be warranted for further improvements and specific recommendations were made in 2016 by both the FDA and stakeholders for further consideration for a future amendment of the legislation:

- Yearly Review of Humanitarian Device Exemptions,
- Possible Modification of Orphan-designated Products from PREA,

- Potential Removal of Vaccines from PREA.
- Paediatric oncology drug development,
- Dependency of the PREA requirements on the adult indications,
- Exclusion of drugs with orphan indications,
- Empowering FDA to require pediatric plans at the end of Phase 1
- Award of 6- month exclusivity upon completion of a Written Request even prior to approval of an adult indication.

From the stakeholders's perspective, mostly agreed that the BPCA and the PREA had been successful in improving information about pediatric uses for approved drugs and biologic products, creating more treatment options for children and significantly improving pediatric patient safety and children's health, and that the permanent reauthorization of the BPCA and the PREA gave necessary insurances to invest in the paediatric research.

Another welcome innovation was the introduction of the international cluster which was seen as an opportunity to minimize existing barriers between the different regions and tackle the challenge of enrolling subjects in pediatric studies, even if an increase in transparency from the authorities in the future would be greatly welcome to further help the paediatric development (summary reports, safety concerns, innovative approaches).

It is certain that significant progress has been made since the FDAMA in 1997 in the US with over 600 products containing new pediatric information in labeling, however it is also clear that all parties still see areas lacking proper structure or support from the legislation in the paediatric development and further evolution in the regulatory landscape will be required in the future.

3.3 EU vs US: Is one system better than the other? *(2, 7, 13)*

Over the years, the culture around paediatric development has changed following the implementation of legislation in the EU and US which have allowed a progressive but definite evolution in both research and clinical practice. Indeed, more attention has

been given to the needs of children, to formulations, extrapolation and off-patent medicines than there was in the past.

All of the above sums up the reasons why there have been significant and continuous advances in the regulatory framework for the paediatric development in the two continents. Nonetheless the systems which have been put into motion have shown limitations and differences which require all actors of the scientific field, regulators, investigators, pharmaceutical companies and parents' associations to work together to address those problems.

A number of issues have been pointed out throughout the use of the regulations in both the EU and the US:

- Ensure a closer relationship between all actors.
- Work around the limitations of incentives and the waiver systems in place to better tackle the unmet need.
- Continue discussion on the ethical issues of the paediatric development.
- Ensure a better cooperation between agencies.

At the core, the primary goal of both European and American legislations is identical and strive to improve children's health through various evolutions in research and advancements to provide a regulatory framework for evaluation of efficacy and safety in the pediatric population.

Figure 3-4 Similarities between US and EU Pediatric Regulations

However due to being developed by separate authorities, one aiming for a more homogeneous regulatory landscape for 27 countries each one having had for too long a time the prerogative to interpret the needs of their own patients through local legislation, and another allowed to control its own regulatory landscape through centralized governmental power, the regulations now into force do show substantial differences on how they tackle the unmet need of paediatric development in their respective regions.

The first major difference between the two regions resides in the fact that in Europe, the EMA has unified the incentives and requirements under one single legislation while in the US the pediatric exclusivity and requirement programs are separate legislations with different legal frameworks in the form of the PREA and the BPCA, Therefore, should the applicant want to obtain the exclusivity reward separate documents, processes, and timelines need to be followed as described in the BPCA which requires FDA to issue a Written Request, on top of those set to meet the pediatric research obligations of the PREA.

Also the changes brought by the new EU regulation occurred in a shorter time frame when compared to the enactment of the US legislation, since 2008 all applications for new marketing authorization must contain results of studies conducted in compliance with an agreed PIP in the EU unless a waiver or deferral had been granted beforehand and the same applies since 2009 for all applications for new indications, new routes of administration, or new pharmaceutical forms. In the US even though the BPCA and the PREA were enacted in 2002 and 2003 respectively, they were only confirmed as permanent in the legislation after the FDASIA in 2012.

