Universidade de Lisboa

Faculdade de Farmácia

PAEDIATRIC MEDICINES REGULATION IN EUROPE: EVOLUTION IN DRUG DEVELOPMENT

Cátia Filipa Guerreiro Abrantes

Dissertation supervised by Professor Catarina Reis
and co-supervised by Professor Dinah Duarte.

Master in Regulation and Evaluation of Medicines and Health Products

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“Healing is a matter of time,
but it is sometimes
a matter of opportunity.”
Hippocrates

To my lovely husband

To my parents and brother

To my grandmother (*In memoriam*)

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ABSTRACT

The European Regulation on Paediatric Medicines adopted in 2007 aimed at solving the problem of the use of non-paediatric medicines. This Regulation creates incentives for the development of medicines in paediatrics which, because of their characteristics, have a low commercial interest in the pharmaceutical industry and, therefore, are lacking in the market without therapeutic alternatives.

Since 2007, there has been a positive impact of this Regulation on the availability of medicines to the paediatric population, considering its objectives. The development of paediatric drugs became integrated into the overall development of the drug, through the consideration of this population in a dedicated Research Plan, considering the potential paediatric use of these drugs. Several new medicines have been authorised, with paediatric indications and pharmaceutical forms suitable for these age groups. The high number of approved Paediatric Investigation Plans also indicates that there are other medicines under development, and information about the paediatric population has definitely had a significant increase.

This dissertation aims to describe the evolution of the implementation of the European regulation on paediatric medicines and, consequently, its impact on the development of new medicines for this population.

Specifically, it will characterize the efforts created to develop new clinical trials and drugs indicated for the paediatric population, identifying the paediatric therapeutic needs as well as best practices in managing "off-label" use.

The use of unauthorised paediatric drugs, while legitimate, is a serious and real concern. The consequences related to the treatment of children with unsuitable formulations and therapeutic regimens that have not been adequately proven in a certain age group (off-label use) may be subtherapeutic - failure of therapy and continuation of the disease - or eventually toxicity and may lead to negative and potentially serious effects on the child's growth and development.

Keywords: paediatric medicines regulation, paediatric formulations, paediatric off-label prescription

RESUMO

O Regulamento Europeu sobre Medicamentos Pediátricos, adotado em 2007, teve como objetivo solucionar o problema da utilização de medicamentos não pediátricos nesta população. Este regulamento cria incentivos para o desenvolvimento de medicamentos em pediatria que, devido às suas características, têm um baixo interesse comercial na indústria farmacêutica e, portanto, estão ausentes no mercado sem alternativas terapêuticas.

Desde 2007, houve um impacto positivo deste regulamento na disponibilidade de medicamentos para a população pediátrica, considerando os seus objetivos. O desenvolvimento de medicamentos pediátricos integrou-se no desenvolvimento geral do medicamento, através da consideração desta população num plano de investigação dedicado, considerando o potencial uso pediátrico desses medicamentos. Vários novos medicamentos foram autorizados, com indicações pediátricas e formas farmacêuticas adequadas para essas faixas etárias. O elevado número de planos de investigação pediátrica aprovados também indica que existem novos medicamentos em desenvolvimento e que as informações sobre a população pediátrica tiveram definitivamente um aumento significativo.

Esta dissertação tem como objetivo descrever a evolução da implementação do regulamento europeu sobre medicamentos pediátricos e, consequentemente, o seu impacto no desenvolvimento de novos medicamentos para esta população.

Especificamente, caracterizará os esforços criados para desenvolver novos ensaios clínicos e medicamentos indicados para população pediátrica, identificando as necessidades terapêuticas pediátricas bem como melhores práticas na gestão da utilização “off-label”.

A utilização de medicamentos de uso pediátrico em "off-label", embora legítima, é uma preocupação séria e real. As consequências relacionadas com o tratamento de crianças com formulações e regimes terapêuticos inadequados que não foram adequadamente comprovados para esta faixa etária podem ser subterapêuticas - falha da eficácia terapêutica e progressão da doença - ou eventualmente toxicidade e podem levar a efeitos negativos e potencialmente graves no crescimento e desenvolvimento da criança.

Palavras-chave: regulação de medicamentos pediátricos, formulação de medicamentos pediátricos, prescrição "off-label" de medicamentos pediátricos

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ABBREVIATIONS

ADI – Acceptable Daily Intake
BPCA – Best Pharmaceuticals for Children Act
EC – European Commission
EMA – European Medicines Agency
EU – European Union
FDA – Food and Drug Administration
FDASIA – Food and Drug Administration Safety and Innovation Act
GVP – Good Pharmacovigilance Practice
ICH – International Conference on Harmonisation
iPSP – initial Paediatric Study Plan
IV – Intravenous Administration
MA – Marketing Authorisation
MAA – Marketing Authorisation Application
MHLW – Ministry of Health, Labour and Welfare
NDA – New Drug Approval
ODT – Orodispersible Tablets
PAC – Paediatric Advisory Committee
PD – Pharmacodynamics
PDCO – Paediatric Committee
PEG – Paediatric Expert Group
PG – Propylene Glycol
PIP – Paediatric Investigation Plan
PK – Pharmacokinetics
PMDA – Pharmaceuticals and Medical Devices Agency
PPSR – Proposed Paediatric Study Request
PREA – Paediatric Research Equity Act
PSP – Paediatric Study Plan
PUMA – Paediatric-Use Marketing Authorisations
SmPC – Summary of product characteristics
SPC – Supplementary Protection Certificate
UK – United Kingdom
US – United States
WR – Written Request

1. PREVIOUS NOTE

Paediatric Regulation came into force in 2007, for the development and authorisation of paediatric medicines aiming to improve children's health in Europe. This regulation was created to enhance the development of more medicines for children, design clinical trials targeted to the paediatric population and, consequently provide more and better information about medicines for children.[1]

Before 2007 and the implementation of Paediatric Regulation in Europe, the majority of medicines were not adequately studied or authorised for the paediatric population. Consequently, paediatric clinical practice was based on off-label prescriptions which led to an increased risk of adverse events. This situation has brought several difficulties and challenges for both prescribers and pharmacists treating children.[2]

This regulation has created the Paediatric Committee, responsible for evaluate Paediatric Investigation Plans (PIP) intended to guide the development of a medicine in the paediatric population. The submission of a PIP is one of the obligations of the pharmaceutical industry to encourage the development of paediatric medicines in therapeutic areas with a greatest need.[3]

At the time of its implementation, Paediatric Regulation also required companies to submit any existing paediatric studies on authorised medicinal products not previously submitted, for scrutiny by regulatory authorities.

The entry of this regulation in Europe resulted in several benefits in paediatric medicines development, such as the growth of high quality information and research towards paediatric needs.[4,5]

However, given the scarcity of medicines with a paediatric indication, off-label use in different pathologies has become a common clinical practice over the years.[6] This reality has led to several associated risks, namely potential prescription errors that can be detected in pharmaceutical validation and unexpected adverse effects.

Problems arising from the inexistence of drugs appropriately adapted to paediatric use include inadequate dosage information that can led to potential overdosage with an increased risk of adverse reactions, including death, and potential ineffective treatment due to underdose. Also, unavailability of appropriate formulas and administration routes for the paediatric population has led to the use of magistral or officinal formulations, which may prove to be of poor quality for the treatment of this population.[7–10]

The purpose of the present analysis is to identify changes in the paediatric medicines field over the years and the efforts that have been made to develop appropriate medicines for children at different ages.

1.1. Objectives

This study aims to describe the evolution of the implementation of the European paediatric medicines regulation and, consequently, its impact on the development of new drugs for this population.

Specifically, it will characterize the efforts to develop new dedicated clinical trials and medicines indicated in the paediatric population, identifying paediatric medical needs and best practices in the management of the off-label use.

1.2. Methodology

The methodological approach will be the narrative literature review, together with critical analysis and evaluation of bibliographic and regulatory sources of information relevant to paediatric medicine's development, since the inception of the Paediatric Regulation.

1.3. Dissertation Structure

The present dissertation is divided in 8 chapters.

Chapter 1 presents a previous note to the dissertation, as well as the proposed objectives and the applied methodology.

Chapter 2 details the developments in European regulation, considering all the initiatives that have been made for the development of paediatric medicines, with a brief comparison with the Food and Drug Administration (FDA) and the Pharmaceuticals and Medical Devices Agency (PMDA) paediatric regulation.

Chapter 3 presents the main stages of paediatric drug development and the underlying limitations of each stage.

Chapter 4 describes the challenges present in paediatric pharmacotherapy, especially for the prescriber as well as the pharmacist in hospital environment.

Chapter 5 presents therapeutic needs in paediatrics, focusing the principal clinical areas of unmet medical need.

Chapters 6 and 7 presents the discussion and conclusion of this dissertation, discussing in general the analysis made during the development of pediatric drug regulation and efforts that have been made through the years, considering all progress and identifying the current paradigm in paediatrics nowadays.

Chapter 8 lists the bibliography quoted throughout the dissertation.

2. INTRODUCTION

2.1. Historical background in the UE

The European environment of Paediatric medicines was discussed in 1997 at a meeting organized by the European Commission (EC), at the European Medicines Agency (EMA), by a group of experts, where the main conclusions were to create a system of incentives.[11] In the next year, the EC required an international discussion on paediatric clinical trials development with International Conference on Harmonisation (ICH) and as a result it was created the guideline "Note for guidance on clinical investigation of medicinal products in the paediatric population" – ICH Topic E11. This guideline came into force in 2004 ensuring children's protection in clinical trials.[12,13]

In November 2001, the EC Pharmaceutical Committee discussed this paediatric medicines paradigm, leading to the publication by the EC in February 2002, of the document "Better Medicines for Children - proposed regulatory actions in paediatric medicinal products".[14–16]

The Paediatric Expert Group (PEG) was established at the EMA also in 2001. This working aimed of issuing scientific opinions on medicines for paediatric use, in an attempt to improve the existing situation regarding the rational use of medicines in this population. Composed by members from different EU countries, this group had scientific expertise related to paediatric use and development of medicinal products as well as scientific knowledge in galenic development of pharmaceutical formulations, pharmacokinetics, toxicology and paediatric pharmacology.[17]

In 2006, the European Parliament adopted the "Regulation of the European Parliament and of the Council on Medicinal Products for Paediatric Use: European Regulation on Medicinal Products for Paediatric Use". In this same year, the EC published 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" to simplify and develop harmonised clinical trials in each Member State.[13,15,16,18]

Concluding, the Paediatric Regulation is comprised by "*Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use*" and by "*Regulation (EC) No 1902/2006*"[10], amending the original text regarding to decision procedures for the EC.

Table 1 - Chronology of Paediatric Drug-related events in Europe - History of Regulatory Initiatives.[19]

Date	Regulatory Initiatives
December 1997	EMA and EC expert meeting: European legislative support needed to encourage research and study of medicines in children
December 2000	Resolution of the European Council of Health Ministers: call for EC to draw up proposals to improve the situation of paediatric medicines
November 2001	EC Pharmaceutical Committee meeting: genesis of the European Commission's Consultation Paper on Medicinal Products for Children (EC 2002a)
February 2002	EC publishes "Better Medicines for Children - proposed regulatory actions in paediatric medicinal products" (EC 2002a)
June 2002	EC publishes Reflection Paper on Better Medicines for Children: document integrating comments received during consultation (EC 2002b)
September 2004	EC approves the first "Proposal for a Regulation": "Proposal for a Regulation (…) on medicinal products for paediatric use". (EC 2004)
November 2005	EC approves the "Amended Proposal for a Regulation": after the European Parliament vote in September 2005 (EC 2005)
March 2006	EC publishes "Commission Communication on the Common Position on the paediatric regulation": Positive opinion on the amendments to the Regulation (EC 2006a)
June 2006	European Parliament approves the "Regulation of the European Parliament and of the Council on medicinal products for paediatric use": Paediatric Regulation (EC 2006b)
July 2006	EC publishes "Commission opinion on European Parliament amendments to common position": Positive opinion on Paediatric Regulation (EC 2006c)
December 2006	Regulation (EC) No 1901/2006 of the European Parliament and of the Council on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20 / EC, Directive 2001/83 / EC and Regulation (EC) No 726/2004 (EC 2006d)

In 2007, the implementation of the Paediatric Regulation came into force with the purpose of facilitate the development and access to medicinal products for paediatric use, to ensure that medicinal products used to treat the paediatric population are investigated with high-quality methods which takes ethical principles into account and is appropriately authorised, improving the available information on the use of medicines in different groups of the paediatric population. These objectives should be achieved without subjecting children to unnecessary clinical trials and without delaying the authorisation of medicinal products for other age groups.[10,15,20]

Therefore, this regulation aims in having more paediatric research, develop more medicines for children, and to give a better product information.

Paediatric Regulation brought the need of a scientific committee, which was established at EMA in August 2007, the Paediatric Committee (PDCO), with knowledge and expertise in the development and evaluation of all aspects of paediatric medicines. The PDCO has the fundamental responsibility on the evaluation and approval of PIP, also assuming an essential role in the various support measures established by the Paediatric Regulation.[16,21]

With the introduction of the Paediatric Regulation, a system of obligations, rewards and incentives was created to encourage the pharmaceutical industry to research and develop medicines for the specific therapeutic needs of children. This system establishes obligations for companies to progressively increase the number of products with paediatric indications, by studying each new product they develop for potential use in paediatrics.[22]

Paediatric Regulation also introduced the Paediatric-Use Marketing Authorisations (PUMA) for medicines that are already authorised, no longer covered by a supplementary protection certificate (SPC) or a patent that qualifies as a SPC, and to be exclusively developed for use in children. The development of a PUMA must follow an approved PIP by the PDCO.[10,16]

After the first three years of the Paediatric Regulation EMA has published a report in 2011, about pharmaceutical companies and products that have undertaken paediatric research, and the development and authorisation of paediatric medicines. This first report identifies companies that have benefited from the incentives and rewards laid down in the Regulation (Article 50(1) of the Regulation), as well as companies that have failed to comply with any of the obligations. Since then, EMA publishes an annual report on benefits and infringements under the Paediatric Regulation.[20,23]

In the same year, the EC invited healthcare professionals and patient associations to be part of the PDCO. In 2013, the European Commission published a progress report on medicines for children covering the five years since the Paediatric Regulation first came into force, which concluded that better and safer research, more medicines for children on the EU market and more information for parents and healthcare professionals has been produced since 2007.[20,24]

This new guideline published in 2014, simplifies the structure of the previous guideline, establishes a list of key elements of a PIP and introduces increased flexibility into the application process.[20]

In 2016 and 2017 an expert meeting with Member States and the EMA and a meeting for responses to the consultation to gather stakeholders' experiences of the EU Paediatric Regulation, have been conducted.[20]

2.2. Regulatory Developments and Initiatives in Paediatric Medicines Development since the Paediatric Regulation

Considering that for several years the paediatric population did not have any specific regulation for their protection, the major regulatory development was the implementation of the Paediatric Regulation with a great impact on the development of paediatric medicines in the EU.

The data collected during the last 10 years, since the implementation of the Paediatric Regulation, from 2007 until 2016, allow us to conclude that the impact was positive, with 267 new medicines for use in children and 43 new pharmaceutical forms appropriate for children authorised in the EU. In fact, it resulted in more medicines for children as well as better and more information for prescribers and patients, better paediatric research and development, more regulatory support in paediatric challenging areas and has confirmed paediatric development as being an integral part of medicine development.[22]

After 10 years, the Paediatric Regulation has brought an EU network of researchers and trial centres carrying out paediatric research, an inventory of paediatric needs, a public database of paediatric studies, and a requirement for companies to submit any existing paediatric studies on authorised medicinal products for scrutiny by regulatory authorities.[20]

The mandatory requirements for the pharmaceutical industry foreseen in the EU paediatric regulation have also brought incentives and rewards. This system of requirements and incentives was necessary, so that there could be more industry involvement in the development of paediatric medicines.

Paediatric medicines have an extra 6 months of patent protection for unauthorised and/or patented medicines and an extra two years of market exclusivity for orphan medicinal products.

Table 2 demonstrate the key elements of the Paediatric Regulation in relation to the different phases of the medicine during its development:

Table 2 - Paediatric Regulation key elements.[15]

Innovative and/or patent-pending medicines	Non-Patent Drugs
Paediatric Investigation Plan (PIP)	AIM for paediatric use
Extension (6 months) of supplementary protection certificate	Possibility of public funding under Community research support programs
Extension (2 years) of commercial exclusivity for orphan medicinal products	

Naturally, before Marketing Authorisation (MA) requested for unauthorised and/or patented medicinal products, there is a need for agreement with the PDCO on the paediatric development and compliance with the agreed PIP.

To ensure that research in children is safe and according to ethics, in some cases, paediatric studies will be deferred until after the adult studies have been conducted, to ensure that research with children is done only when it is safe and ethical. The PIP is required to cover all paediatric age subsets, from neonates to the adolescent, in all paediatric and adult conditions, with an age-appropriate formulation.

Another initiative of the paediatric regulation was the creation of a new type of marketing authorisation (PUMA), that promote the development of off-patent products for use in the paediatric population, to help transform the known off-label use into authorised use that is safer and better framed through the MA, with a 10 year data protection.[1,25]

The European Commission in its 2017 Report has compiled the main developments after ten years of the inception of the Paediatric Regulation[10], based in the EMA's "10-year Report to the European Commission".[22] Some positive trends are presented in the below figures, that could highlight the significant impact of this regulatory tool in paediatric medicines development.

Figure 1 - Evolution of the proportion of clinical trials that include children in the European clinical trial database EudraCT during 10 years of Paediatric Regulation.[25]

Figure 1 shows a notable expansion in the proportion of clinical trials that include children, detailed in the 10-year of the EU Paediatric Regulation Report, with an increase of 50% from 2007 to 2016 (8,25% to 12,4%).[22] It is also important to mention that prior to the Regulation research with neonates was almost non-existent in medicine development and it has raised considerably.[26]

Paediatric Regulation is marked with over 249 new paediatric medicines authorised until 2015, including new marketing authorisations and new indications, as illustrated in Figure 2.

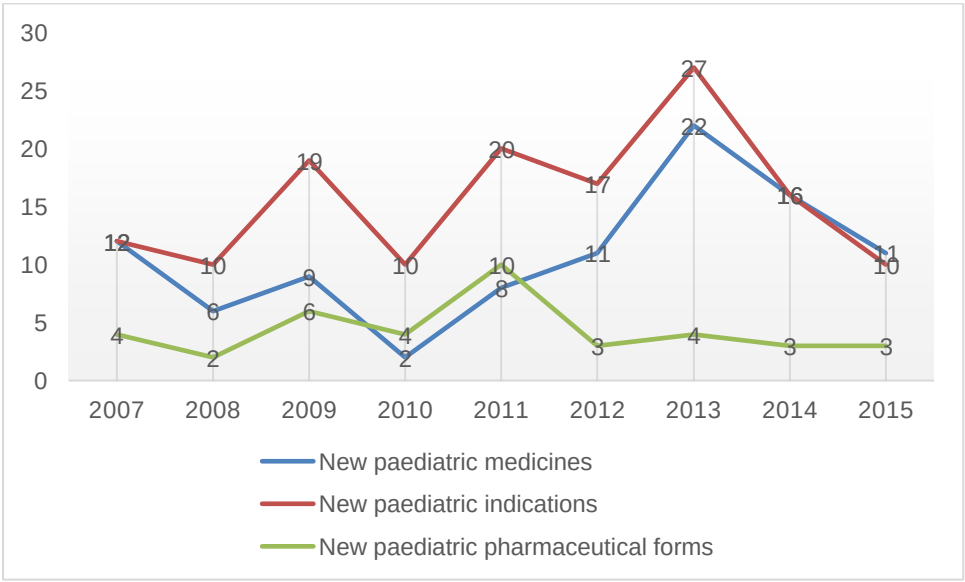

Figure 2 - Number of medicines for children authorised after the implementation of the Paediatric Regulation.[25]

Paediatric Regulation brought, among other major developments discussed in this dissertation, an EU network of networks of investigators and trial centres carrying out paediatric research (Enpr-EMA), an EU inventory of paediatric needs, a public database of paediatric studies, and a requirement for companies to submit any existing paediatric studies on authorised medicinal products for analysis by regulatory authorities. All of these combined promoted high-quality information and high-quality research through other measures, as we can see in Figure 3 the data is remarkable.[22]

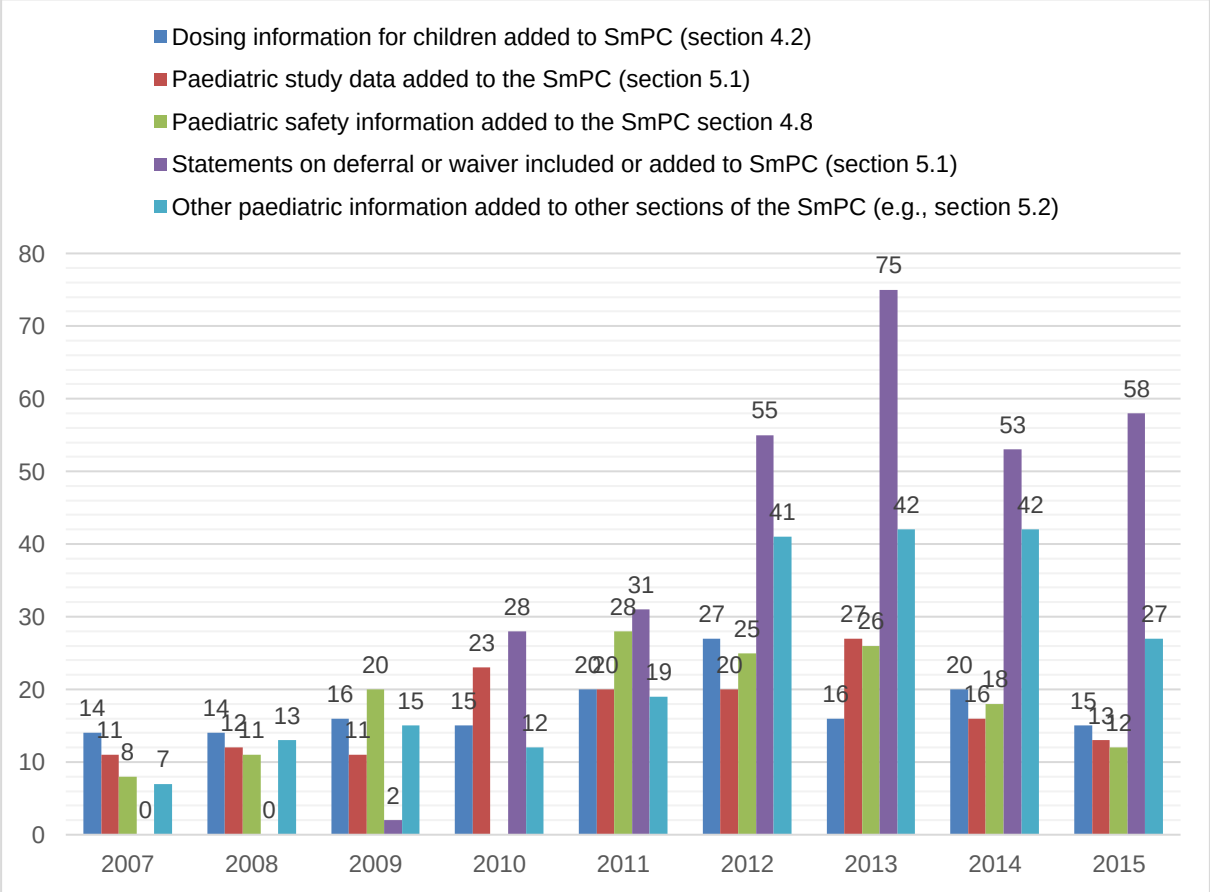

Figure 3 - Increased information on centrally authorised medicines for paediatric use, in Summary of product characteristics (SmPC).[25]