The PeRC in the US and the PDCO in the EU have similar responsibilities, mainly to review the WR and the PIP, respectively. The WR and the PIP differ as well. The WR is voluntary and issued by the FDA, usually following a proposed pediatric study request (PPSR) from the sponsor. The PIP is mandatory and proposed by the sponsor. The PIP addresses non-clinical requirements, complete product quality including age-appropriate formulation, and includes waiver and deferral requests, whereas the WR includes age-appropriate formulations statements, might include non-clinical studies, and does not include a waiver or deferral.

Orphans are also a point where both legislative framework diverge. In the EU, pediatric development is mandatory for all new medicinal products under development unless a waiver is granted, however in the US orphan-designated drugs are exempted from paediatric development under the PREA while still being eligible to the voluntary process of the BPCA which in turn may allow if complied with to get the exclusivity reward. Interestingly, the contrary applies when biosimilar products are concerned, they are exempt from paediatric studies in the EU but not from the US where PREA requirements for pediatric product development apply.

Another important contrast between the framework in the EU and the US is the timing of the paediatric development plan. The European PIP should be agreed at the end of Phase 1 while the American PSP should be agreed at the end of Phase 2, even if experience has shown that the theoretical advantages for early engagement are often outweighed by the fact that studies included in paediatric plans are deferred for considerable periods.

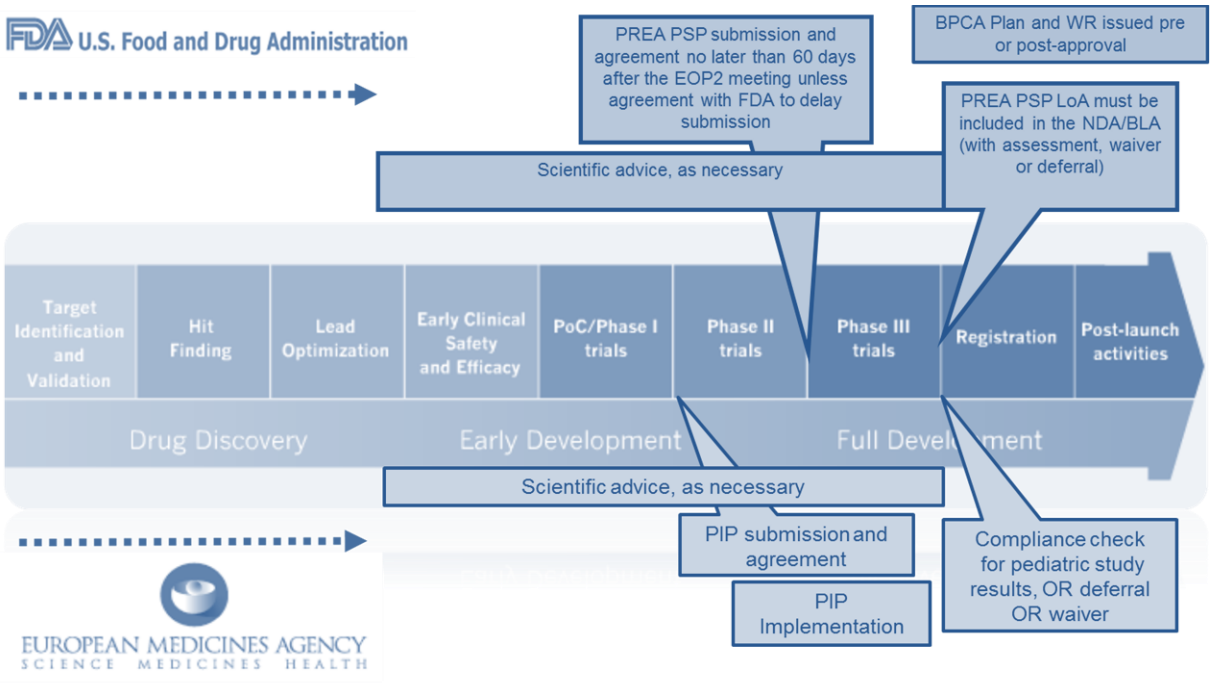

Figure 3-5 Interactions with EMA and FDA for Pediatric Plans

The scope of the legislative requirements is another notable difference for the EU and the US. The EU legislation uses the term "*condition*" and broadly interprets this term, contrary to the US where legislation for the requirement applies only to the adult indication. Therefore, should the adult indication not occur in the pediatric population, a full waiver will be granted under PREA for the conduct of pediatric studies. Hence, in the US, pediatric-specific diseases must be approached using the BPCA exclusivity process.

Like for any medicinal product put on the market, post-marketing surveillance is performed by FDA and EMA. The difference lies in that fact the in the EU for paediatric products the same safety monitoring approach as the one used for the adult population, and in the US an additional process mandated by the US pediatric legislation requires the FDA to have a pediatric public safety assessment by the Pediatric Advisory Committee for all products evaluated under BPCA or PREA.

A common prerogative of the EMA and the FDA is that both agencies can impose post-authorisation measures to the paediatric development, in the EU, this process is supervised by the Pharmacovigilance Risk Assessment Committee (PRAC) while in the US, it is under the control of the FDA Review Divisions.

However, since the paediatric trials are often initiated by the pharmaceutical companies in both regions, the differences observed in the process, even if taken into account while preparing the applications, timing gaps between the PIP and the PSP can happen and sometimes result in the need to modify the trials. In that aspect another legislative difference is found in the ability of the FDA to modify the required paediatric development plan, either the PSP or the WR on its own, while the EMA depends on the applicant to propose a request for modification to the agreed PIP.

Despite the abovementioned differences in legislation and processes which can at times hinder the proper development of the paediatric drugs, both legislation frameworks do align on common scientific principles and are designed to incentivise and ensure a timely, ethical, and scientifically sound development of products in the paediatric population. The goal of both agencies is to achieve in the future global development of more therapeutics in pediatric patients with the objective of labeling them for safe and effective use and also ensuring that this applies to negative pediatric studies which must be reflected in product labeling.

	EU	US
Legislation	• 1 piece of legislation • **Paediatric Regulation** (Mandatory): PIP	• 2 pieces of legislation • **PREA** (Mandatory): applies to drugs and biologics, for all NME and line extensions (PSP) • **BPCA** (Voluntary): applies to drugs and biologics in exchange for 6 months exclusivity (PPSR : WR)
Orphan drug	No exemptions	Exempted from PREA/eligible under BPCA
Timing of submission	No later than the completion of adult human PK studies ("End of phase 1")	No later than 60 days after EoP2 Meeting (The LoA received is expected to be submitted with the NDA/BLA)
Submission of Pediatric data	At time of MAA submission unless deferral, product-specific or class waiver is agreed	Data to be included at the time of NDA/BLA unless a deferral or waiver is granted
Indications	PDCO may request widening of the proposed pediatric indication, but only within the condition	FDA has authority to require pediatric studies only for on-label indications for PREA (not for BPCA)
Consequence of non-compliance	• MAA, Type II variations, line extensions will not be validated (+ no reward) • Financial penalties, "Name & Shame"	• US dossiers can be 'Refused to File' if no PSP is included in the NDA/BLA • Companies can receive a Warning Letter if studies are not PREA compliant
Reward	• Non-orphan products : 6 months SPC extension • Orphan : 2 years' market exclusivity • PUMA : 8+2 years data protection	For BPCA: 6 months data exclusivity to be attached to other exclusivities and patents of small molecules (exclusivities only for biologics)
Latest time to submit data for reward	2 years before patent expires	For BPCA: 15 months before patent or data exclusivity expires

Figure 3-6 US Pediatric Requirements incorporating FDASIA in relation to EU Paediatric Regulation

3.4 Tomorrow: A unique way to look at a global paediatric development? *(7, 13, 15, 16, 17, 23, 24, 30, 33)*

Children deserve medicines that are adapted to their needs and that is why the need to include children in drug development has been recognised increasingly over the past few decades.