Figure 4 demonstrates very well how PIPs contributed for new developments in therapeutic areas in need for children. The number of agreed PIPs for anti-cancer medicines covered more than 30 different mechanisms of action, which are a promise for further improvements in the future. Data from the "10 years of the EU Paediatric Regulation" shows the number of agreed

PIPs exceeded 1000 in 2017, of which 131 were completed at the end of 2016. There is a clear upward trend in the number of completed PIPs, with over 60% finalised in the last three years.[22]

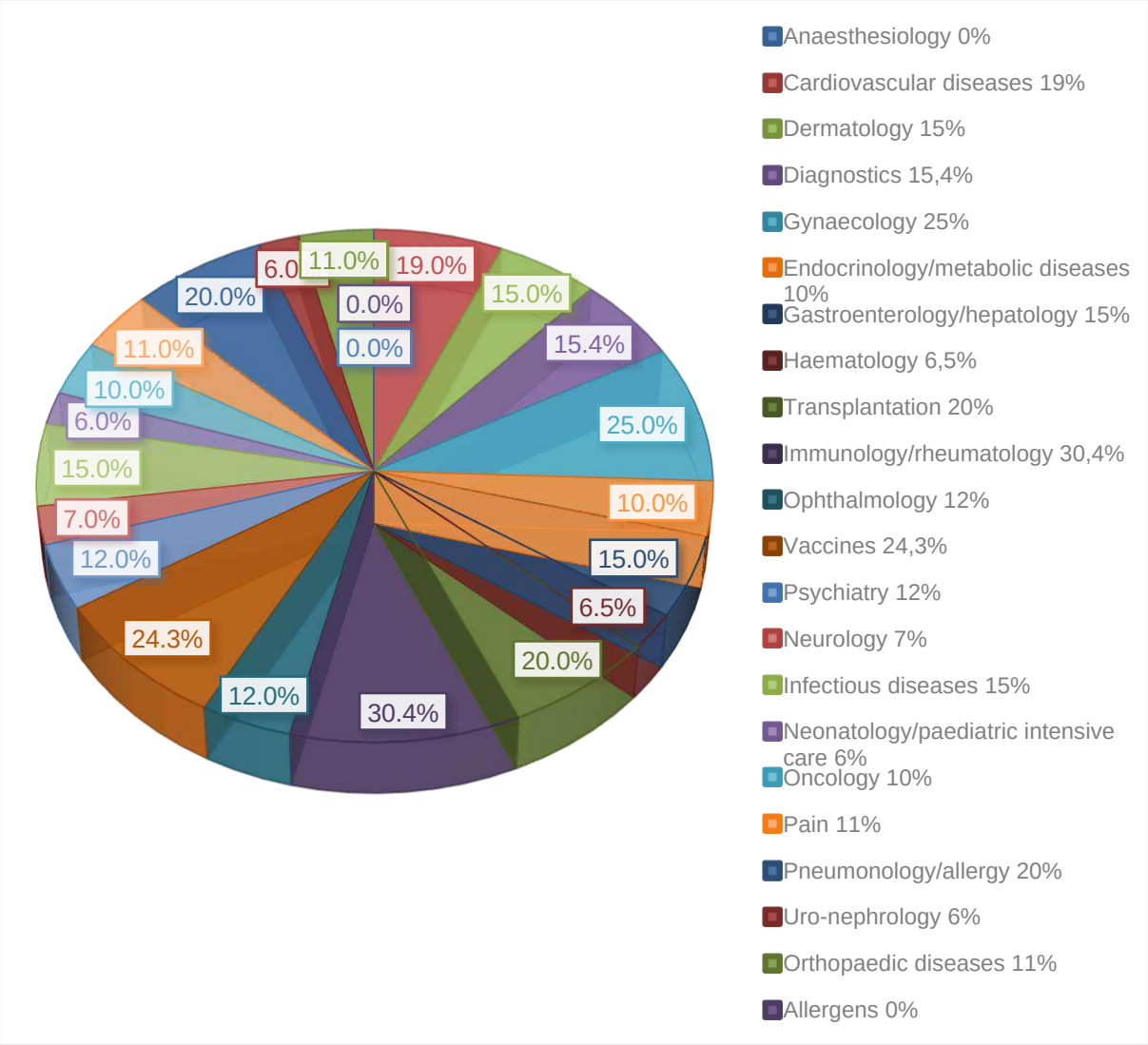

Figure 4 - Therapeutic areas addressed by the Paediatric Investigation Plans (2007 - 2015).[25]

2.3. FDA and PMDA Regulatory Aspects

Regulatory measures on the paediatric development of medicines, taken by other regions, deserve also to be mentioned and analysed.

In 1989, officials from Japan, EU and US gathered in the International Conference of Drug Regulatory Authorities due to the need for harmonization for the new innovative drugs. This led to the establishment in 1990 of the ICH of Technical Requirements for the Registration of Pharmaceuticals for Human Use, a collaborative initiative between the EU, Japan and the US.[4,27]

Food and Drug Administration (FDA)

FDA was the first agency establishing a legislative and regulatory basis for paediatric medicines development, back in 1997.

Currently there are two legislations in force: the Best Pharmaceuticals for Children Act (BPCA)[28] in 2002, which provides incentives although it is voluntary; and, the Paediatric Research Equity Act (PREA)[29], implemented in 2003, which establishes requirements to perform paediatric development under certain circumstances but does not offer incentives. BPCA and PREA were made permanent in 2012, with modifications, in Title V of the Food and Drug Administration Safety and Innovation Act (FDASIA).[2]

The incentives from BPCA are an additional 6-month marketing exclusivity extension of an existing patent or exclusivity for the entire moiety, if the sponsor conducts the studies requested in the Written Request (WR) for which the first period of exclusivity will be granted by FDA. Therefore, the second period of exclusivity will attach only to the specific product studied. The sponsor is under no obligation to conduct the studies specified in a WR, since their conduct is voluntary. Sponsors may request that a WR be issued by submitting to FDA a Proposed Paediatric Study Request (PPSR) and amendments to a WR are feasible only before the requested studies are submitted by the sponsor.[2,28]

Table 3 - Differences between BPCA and PREA.[30]

BPCA	PREA
Provides a financial incentive to companies to voluntarily conduct paediatric studies	Requires companies to assess safety and effectiveness of new drugs/biologics in paediatric patients (Paediatric Assessment)
Drugs and biologics	Drugs and biologics
Voluntary studies	Mandatory studies
Studies relate to entire moiety and may expand indications	Requires studies only on indications under review
Studies may be requested for orphan indications	Orphan indications exempt from studies
Paediatric studies must be labelled	Paediatric studies must be labelled
Incentives: additional 6-month marketing exclusivity extension	Submission of Paediatric Study Plan (PSP) at the NDA to FDA
Written Request issued by FDA	May be a full waiver (all paediatric ages) or partial waiver (a subset of the paediatric population)

BPCA legislation provides the possibility to obtain studies for diseases not encompassed by the adult indication or condition, which is especially relevant for rare conditions and orphan medicines and paediatric-only conditions.[31]

PREA is applicable to determine the safety and efficacy of any product application, either it is a new indication, new active ingredient, new dosage form, new dosing regimen, or new route of administration. In a similar way to the PIP that is submitted in Europe, the PREA requires the submission of a Paediatric Study Plan (iPSP) in the development of any product as described previously.[31]

The PSP is a development plan aimed to identify necessary paediatric studies early in any product development and guarantee that the required data are obtained through studies in children, to support the authorisation of a medicine for children. Therefore, an agreed initial PSP should be submitted as part of any marketing application subject to PREA.[2]

For studies conducted under BPCA or PREA, the US legislation also requires a paediatric-focused safety, quality and efficacy review by the Paediatric Advisory Committee (PAC), similar to PDCO, 18 months after FDA approves a labeling change.[1,2,32]

Pharmaceuticals and Medical Devices Agency (PMDA)

Currently, there is no mandatory regulation for conducting paediatric studies in Japan. That is, PMDA follows ICH E11 "Clinical Investigation of Medicinal Products in the Paediatric Population". There have been several improvements on paediatric drug development, such as the extension of exclusive period, similar to data protection extension as in EU, the council for unapproved drugs/off-label use and national network for paediatric clinical studies.[33,34]

In Japan, the incentives for paediatric research are based on an extension of a product's re-examination period. During this period, data that have been submitted to Japan's Pharmaceuticals and Medical Devices Agency for an innovator drug is protected and not available to generic competitors for their regulatory use. Under Article 14-4 of the Pharmaceutical Affairs Act (2000/12/27), the re-examination period of an approved drug can be extended from 8 to 10 years on the consideration of paediatric use surveys and clinical studies, if the drug is intended for paediatric use. Table 4 describes the re-examination period and the drug type. Currently, this incentive has been of modest value in encouraging

investment in paediatric development.[32] The number of paediatric approvals in Japan is briefly described in Figure 5.

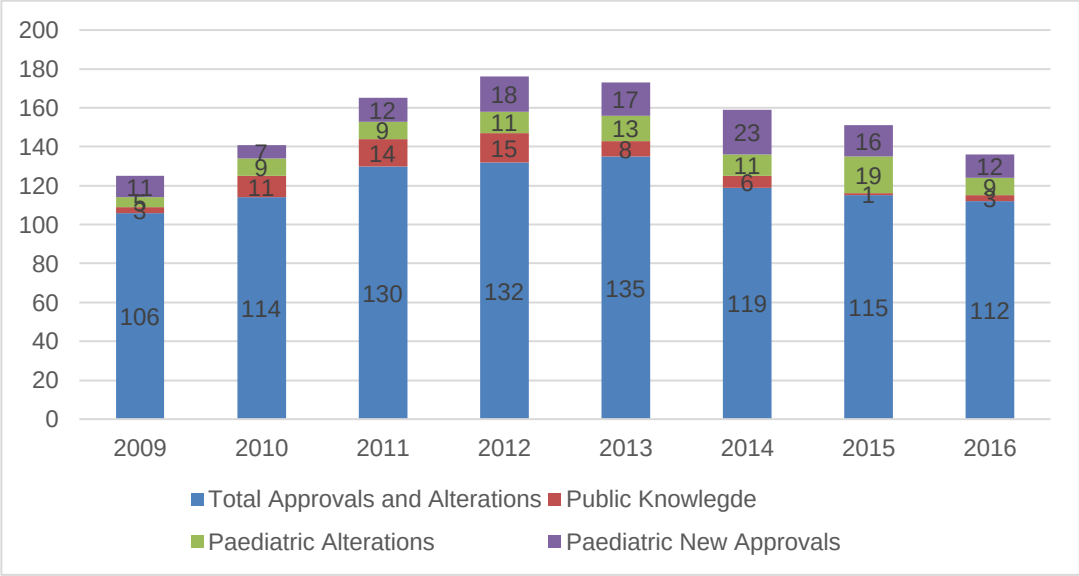

Figure 5 - Number of Paediatric Approvals in Japan (2009 – 2016).[33]

Table 4 - Re-examination Period (market exclusivity and data protection) of New Drugs in Japan.[33]

Re-examination period	Drug type
10 years	Orphan Drugs, Drugs need to be surveyed by pharmacoepidemiological method
8 years	Drugs with new active ingredients
4 years	New combination drugs, Drugs with a new route of administration
4~6years	Drugs with new indications, Drugs with a new dosage

Re-examination period is similar to marketing exclusivity period, re-examination period can be extended to utmost 10 years, if a clinical trial is planned to study paediatric dosage during or after Marketing Authorisation Application (MAA) of a drug, taking into consideration the necessary time to conduct special drug use survey or post authorisation clinical trials.[33]

The Council for Unapproved Drugs/Indications was established in 2010 as advisory council of Ministry of Health, Labour and Welfare (MHLW). This council aims to identify highly-needed unapproved drugs/indications, including paediatrics, which are widely used in at least one of the 6 countries (Australia, Canada, France, Germany, UK and US).