For more than 20 years, paediatric development underwent progressive changes in both the American and European legislations. The agencies set their own regulations and subsequent amendments to make the legislation evolve in order to finally cross the terms "therapeutic orphans" from their records.

The regulatory authorities have reviewed a substantial number of pediatric evaluations in recent years and pharmaceutical companies have gained insight and become familiar with the pediatric regulations. Furthermore, numerous regulatory documents have been provided in the hopes of streamlining and helping the pharmaceutical

industry go through the specific procedures and to answer specific scientific questions regarding study design and conduct. However since pediatric drug development is a very complex area, many questions remain open, and close collaboration and communication between industry and health authorities is essential.

The health authorities in the U.S. and the E.U. show a strong commitment to promote better medicines for children. The pediatric legislations have built a complex framework for pediatric drug development and the pharmaceutical industry has to deal with different requirements and special obligations to receive the incentives. The preparation of the PIP in the EU or of the PSP in the US is a major task for each clinical development team and pediatric aspects have to be integrated early in the drug development.

These differences can be largely attributed to the two legislations in the US. While the PIP in the EU covers both the requirements and the incentives, in the US, the incentives are covered by the WR (under the BPCA) and the requirements by the pediatric plan (under PREA).

Even before full implementation of European pediatric regulation, it became clear that pediatric trials must be coordinated on an international level in order to prevent children from being enrolled in duplicative trials.

As a result of these differences, the Office of Pediatric Therapeutics is working with the scientific experts in the various FDA Centers to coordinate monthly conference calls with the EMA alongside Japanese, Canadian and Australian regulators, collaborators with whom was created through the Paediatric Cluster a transatlantic framework of complementary incentives and obligations that are intended to increase the development and availability of age-appropriate medicines for pediatric use and facilitate regulatory discussions on global development of paediatric medicines. This collaboration between health authorities with exchange of information has three main goals related to the paediatric development:

- Avoid exposing children to unnecessary trials,
- Enhance the science and

- Decrease the risk to children during pediatric drug development.

The meetings of the Paediatric Cluster first took place in 2007 shortly after the first PDCO meeting. The cluster meetings are monthly teleconferences held between EMA and FDA, and also representatives from the Canadian, Japanese, and Australian agencies participate.

The agencies, each month, exchange documentation on ongoing procedures. Ongoing PIP, iPSP, and PPSR applications are discussed at the meetings, where the FDA and EMA strive to seek a harmonized approach and, whenever possible, consensus on their requirements for the individual plans. Thus the paediatric cluster meetings can hopefully assist in creating a true global development program for the pediatric population, and in the first ten years since the cluster inception, 438 products and 138 more general topics have been discussed, and by the end of 2016, the cluster had held 129 virtual meetings, with exchange of information on paediatric developments of common interest.

Over two dozen different issues were discussed, with the most common topics being the scope of pediatric development, safety issues, and study design. This international collaboration resulted in the resolution of many pediatric trial and safety issues, and it has been critical to development of common trial designs and publications.

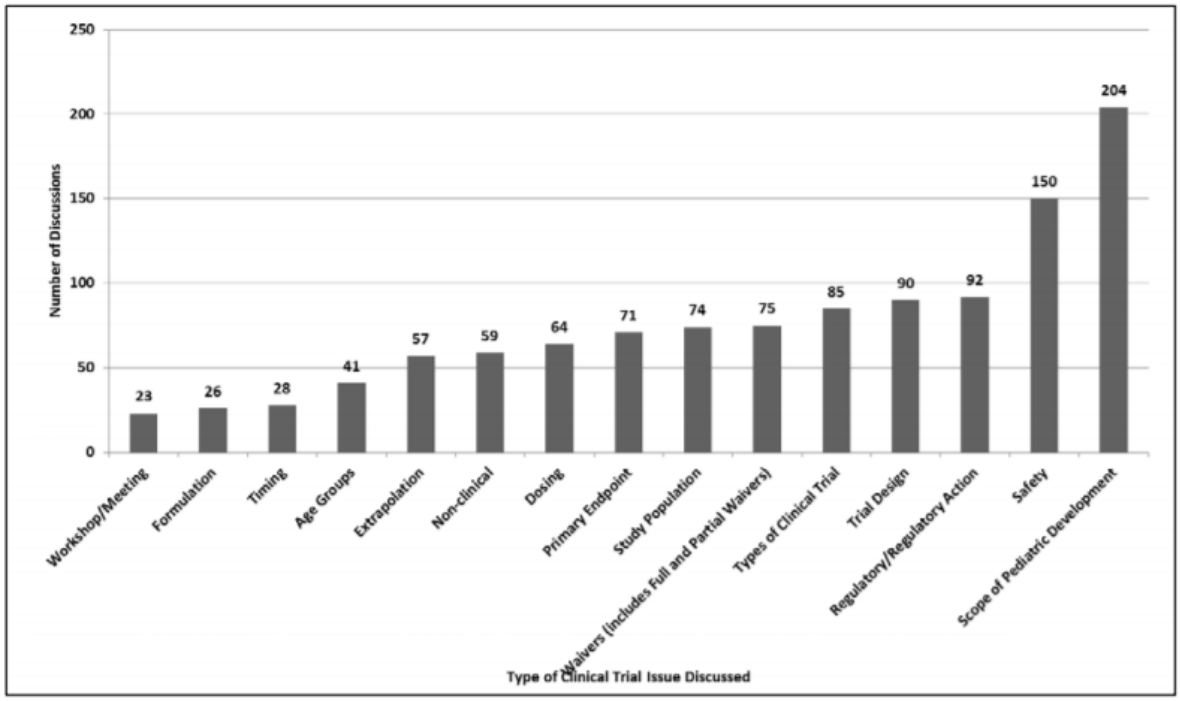

Figure 3-7 Frequency of clinlical trial issues discussed at Pediatric Cluster between 2007 and 2015

Since 2012, for topics meeting certain criteria, the FDA and the EMA developed a one-page “Common Commentary” document to inform sponsors about the discussion and any high-level conclusions by the regulators and as of 2016, 16 Common Commentaries had been completed.

This inter-agency communication does not imply that pediatric development programs will turn out to be exactly the same protocols or objectives or even afterwards arrive at the same regulatory decisions, but it is nonetheless a first and important step towards a harmonized regulatory framework for pediatric drug development.

The “Pediatric Cluster,” is only one of several similar groups addressing a variety of topics related to medical product development and regulation, all of which have one common goal, to work towards a harmonized global regulatory landscape for the paediatric population.

3.5 Résumé de la troisième partie

En Europe et aux Etats-Unis les données recueillies durant cette première décennie depuis la mise en place des réglementations pédiatriques démontrent que ces dernières ont eu un impact significatif sur le développement pédiatrique. Cela a permis d'aboutir à des modifications dans les processus de développement et d'autorisation, et a renforcé la détermination des acteurs pour continuer de développer le cadre règlementaire maintenant en place.

Les autorités ont montré un intérêt grandissant au fil des ans afin de promouvoir de meilleures possibilités thérapeutiques pour la population pédiatrique. Ainsi un cadre réglementaire complexe s'est mis en place dans chacune des régions, que cela concerne la préparation du PIP en Europe ou bien celle du PSP aux Etats-Unis, imposant de cette façon à l'industrie pharmaceutique d'adapter le développement thérapeutique afin de répondre aux nouvelles obligations mais également dans le but de pouvoir prétendre aux récompenses prévues par les réglementations.

Malgré le nombre grandissant de soumissions effectuées et évaluées, permettant aux acteurs de devenir de plus en plus efficaces dans la mise en place d'études pédiatriques, le développement de tels médicaments reste une tâche complexe et une poursuite de la collaboration entre les acteurs dans les années à venir est primordiale afin d'assurer au mieux la protection de la population pédiatrique.