MHLW requests pharmaceutical industries to develop or submit the New Drug Approval (NDA) of designated drugs/indications and, therefore, PMDA reviews NDA on fast track and can accept public knowledge as the basis for approval such as large experience of off-label clinical use in Japan plus clinical data submitted to regulatory authority in one of the 6 countries or utilization described in major medical textbooks or guidance documents.[34]

In August 2007, EMA and FDA monthly established teleconferences between regulators called the Paediatric Cluster to discuss product specific paediatric development (Paediatric Study Plan (PSP) and PIP) and topics related to product classes under the terms of confidentiality agreement. This aims to enhance the science of paediatric trials and to avoid the exposition of children to unnecessary trials. PMDA joined these teleconferences in November 2009 and are now active participants in these monthly exchanges.[33]

In conclusion, although paediatric regulatory framework for these ICH regions have similarities and differences, efforts have been made for the harmonisation of requirements in this field. Such as clinical trials for adult medicinal products, the USA represents the largest percentage of clinical trial developments, followed by the EU and finally Japan. In 2016, 511 paediatric clinical trials were registered by the three major agencies as demonstrated in Figure 6.

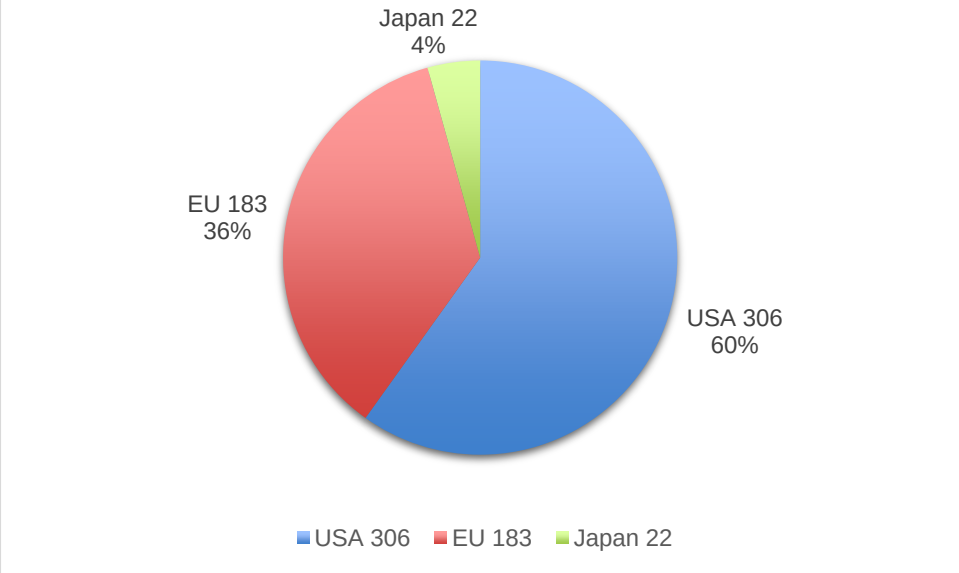

Figure 6 - Paediatric trials in 2016, includes only open studies (source: ClinicalTrials.gov).[33]

2.4. Future Perspectives

The primary goal for these three agencies is identical, although the legislation shows substantial differences. All of them want to improve children's health through improvements in clinical research and to provide a solid system for evaluation of efficacy and safety in the paediatric population through international collaboration.[4,35]

The future perspectives in the UE are now based on putting into practice the action plan proposed by the EC and EMA at the end of 2018, to support the development of medicines for children in Europe. This action plan intent to identifying paediatric medical needs, strengthening

cooperation between decision makers, ensuring timely completion of PIP, improving the handling of PIP applications and increasing transparency around paediatric medicines.[29]

The 2018 Action Plan on Paediatrics[36] was developed focusing in five major improvements: identifying paediatric therapeutic needs, reinforce cooperation of decision makers, ensuring timely completion of PIPs, improving the handling of PIP applications and increasing transparency around paediatric medicines, hoping to perform and accomplish these goals by 2020.

The first one is obviously the factor that has most impact in paediatric drug development, once the therapeutic needs are identified, it becomes easier to work in the specialties in greatest need and thus creating a higher quality of life for paediatric patients.

The second point of this action plan aims to move together towards continuous improvement of efforts and developments, with a view to making progress on sharing experience and information. Cooperation between agencies has proven to be valuable, particularly to the paediatric health advances. When we optimize procedures, we minimize time spent and make progress by sharing experiences and creating strategic alliances.

The third and fourth points are related to PIPs and, in a general way, administrative submission requirements improvements. One of the actions proposed have great importance for paediatric clinical trials progress, which is to publish recommendations to support the conduct of paediatric clinical trials. To facilitate the conduct of paediatric clinical trials by focusing on identification and resolution of factors impeding the conduct of trials in children.

Last but not least, the fifth chapter aims to increase transparency around paediatric medicines, allowing this way to have an Update Community Register of medicinal products with paediatric information and provide information on paediatric trials open for recruitment in a public register, as well as results of such trials in lay language.[36]

3. PAEDIATRIC MEDICINES DEVELOPMENT

The need to develop medicines for paediatric use is due not only to the fact that frequently there are no targeted doses but also because we do not have the appropriate pharmaceutical forms for this population. There are numerous references that demonstrate the high prevalence of "non-appropriate" medicines for children, both at primary and hospital levels.[9,17]
The fact that the use of most drugs in children is not supported by pharmacodynamic or pharmacokinetic results in the different paediatric subpopulations is a common practice. The use of unauthorised or off-label medicinal products is associated with an increased risk of adverse reactions in relation to authorised medicinal products. The lack of adequate information and adequate pharmaceutical formulations may expose children to undesirable adverse effects or under-dosing without the expected efficacy or overdose with consequent toxicity.[37–39]
There are currently existing medicines in the EU, which often do not include information on their safety and efficacy in the paediatric population. Consequently, paediatric clinical practice (particularly in critical situations) involves decisions based on accumulated experience on dose, safety, and efficacy. Prescribing doctors are faced with the dilemma of prescribing medicines for children, without enough information to give them security, or leave their patients without potentially effective and sometimes essential therapy.[40]
Thus, the need for more studies to obtain information on medicines used in the paediatric population is a matter of global consensus. Therefore, it was clear in 2007, that there was a need for a legal obligation for pharmaceutical companies to be able to carry out studies aimed at the development of medicines for use in the paediatric population.[17,41]

3.1. Research in Paediatrics

Over the years, drug research has evolved into continuous improvement allowing its use to be safe, effective and of high quality. The adult population has benefited from this evolution, representing the largest number of the population where the pharmaceutical industry invests the most, unlike the paediatric population.[15]
According to several authors, many of the formulations used in paediatrics are rarely studied in children, which proves the off-label use in paediatrics. This reality indicates that clinical practice in paediatrics is based on experience over the years about the dosages, safety profile and efficacy of some drugs. As a consequence, drugs that are not approved or outside the marketing authorisation terms are used, either for a different indication, dosage or dose.[42,43]
The scarcity of specific drugs and labelling recommendation for the paediatric population is a long-established worldwide problem and evidence-based prescribing for children is

compromised by lack of satisfactory data on many drugs, since around 50% to 75% of medicines used in children have not been studied adequately in the paediatric population.[44,45] What happens in practice is that doses are extrapolated to the paediatric population or the adult formulations are modified, completely ignoring the physiological differences that exist between children and adults. Since pharmacodynamics and pharmacokinetics are not considered and the pharmacotherapeutic choice is made through the practice and responsibility of the paediatrician, safety and absence of risk cannot be guaranteed.[46]

Paediatric research is a controversial subject, there is a need to create clinical trials that prove safety and efficacy in this age group, but questions arise about subjecting children to the potential risks inherent in a clinical trial.[46]

The main reason for this situation concerns economic issues, because the market of paediatric medicines is low. On the other hand, the risks associated with the treatment of the paediatric population are generally higher, requiring monitoring over longer periods of time. In addition, paediatric clinical trials are difficult to design and develop, therefore more expensive, which means that perceived benefit of paediatric drug development does not justify the costs involved in the clinical trial.[47]

The need arose for regulators to create incentives for industry to invest in paediatrics. The introduction of PIP aimed to ensuring that the development of medicinal products that are potentially to be used for the paediatric population becomes an integral part of the development of medicinal products.[48]

Regulatory authorities reviewed a substantial number of PIPs in recent years and pharmaceutical companies became familiar with the paediatric regulations, allowing access to paediatric medicines.[2,44,49]

3.2. Paediatric Pharmacology, Pharmacokinetics and Pharmacodynamics

The importance of studies in children is due to the fact that this age group has large physiological and metabolic differences among themselves, which change the way the drug will act in the body. According to the ICH Guideline[12], the paediatric population can be divided by age subpopulations including preterm and term new-born infants (0 to 27 days), infants and toddlers (28 days to 23 months), children (2 to 11 years) and adolescents (12 to 18 years).[50]

To achieve an accurate dose that is safe and effective for a drug to be used in a neonate, infant, child or adolescent, considerations and interpretations have to be made on the pharmacokinetics (PK) and pharmacodynamics (PD) of the drug, beyond pharmacology.[51]

The absorption of drugs is one of the parameters with great variability between ages. The oral route is preferably in paediatric population, such as inhalation or topic administration, rather than intravenous administration for being more invasive and hardly acceptable by this population.

Oral administration of drugs presupposes that gastrointestinal absorption will be influenced by drug's physicochemical factors and the age-specific physiological parameters, such as gastric pH, intestinal transit time, drug-metabolizing enzymes, and drug transporters., Food and drug formulation are also factors to consider.[52–54]

The drug absorption capacity for each individual of a paediatric population will vary as a result of maturational changes accordingly with all the factors described above.[55–57]

The age difference in the paediatric population translates into different types of maturation, such as changes in intestinal transporters and enzymes and gastrointestinal physiology. One of the most striking examples it is the gastric pH, which is neutral at birth, due to the presence of amniotic fluid in the stomach, and which progressively decreases to acidic values within the first three days after birth.[58]

Another factor to be taken into consideration in the paediatric population is the impact of body composition, namely its influence on drug distribution.[51]

At birth, the percentage of water per kilogram of body weight is much higher than that of adults and decreases over the years, with a marked decrease in the first 2 years of life with subsequent stabilization. Thus, at birth the lipid compartment increases from 10 - 15% to 20 - 25% in late childhood and decreases again to 10 - 15% until adolescence.[50,52,54,59]

Other parameter that influences drug distribution is the lower plasma protein binding that characterizes the paediatric age. Reduced protein binding will increase the free concentration and the free fraction of drugs, thereby enhancing the capacity of the active drug to diffuse more easily to other compartments. This results in more interaction with receptors, but it also increases the clearance rate of the drug.[51,60]

Drug distribution through blood brain barrier is delayed and limited due to the lack of sufficient maturation of the endothelial tight junctions in combination with efflux transporters. These maturational changes in this barrier, create a progressive increase in both efflux transporter (P-gp) expression and function as well as tight junction (higher passive diffusion in early infancy) capacity.[61,62]

With regard to drug metabolism and elimination and as would be expected, it will also vary depending on the paediatric age concerned. Each one of these processes exhibits an independent rate and pattern of development which is age-dependent.[51]

From a PD perspective, differences between adults and children are related to receptor functions, effector systems and homeostasis mechanisms.

Developmental changes in PD can be defined as the age-related maturation of the structure and activity of biologic systems and how they impact the response to pharmacotherapy across the continuum of paediatrics.[51]

Receptor functions are not yet fully developed in the paediatric population and the expected pharmacological effect (determined by the receptor's mechanistic pathway) may be qualitatively different from that observed in adults.

Knowledge regarding ontogeny and receptor maturation in the paediatric population is not developed. Thus, inadequate response to an apparently effective pharmacological concentration may be due to the presence/absence of receptors, inadequate binding of the drug to the receptor, poor metabolic/cellular signaling following drug-receptor interaction, or inability to respond to it of organs or tissues.[52,63]

Each of these processes (biochemical and structural maturation) evolves at different rates during development, to the point where the organ fully acquires the responsiveness to a pharmacological stimulus.

The maturation that occurs at different stages of human development allows some paradoxical effects to be explained (e.g. amphetamine sedation, hyperexcitability with H1 antihistamines) and also some conditions (jaundice due to unconjugated bilirubin increase or premature closure of ductus arteriosus by use anti-inflammatory drugs).

It is crucial to recognize the pharmacological effects on organism growth (e.g. corticosteroids, quinolones).[46,50]

Pharmacodynamic differences between adults and children are more important and complex than pharmacokinetics because they are more difficult to anticipate.[15]

3.3. Safety and Efficacy Assessment in Paediatrics

The guideline on clinical investigation of medicinal products in the paediatric population (ICH E11(R1)) identifies the main critical points in the development of medicines in paediatrics and proposes measures for an ethical, safe and efficient evaluation of medicines in this population. The assessment of pharmacological effects in the paediatric population should be done without compromising their well-being. In addition, the paediatric development program should not delay the completion of ongoing trials or the availability of adult medicines (ICH E11(R1)).

In this guideline, it is referred that the onset of paediatric clinical development will depend on the type of drug, the condition to be treated, and the safety and efficacy of existing pharmacological alternatives should be taken into account.

In case of specific paediatric disorders, the paediatric program should be complete and performed in children, except for initial safety or tolerance (usually obtained in adults).
For other conditions, the onset of paediatric clinical development may be deferred (to avoid unnecessary exposure to potentially ineffective and unsafe drugs) to Phase II and III trials, depending on the severity of the condition and/or alternative therapeutic options.[15]

The 21st century brought us challenges such as the substantial time delay between adult approval and the incorporation of information on paediatric use in labeling, the feasibility of conducting clinical trials for rare paediatric and early onset diseases (neonates, oncological and genetic diseases) and the ability to establish long-term drug safety in paediatric patients.
According to the EU Paediatric Regulation for certain authorised products, pharmaceutical companies may already hold data on safety or efficacy in the paediatric population at the time the Regulation has entered into force. To improve the information available on the use of medicinal products in the paediatric populations, companies holding such data were required to submit them to the competent authorities where the product was authorised. In this way, this data was assessed and, if appropriate, information was included in the authorised product information aimed at healthcare professionals and patients.

Because the reward is for conducting studies in the paediatric population and not for demonstrating that a product is safe and effective in the paediatric population, the reward (extension of the certificate of protection) should be granted even when a paediatric indication is not authorised. However, to improve the information available in medicines, relevant information on use in paediatric populations should be included in authorised product information.[10]

3.4. Paediatric Formulations

Paediatric formulations have always been considered a challenge, where the most significant advance has been to develop preservative-free formulations that are present in granules, orally disintegrating tablets, single-use powder (oral suspension/solution), oral soluble films and multiple multiparticulates such as sprinkle capsules, oral powders, oral granules and manipulated mini-tablets.[64] These new formulations are designed to be effective, safe and easier for patients use and access.[65,66]
Advances in this area have also allowed more care to be taken with primary packaging and medical services, allowing the most appropriate form of administration for children.[67]
Strickley has published some age-appropriate considerations which are important for paediatric oral formulations, as seen in Table 5.

Table 5 - Paediatric age range, approximate mass, classification, current dosage forms, and proposed dosage forms.[64]

Age	Mass (kg)	Classification	Age-Appropriate Dosage Forms, Current	Age-Appropriate Dose Forms, Proposed
	<3	Preterm infant	Nasogastric tube using solution or suspension (ready-to-use or powder or granules for constitution)	Nasogastric tube using tablets for oral suspension
0-28 d	3-5	Term new born infants	Solution or suspension (ready-to-use or powder or granules for constitution)	Tablets for oral suspension
1 mo-2 y	5-10	Infants and Toddlers	Solution, suspension, mini-tablets, ODT	Mini-tablet(s)
2-6 y	10-25	Children (preschool)	Mini-tablets, ODT, sprinkle powder, oral powder, oral granules	
6-12 y	<25	Children (school)	Chewable tablets, ODT	Chewable tablets, ODT, mini-tablets
12-18y	>25	Adolescent	Small tablets, capsules	Small tablets, capsules, mini-tablets
>18 y	>40	Adult	Tablets, capsules	Tablets, capsules, mini-tablets

The advances of the last 10 years have allowed the development of two major groups of paediatric formulations: ready-to-use oral formulations and oral formulations requiring manipulation.

The first group includes oral solutions, organic-based oral solution, aqueous-based oral solutions, oral suspensions, oral soluble films, tablets ready-to-use (small tablets, scored tablets, orally disintegrating tablets, chewable tablets and mini-tablets). The oral formulations requiring manipulation includes multiparticulates, sprinkle capsules, oral powder, oral granules, oral suspension concentrated to be diluted, powder or granules for oral solution or oral suspension, powder for oral solution, powder for oral suspension, granules for oral suspension and tablets that require manipulation (scored tablets, dispersible scored tablets, tablet for oral suspension).[64]

Figure 7 illustrates a decision-making flow-chart with several types of paediatric oral formulation to develop, depending on multiple factors and properties of the drug substance. The yes and no decision points starting with the decision to develop a preserved or preservative-free formulation, then upon drug substance properties of acceptable taste-masking, then water soluble, and then chemically stable. The left half of Figure 7 are preserved multiuse or single-use formulations, whereas the right half are preservative-free single-use formulations.[64]

This decision-making flow-chart was made based on multiple factors and properties of the drug substance that will influence the decision on the type of paediatric oral formulation to develop.

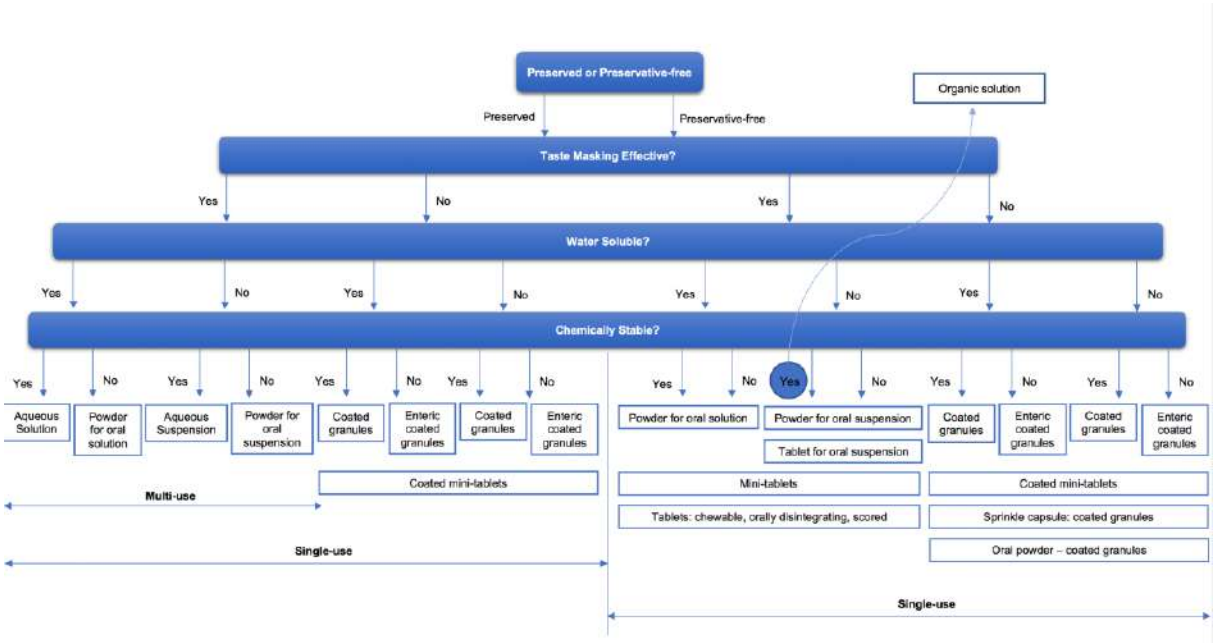

Figure 7 - Decision-making flow-chart for the choice of a paediatric oral formulation.[64]

One of the factors that influence oral administration in children is the organoleptic characteristics, especially the taste. There were also new developments in this area as seen in Table 6, regarding the excipients used in oral paediatric formulations marketed since 2007.