Il devint évident que cette collaboration ne pouvait se limiter au pays ou la soumission est effectuée, c'est pourquoi les autorités américaine, européenne, australienne, canadienne et japonaise ont mis en place un réseau de collaboration réglementaire nommé le « Pediatric Cluster » dont l'objectif est de discuter des différentes études, des problèmes rencontrés, ou des évolutions potentielles des réglementations afin de voir un jour apparaître un cadre commun d'obligations et récompenses et améliorer le développement à l'échelle mondiale et la mise à disposition de médicaments pour la population pédiatrique.

Cette collaboration inter-agences n'est en réalité qu'une parmi d'autres adressant le problème de la divergence des obligations de développement ou de cadre

réglementaire entre les continents, sans pour autant assurer que les objectifs des études discutées seront identiques entre les différents pays. Cela laisse entrevoir la volonté des autorités d'aboutir un jour à un cadre réglementaire harmonisé.

Conclusion

Il y a près de trente ans, l'Europe et les Etats-Unis ne disposaient d'aucun cadre réglementaire pour les produits pédiatriques. Aujourd'hui, après des décennies passées à faire évoluer les législations en place, au travers de nouvelles lois, actes ou amendements et ce dans l'optique d'arriver à une harmonisation réglementaire entre les deux régions. Il est possible d'arriver à la conclusion que, même si des évolutions et améliorations du cadre en place restent encore à réaliser, les autorités ont enfin pris conscience de la nécessité d'outils permettant un développement pédiatrique aussi strict que celui observer dans la population adulte.

Les résultats présentés ici étant basés sur des réglementations différentes, une analyse comparative objective de ces derniers reste complexe, toutefois les avancées observées et les résultats propres à chaque région montrent distinctement que les réglementations pédiatriques ont eu un impact bénéfique et permettent d'espérer une augmentation significative des produits disponibles en pédiatrie dans les années à venir.

Cette évolution de la réglementation pédiatrique est malheureusement limitée à ces deux régions du globe, il est possible d'espérer qu'une harmonisation globale verra le jour dans un future proche et permettra à la population pédiatrique mondiale de bénéficier des mêmes avancées règlementaires.

From no regulation almost thirty years ago in both the EU and the US, to two major regions with thriving legislations and agencies striving through new laws, acts or amendments to attain a globally harmonized regulatory framework, it can be said that paediatric drug development is now, if not completely addressed, at least the authorities have recognized the need for a continuous effort in ensuring the safety and efficacy of the drugs in such a fragile population.

Although the results presented above are based on different legislations and thus difficult to compare, both evaluations show clearly that the pediatric legislations overall

have been very successful and will further increase the number of drugs tested and labeled for children.

One can hope that one day these ever-evolving regulations will change alongside those developed for adults on a global scale and not involve only some restricted parts of the world.

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Titre de la thèse : American and European Paediatric Regulations: After decades in the making, a worldwide concern addressed by uneven local regulations

Mots-clés : regulation, act, paediatric development, paediatric committee, incentives, rewards, global harmonization, EMA, FDA, ICH, PREA, BPCA, FDASIA

Résumé:
Clinical trials are the backbone of modern evidence-based medicine. However, the volume of clinical trials involving children had been substantially lagging behind their adult counterparts in the early 1990's for a simple reason, the lack of a proper regulatory framework promoting such development in a very peculiar population.
Sadly, because of a lack of knowledge on either the efficacy or the safety of the drugs in the paediatic population at the time, medicine-related tragedies occurred and prompted the authorities to reach a consensus on a much needed regulatory framework, allowing more studies to be initiated in order to obtain paediatric information for medicines used in children.
Decades were necessary to define the current regulations in both Europe and the United States, allowing a better development and standard of care for paediatrics thanks to different systems of incentives and rewards put in place to stimulate the development of those drugs.
Nonetheless hurdles still exist which hopefully will be tackled in the years to come in this ever evolving field in order to finally reach the same standards of care as the ones observed in the adult population.

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