Table 6 - Excipients in new oral paediatric formulations marketed since 2007, extracted from Strickley, R. G. *Paediatric Oral Formulations*.[64]

Taste		**Solid Formulations**			**Solution and Suspensions Formulations**	
Flavors	***Sweeteners***	***Binders***	***Capsule Shells***	***Glidants***	***Antifoam***	***Solvents***
Banana	Acesulfame potassium	Hydroxypropyl cellulose	Gelatin	Silicon dioxide	Simethicone	Ethanol
Berry	Ammonium glycyrrhizate	Povidone	Hydroxypropyl methylcellulose	Talc	***Buffers and pH modifiers***	Glycerol
Cherry	Aspartame	***Buffers and pH modifiers***	***Coating Agents***	***Lipids***	Acetic acid	Propylene glycol
Grape	Glucose	Ammonium hydroxide	Amino methacrylate copolymer	Medium chain triglycerides	Citric acid	Sesame seed oil
Grapefruit	Maltitol	Calcium carbonate	Basic butylated methacrylate copolymer	Oleic acid	Disodium phosphate	Water
Mixed berry	Saccharin sodium	Calcium hydrogen phosphate	Diacetylated monoglycerides	***Lubricants***	Hydrochloric acid	***Surfactants***
Orange	Sorbitol	Citric acid	Dibutyl sebacate	Magnesium stearate	Sodium citrate	Poloxamer 188
Orange-vanilla	Sucralose	Magnesium hydroxide	Ethylcellulose	Sodium stearyl fumarate	Sodium hydroxide	Polysorbate 80
Peppermint	Sucrose	Sodium bicarbonate	Glyceryl behenate	***Polymers***	***Dyes or colorant***	***Suspending and dispersing agents***
Raspberry		Sodium carbonate	Glyceryl monostearate	Hypromellose	FD&C Red 40	Carboxymethylcellulose sodium

Strawberry	Sodium citrate	Hypromellose phthalate	Hypromellose acetate succinate	FD&C Yellow 6	Hydroxyethyl cellulose
Strawberry-vanilla	Sodium phosphate	Methacrylic acid copolymer	PEG 400	D&C Yellow 10	Magnesium aluminum silicate
Tutti-frutti	Tartaric acid	Triethyl citrate	Polyethylene oxide	Titanium dioxide	Microcrystalline cellulose
	Bulk agents and diluters	PEG 3350	Poly (vinyl alcohol)	***Isotonicifier***	Xanthan gum
	Dextrose	***Colorants***	***Preservative***	Sodium chloride	
	Erythritol	Iron oxide	Butylated hydroxytoluene	***Preservatives***	
	Fructose	Titanium dioxide	***Surfactants***	Benzyl alcohol	
	Lactose	***Disintegrates***	Poloxamer 188	Methylparaben	
	Lactose monohydrate	Corn starch	Poloxamer 407	Potassium sorbate	
	Mannitol	Croscarmellose sodium	Polysorbate 80	Propylparaben	
	Maltodextrin	Crospovidone	Sodium lauryl sulfate	Sodium benzoate	
	Microcrystalline cellulose	Pregelatinized starch	***Suspending and dispersing agents***		
	Silicified microcrystalline cellulose	Sodium starch glycolate	Carboxymethylcellulose sodium		
	Sucrose		Xanthan gum		
	Sugar spheres				

As we already discuss through this dissertation, whenever unauthorised and off-label adult medicines are used, after a careful risk–benefit assessment, children can still be exposed to potentially harmful excipients.[68]

Therefore, oral liquid formulations are an election choice for young children, such as solutions and suspensions, due to facility to swallow. However, many liquid formulations have not been studied extensively, or authorised for paediatric use. Children may not be able to metabolize or eliminate an excipient in the same way as an adult, because of their physiological and developmental differences. Pre-term, low-birth neonates and infants are particularly vulnerable owing to the immaturity of their hepatic and renal systems for metabolism and elimination.[69]

As an example, propylene glycol (PG) and ethanol, two solvents widely used in pharmaceutical formulations aren't indicated in all ages. Accumulation of PG can occur in neonates and young children as they cannot adequately metabolize and eliminate the excipient, which can lead to depression of the central nervous system. Ethanol used in formulations for children is associated with risk of acute intoxication with accidental overdose and chronic toxicity with long-term use.[70,71]

These are some examples that depending on the age of the child and the type of excipients used, it may be necessary to calculate the maximum safe amount for each particular case and may need to make adjustments for the various age groups.

Table 7 lists the most common excipients used in oral, topical and intravenous formulations and the relatable adverse effects.

Table 7 - Examples of excipients for paediatric medicines, their role in formulations and potential adverse effect(s).[68,70,72]

Excipient	Role in formulation	Adverse effect(s)
Propylene glycol	Solvent	Central nervous system (CNS) effects, especially in neonates and children under four years
Ethanol	Solvent	Intoxication
Polyoxyl castor oil	Vehicle	Severe anaphylactoid reactions
Polysorbate 80	Solubilizing agent	E-Ferol syndrome, hypersensitivity reactions
Benzyl alcohol	Preservative	'Gasping syndrome' in neonates
Benzoic acid	Preservative	Jaundice in neonates
Parabens (methyl-, ethyl- and propyl-hydroxybenzoates)	Preservative	Suggestion of estrogenic activity with potential reproductive effects (with propylparaben), hypersensitivity reactions, hyperbilirubinemia in neonates
Benzalkonium chloride	Preservative	Bronchospasm from anti-asthmatic drugs
Sodium metasulfites	Antioxidant	Wheezing, dyspnea and chest tightness in asthmatic children
Sorbitol	Sweetener	Osmotic diarrhea and gastrointestinal discomfort
Glucose and sucrose	Sweetener	Obesity and tooth decay
Saccharin	Artificial sweetener	Hypersensitivity and photosensitivity reactions
Aspartame	Artificial sweetener	A source of phenylalanine that should be avoided in patients with phenylketonuria
Colorants	Coloring agents	Sensitivity reactions and hyperactive behavior in children
Propylene glycol	Solvent	Central nervous system (CNS) effects, especially in neonates and children under four years

One of the most important factors in the oral administration of medicines to children is undoubtedly the palatability, recognized as an important part of compliance, adherence and concordance. The Guideline on pharmaceutical development of medicines for paediatric use has a chapter dedicated to palatability, since if it is not pleasant for the child, an incomplete administration (caused by coughs or a bit of gag reflex) implies an inappropriate dose and bioavailability, this means valid and reliable pre-clinical taste assessment methods are needed.[73]

Consequently, artificial sweeteners and coloring agents constitute an important part in paediatric formulations. Aspartame and saccharin are some examples of artificial sweeteners that are low-calorie or calorie-free, non-cariogenic, and, within the acceptable daily intake (ADI), considered safe for consumption by diabetic patients. ADIs for the general population are 40mg/kg/day and 5mg/kg/day for aspartame and saccharin, respectively. They are used to increase palatability and to mask unpleasant taste. Coloring agents are used in medicinal preparations to improve acceptability to patients, to aid identification and prevent counterfeiting. They are also used to increase the stability of light-sensitive drugs.[68]

Another point that has evolved considerably in recent years is proper packaging for paediatric patients, namely primary packaging and delivery devices.
Alternative paediatric oral formulations are this drinking straws, as shown in Figure 8, the XStraw® device is made to contain a pre-measured dosage of drug pellets or granules. The patient simply dips it into their favorite beverage and aspirates on it like a conventional drinking straw.

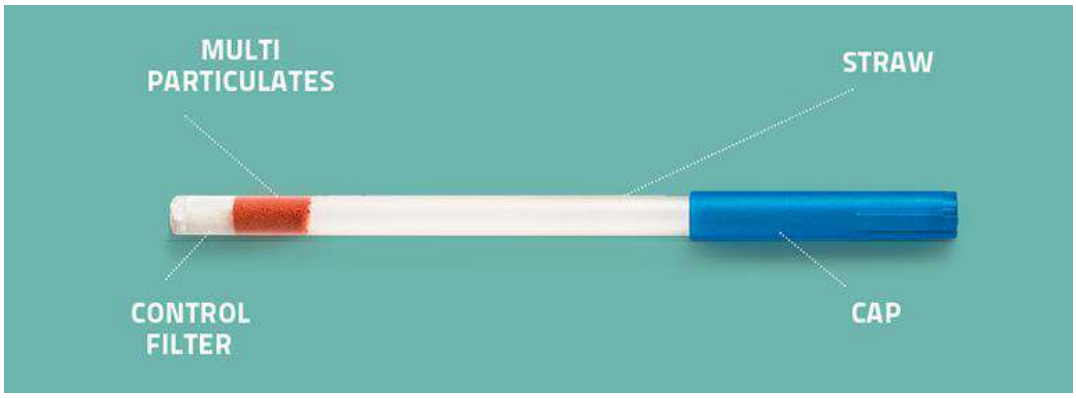

Figure 8 – The XStraw® device. Derived from: *XStraw Makes Swallowing Oral Meds Easier*. September 24th, 2019 (https://www.medgadget.com/2019/09/xstraw-makes-swallowing-oral-meds-easier.html).

Considering the Aqueous-Based Oral Solutions, Figure 9 demonstrates two different examples of this pharmaceutical formulation class innovations.

Desitrend® (levetiracetam) oral solution was approved in 2011 for the treatment of seizures with a dose of 10-30 mg/kg twice daily using a dose volume of 0.1-0.3 mL/kg of a 100 mg/mL formulation containing sodium citrate, citric acid, methylparaben (2.7 mg/mL), propylparaben (0.3 mg/mL), ammonium glycyrrhizate, glycerol, maltitol liquid 300 mg/mL, acesulfame potassium, grapefruit flavor, and water.

Epaned® (enalapril maleate) oral solution was approved in 2017 as a ready-to-use replacement to the kit that required manipulation and included a bottle of powder and a bottle of Ora-Sweet diluent. Epaned® is indicated for the treatment of hypertension with a dose of

0.08 mg/ kg up to 5 mg once daily using a dose volume of 0.08 mL/kg up to 5 mL of a 1 mg/mL formulation containing citric acid, mixed berry flavor, sodium benzoate, sodium citrate, sucralose and water.[64]

Figure 9 - Desitrend®. Derived from: *Desitrend® - Because tablet size matters*. May, 2018 (http://tabletsizematters.co.uk/desitrend.html#Desitrend-001) and Epaned®. Derived from: ***READY. SET. USE.*** *The First and Only Ready-to-Use Enalapril Oral Solution.* December, 2018 (https://epaned.com).

Buccolam® (midazolam) it's a great example of a new improvement in oral solutions, it was approved in 2011 for the treatment of seizures and is available in prefilled age-specific syringes with unit doses of 2.5 mg, 5 mg, 7.5 mg, or 10 mg in volumes of 0.5 mL,1 mL, 1.5 mL, or 2 mL of a 5 mg/mL preservative-free formulation containing sodium chloride and water with pH 3.3 (HCl or NaOH). Buccolam® oral solution is oromucosal midazolam that provides for convenient buccal (i.e., via the cavity between the cheek and gum) delivery. Buccolam® (midazolam) oral solution appears to be only available in the United Kingdom, European Union, and European Economic Area.[64]

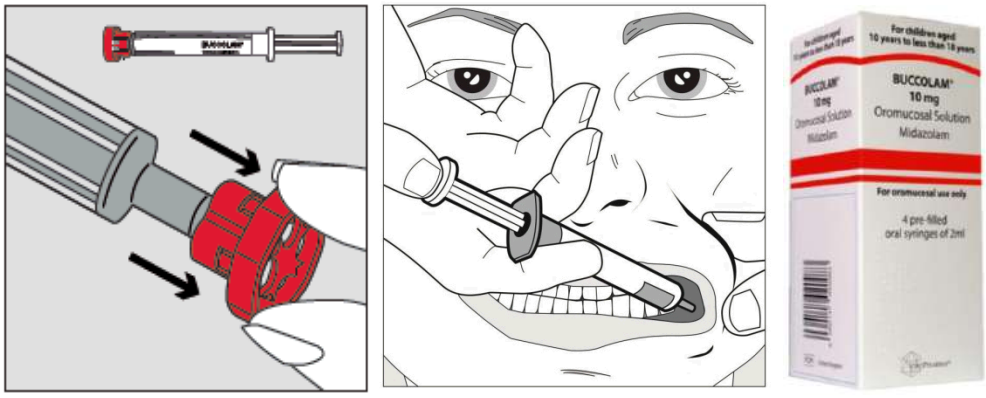

Figure 10 - Buccolam®. Derived from: *Summary of Product Characteristics BUCCOLAM, INN-Midazolam.* September 5th, 2011 (https://www.ema.europa.eu/en/documents/product-information/buccolam-epar-product-information_en.pdf).

An example of new Oral Soluble Films there is Zuplenz® (ondansetron) oral soluble film was approved in 2010 for the prevention of nausea and vomiting associated chemotherapy, radiotherapy, or postoperative nausea with unit doses of 4 mg or 8 mg for a dose of one 4-mg film 3 times a day of a preservative-free formulation containing butylated hydroxytoluene, calcium carbonate, colloidal silicon dioxide, erythritol, hydroxypropyl methylcellulose, monoammonium glycyrrhizinate, peppermint flavor, polyethylene oxide, sodium bicarbonate, sucralose, titanium dioxide, and xanthan gum. The film is applied on top of the tongue (as described in Figure 11) where it will dissolve in 4 to 20 seconds and then is swallowed with saliva and does not require water to aid dissolution or swallowing.[64]

Figure 11 - Zuplenz®. Derived from: *ZUPLENZ: Designed to Help Make Treatment More Comfortable*. September, 2019 (https://zuplenz.com/about-zuplenz-anti-nausea-treatment/).

Coartem® (artemether and lumefantrine) is a dispersible scored tablet which was approved in 2009 for the treatment of acute, uncomplicated malaria infections due to *Plasmodium falciparum* with a twice daily dose of 1-3 tablets for 3 days of unit fixed-dose combination scored tablet with 20 mg artemether and 120 mg lumefantrine of a preservative-free formulation containing colloidal silicon dioxide, croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, and polysorbate 80. The scored Coartem® tablet can be administered whole, split, or may be crushed and mixed with 1-2 teaspoons of water in a clean container, and its formulation is suitable for adults, children and newborns as we can see in the packaging demonstrated in Figure 12.[64]

Figure 12 - Coartem®. Derived from: *A qualitative study of the feasibility and community perception on the effectiveness of artemether-lumefantrine use in the context of home management of malaria in south-west Nigeria. February, 2008* (https://www.researchgate.net/figure/Picture-showing-the-packs-of-CoartemR-Used-2-6-1-6_fig2_5338436).

3.5. Paediatric Clinical Trials

Clinical trials in children are just as important as clinical trials in adults, so it is essential that no adaptations or simplistic allometric dose extrapolation of the results obtained for the adult population are made. These paediatric clinical trials should only be performed for the age groups in which the medicinal product will be used, excluding the other groups from the paediatric population.[74]

Accordingly to Regulation (EC) No 1901/2006 of the European Parliament and of the Council of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004, clinical trials in the paediatric population may require specific expertise, specific methodology and, in some cases, specific facilities and should be carried out by appropriately trained investigators.[10] There are many paediatric research networks in Europe, partially coordinated by the EMA under the European Network for Paediatric Research (Enpr-EMA).[75]

While in the last century the prevailing opinion was that exposure of children to clinical trials was unethical, it is now unethical and potentially unsafe/toxic to treat children with drugs that have not been properly investigated in paediatrics.

Phase I trials, which test the safety and pharmacokinetics of a new intervention for the first time, are discouraged in children due to the unknown effects of the intervention. However, phase I trials are more acceptable in children with severe or life-threatening conditions where there is no proven treatment or when standard therapies have failed.[76]

Paediatric clinical trials registered in the European clinical trial database EudraCT have increased by 50% in 2007-2016 from 8,25 % to 124 % as shown already in Figure 1. Furthermore, research with previously neglected paediatric subpopulations has risen considerably, once previously to the Regulation, research with neonates was almost non-existent in medicine development.[24,77]

4. CHALLENGES IN PAEDIATRIC MEDICINES

The development of paediatric drugs presents several challenges already presented earlier in this dissertation. Undoubtedly, there is a "before regulation" and a "after regulation" paradigm in the development of paediatric medicines and the EU Paediatric Regulation has brought several greatest advances for the paediatric population.

According to EMA and FDA, it is possible to extrapolate to children the efficacy results of investigated medicinal products in adults, provided that the course of the disease to be treated and the effects of the medicinal product are sufficiently similar in adults and children. These efficacy data are usually supplemented with pharmacokinetic trials in children. The same does not apply to the safety assessment of medicinal products for children. The safety of a medicine in children generally cannot be extrapolated from data obtained in adults, because medicines may be more or less toxic in this population. Moreover, accurate dosing information for different age groups is of utmost importance because of the risk of using inappropriate doses (sub-therapeutic or toxic).[21,78] During the last 10 years, new paediatric formulations have been made to avoid errors that were once common, such as the sulphanilamide in oral solution which, due to the excipients used, had numerous adverse effects including the death of several children.[79] A major challenge in the development of paediatric medicines is studying paediatric diseases, because they have a relatively low incidence rate or mainly due to the uniqueness of some disorders and differences with etiology, progression, comorbidities and prognosis in children.[9,80]

Another factor that was already discussed is the changes occurring during development and differences between age groups, which led to form age subgroups in the international regulation on paediatric clinical drugs.[81]

Naturally, as we have been discussing, the dose and drug response will differ from the adult population because there are anatomical and physiological differences which will translate into differences in PK and PD profiles with different receptor profiles and different adverse drug reactions. Also, many times the drug formulation should be adapted.[82–87]

Another issue to be considered in the design of a paediatric clinical trial is the lack of tools and methods for quantitative and qualitative assessment of the paediatric population and its sub-groups, such as study endpoints, questionnaires and scales for the measurement of psychophysical parameters and tools for the assessment of adverse reactions.[88]

Last but not least, pricing and reimbursement policies of drugs administered to paediatric population are strictly related to the mechanisms of drug marketing. As known, everyday worldwide most of the drugs used in children have a marketing authorisation for adults but are used "off-label" in the paediatric population. The introduction of regulatory requirements for clinical studies in paediatric populations has altered the paradigm of not having previously incentives to perform further studies in a paediatric population, but has not changed the situation regarding paediatric off-label use of medicines already approved in adults. This area remains a daily challenge with dangerous implications.[88]

4.1. Off-label use in children

The use of unauthorised and off-label medicines in children is widespread and has been an increasing concern over the last years. In the EU, 50% or more of medicines used in children have never actually been studied in this population, but only in adults, and not necessarily in the same indication (or the same disease).[45]

The general lack of information and appropriate pharmaceutical formulations to support the use of many medicines in children may expose them to unwanted side effects or underdosing without the expected efficacy. The need for more studies to obtain paediatric information for medicines used in children is now a matter of consensus on a global basis. Based on this, it was clear in 2006 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.[13]

There are at least five reasons why the use of a medicine could be classified as "off-label". First, whenever the drug is not approved for use by the national authority; when the dose used is not approved in the intended age; if the medicine is used for patients outside of the approved age range; whenever it is used for an unapproved indication; and, if the administration route is different from the approved one.[89]

Approximately 50% of drugs used in children are estimated to be used under conditions other than those authorised, and approximately 70% of paediatric patients receive prescriptions with at least one drug under those conditions.[90]

According to this reality, paediatric clinical practice involves decisions based on accumulated experience, about doses, safety and efficacy.[16]
The scarce research in paediatrics makes drug therapy in children guided by theories, professional experience and extrapolations of the adult population, to the detriment of scientific

evidence. As we already have seen, simple extrapolation of doses based on body weight does not guarantee the safety and efficacy of treatment and may even cause harm given that pharmacokinetic and pharmacodynamic differences exist between children and adults. Still, off-label prescription and use of drugs is recognized as necessary, sometimes representing the only viable option in the paediatric population.[91–93]

A study published by EMA in 2010 presented data on paediatric use of off-label and unauthorised medicines in the various EU member countries.[63] The results confirmed a high frequency of prescriptions on these terms across Europe - between 45% and 60% of the total study prescriptions. The most commonly used off-label and unauthorised medicines in paediatrics were in the following therapeutic classes: antiarrhythmic drugs; antihypertensives; proton pump inhibitors; H2 receptor antagonists; anti-asthmatics and antidepressants.[63]

The use of off-label medicines should always comply with criteria that minimize risks and be determined by factors that preserve patient safety. It should be based on a scientific basis and should be restricted to cases where the benefit appears to be considerable and there is no approved effective therapeutic alternative. An adequate patient monitoring should be also provided.

When there is no approved alternative, off-label use of certain medicinal products can and should serve as a driver for therapeutic innovation and encourage the eventual development of clinical trials in the situations concerned that may lead to decisions by regulatory authorities. legitimizing the widespread use under the conditions initially described as experimental.[94]

EMA has published a report on the off-label use of medicines in children[63], which explains that off-label use is associated with more adverse reactions to medicines for children and that adverse reactions in children may be more severe or different from what is known in adults.
The level of published evidence on the harm from off-label and unauthorised medicines use in children is scarce. There is, however, sufficient evidence that harm actually occurs and is under- reported. This supports measures to improve information on medicines used in children. This also supports setting up prospective monitoring of adverse drug reactions in children, including for children in the community, in order to obtain an objective picture of the risks and benefits of paediatric medicines.[7]

The study on off-label use of medicinal products in the European Union[95], published in 2017, specifies the principal conclusions about this practice. There were 32 studies on off-label use in various paediatric populations in the hospital setting that showed a range of 13-69% of the

investigated prescriptions being off-label. In 40 studies in the outpatient setting, a wider range of 2-100% was found.
The variation in off-label prevalence is not only observed between but also within countries, depending for example on the methodology used and the population studied. So far, the introduction of the Paediatric Regulation (1901/2006/EC) does not seem to have led to a lower prevalence of off-label use.[95]

In Portugal Off-label use is not illegal neither restricted, the prescriber is responsible for off-label use and patients have to provide informed consent for off-label use. The use of medicines for therapeutic indications or conditions different from the approved ones was clarified by the Portuguese National Competent Authority (INFARMED, I.P.) in a public information (Circular Informativa No. 184 / 11.12.2010 CD). The use of a medicine outside the approved indications is the responsibility of the prescribing physician, who understands that a particular medicine is suitable for a given therapeutic indication, given the specific patient's case. The Committees of Pharmacy and Therapeutics and/or Ethics of the National Health Service, are responsible for the decision about the correctness of the therapy prescribed to patients.
For greater protection, the Portuguese National Committee of Pharmacy and Therapeutic has included reference to the use of medicines in some non-approved indications (off-label) with the corresponding clinical support in the national formulary, assuring safeguard of patients through case-by-case approvals at a local level.[95]

4.2. Paediatric Medicines for hospital use

Nowadays, children who are hospitalized have severe illnesses than ever before. Many common acute paediatric conditions that traditionally required hospitalization are now both effectively and safely managed by the general paediatrician in the outpatient setting or have become rare because of widespread use of contemporary vaccines. Thus, the population of hospitalized children today is primarily composed of patients with acute and/or serious complications of common problems, multiple comorbidities and/or injuries, complex chronic diseases, acute mental health problems, special health care needs, technology-dependent conditions, and those needing palliative care. Optimal hospital care is often a team effort requiring physician-led care coordination and communication involving a paediatrician, paediatric subspecialist pharmacists, surgeons, mental health professionals, and other care providers.[96–98]

The pharmaceutical intervention is defined as a recommendation initiated by the pharmacist in response to a drug related problem in a patient at any stage of the drug circuit. This

intervention is carried out with the multidisciplinary team and focuses on patient care, aiming to improve the clinical results of the drug and, consequently, the health outcomes. Pharmaceutical intervention is even more relevant in paediatrics because it's an age group in which exposure to dose calculation errors is higher, and errors associated with medications are more severe. In daily pharmaceutical practice, it is essential to document these interventions for further characterization and identification of opportunities for improvement.[99]

The most common drugs presented in paediatric pharmaceutical intervention in Portugal includes[100]:

- Prednisolone tablets
- Methylprednisolone IV
- Antibiotics: amoxicillin clavulanic acid (IV and oral), oral amoxicillin, vancomycin, gentamicin, ampicillin, cefotaxime, cefazolin, piperacillin-tazobactam, flucloxacillin, clindamycin, azithromycin (oral suspension), trimethoprim (oral solution)
- Insulins: lispro, glargine
- Pantoprazole IV
- Ondansetron IV
- Ketorolac IV
- Enoxaparin
- Baclofen
- Clonidine
- Spironolactone + hydrochlorothiazide and spironolactone (oral solution)
- Captopril (oral solution)
- Furosemide (ampoule IV - the corresponding dose is administered orally)
- Inhalers: salbutamol and ipratropium bromide
- Nystatin
- Ranitidine
- Acetaminophen (IV and oral)
- Ibuprofen
- Metamizole
- Pyrazinamide, sulfadiazine, pyrimethamine (oral suspension)
- Calcium folinate

The most common drugs used in Neonatology are[100]:

- Vancomycin IV
- Gentamicin IV
- Ampicillin IV
- Meropenem IV
- Cefotaxime IV
- Flucloxacillin IV
- Acyclovir IV
- Cholecalciferol
- Multivitamins
- Iron (Ferric hydroxide-polymaltose complex)
- Caffeine citrate (oral and IV)
- Domperidone (oral suspension)

In order to facilitate the prescriber's decision and to ensure greater confidence in pharmaceutical validation and nursing administration, some decision flowcharts for off-label medicines are already being implemented for example in New Zealand hospitals.[101] Typically, the use of an unapproved medicine or use of medicine for an unapproved indication will be accepted provided that best practice, outlined in this protocol has been followed.

4.3. Decision making process for off-label of medicines

Data from scientific literature reveal that the prevalence of off-label use in the EU within the paediatric population is generally high, covers a broad range of therapeutic areas and is common practice for many prescribers in both the hospital and the outpatient settings. Thirty-two studies taken place in various paediatric populations within a hospital setting (covering data from 16 EU Member States) showed that a range of 13-69% of the prescriptions investigated was off-label.[95]

In a decision-making process, the risk assessment of unapproved medicines or unapproved indication/dose/route of administration for paediatric medicines must be considered. Medical prescription and pharmaceutical validation of an off-label drug requires more time to identify all inclusion/exclusion parameters, as well as scientific and clinical evidences. To facilitate this operation, one way would be to create a decision flowchart that allows a quick consultation for all necessary steps that should be taken before administration of the medicine.

The decision flowchart presented in Figure 13, is based in the use of unapproved medicines or medicines for unapproved indication (off-label use) in New Zealand. The authors have

characterized one green category for approved medicines but that are prescribed for an unapproved indication or dose or administration route, which means that professional consensus supports their use. This category also includes medicines obtained from other regulatory area which are approved for the indication, dose and route of administration within that regulatory area and have been endorsed by the Combined Medicines Review Committee. There is no requirement for a patient informed consent in this category, as the example of some palliative care medicines.[101]

The amber category represents medium risk and should be applied to those medicines which are not approved for use in New Zealand. However, professional consensus supports the use of these medicines for the indication, dose or route proposed. In the amber category, an informed consent to use the medicine must be obtained from each patient and documented in the patient's health record by the prescriber doctor. Medicines included in this category should have a Medication Clinical Practice Manual protocol developed and approved subject to controlled document standards.

Lastly, the red category clearly represents the high risk, and includes medicines that are not included neither in green or amber categories. In other words, it includes medicines approved or unapproved where the proposed indication for use is not supported by professional consensus. In these cases, the prescriber, with the supporting pharmacist, must request to use such a medicine by submitting to the Combined Medicines Review Committee a specific form for unapproved medicines.[101]

In Portugal, there is also the above described situation. In these cases, the prescribing physician submits a request form, for the use of off-label, extra hospital or conditioned medicine, which is subsequently reviewed by the specialist pharmacist in the therapeutic area and, finally, evaluated and decided by the Pharmacy and Therapeutics Commission of the hospital.

Both countries require a patient written consent before use the prescribed medicine, for the patient to understand that there is minimal evidence to support the (off-label) use of the medicine, or that the evidence on the efficacy or safety is scarce for the proposed off-label use.

Ideally in a hospital setting, all off-label uses that are prescribed daily need an established procedure, such as a protocol to follow. As we know off-label use is and will continue to be common in the daily life of clinicians, hospital pharmacists and nurses. Safeguarding the patient and the Healthcare professionals involved becomes easier and faster if there are well-

defined steps to be taken to expedite and informed off-label use, similar to what is done in New Zealand.

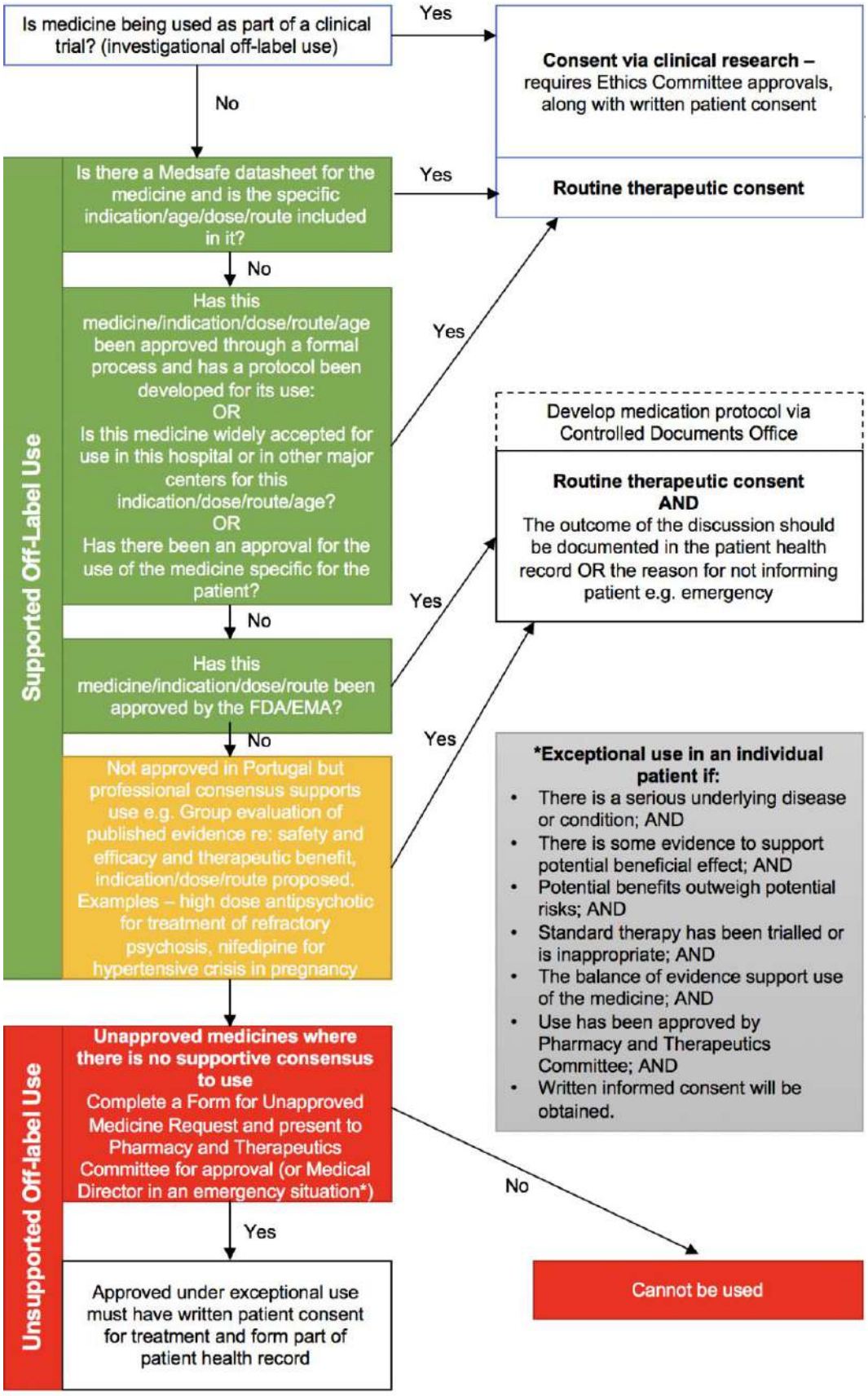

Figure 13 – Decision making process flowchart in the use of unapproved medicines or medicines for unapproved indication (off-label use) based on the New Zeeland Flowchart.[101]

4.4. Pharmacovigilance of paediatric medicines

Many developments have been made in paediatric medicines field, especially guaranteeing that drugs are suitable for this population as effectively as those in the adult population. Similarly, it is equally important to ensure its safety throughout the medicine life cycle. Therefore, it is important that pharmacovigilance be ensured to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

EMA has published a guidance on safety monitoring medicines used in children in the new Good Pharmacovigilance Practice (GVP) chapter IV[102] on specific considerations for the paediatric population. This new GVP chapter covers approved medicines with a paediatric indication or with an ongoing paediatric development, but also medicines only approved for adults when they are used off-label to treat children.

The guidance focuses on aspects of pharmacovigilance of particular relevance to the use of medicines in children, such as off-label use and medication errors, and contains paediatric-specific guidance on all major pharmacovigilance tools and processes, including risk management plans, periodic safety update reports, post-authorisation safety studies, signal management and safety communication.

It also includes the extended definition of adverse reaction, comprising adverse reactions that arise from use of the medicine within or outside the terms of the marketing authorisation or from occupational exposure. Use outside the marketing authorisation includes off-label use, overdose, misuse, abuse and medication errors, which are all important aspects related to the pattern of utilization of medicines in the paediatric population.

GVP Chapter IV brought guidance on how to make best use of the pharmacovigilance tools and processes to address the needs and specific challenges of the paediatric population, and supports the interpretation of how regulatory requirements should be adapted to target this specific population.[102]

5. THERAPEUTIC NEEDS IN PAEDIATRICS

With all the developments that have enabled this breakthrough in the regulation of paediatric medicines, we still have a long way to go regarding "real world" paediatric needs.

Thus, EMA has been identifying the main therapeutic needs in paediatrics[103] to facilitate researchers to identify developmental opportunities.[36,104]

The major areas in need are: anesthesiology, cardiovascular, diabetes (types I and II), endocrinology, gastroenterology, immunology, infectious diseases, nephro-urology, neurology, obstructive lung disease, oncology, ophthalmology, pain, psychiatry, respiratory, rheumatology. The principal development needs identified are data on PK/dose, safety and efficacy in children including preterm and term neonates, and age appropriate formulation.[104]

According to the study on off-label use of medicinal products in the European Union[95] sometimes high-level evidence is hard to get, even for those treatments that may be effective. This condition may occur for rare diseases or in paediatrics when a range of age-appropriate formulations should be developed to attend the different age groups. In those circumstances, large clinical studies are not easy to perform. As an example, Ivanovska et al.[9] presented a review on challenges in children's medicinal products and state that new paediatric formulations address only a small part of the therapeutic needs.[95]

To meet the Paediatric Regulation's objectives, the Regulation has set up a system of obligations, rewards and incentives. It also comprises measures to ensure that medicines are regularly researched, developed and authorised to meet the specific needs of children. It is based on the idea that a company should be obliged to screen every product it develops for its potential use in children, thereby progressively increasing the number of products with paediatric indications.[105]

5.1. Rewards and Incentives

The PIP was established to ensure that the necessary data are obtained through studies in children, to support the authorisation of a medicine for children. All applications for marketing authorisation for new medicines have to include the results of studies as described in an agreed PIP, unless the medicine is exempt because of a deferral or waiver.[106]

This requirement also applies when a marketing-authorisation holder wants to add a new indication, pharmaceutical form or route of administration for a medicine that is already authorised and covered by intellectual property rights.

Pharmaceutical companies should submit proposals for PIPs to the PDCO. This Committee is responsible for agreeing or refusing the plan, and the Paediatric Regulation requires PIPs to be submitted to the Agency early.

The development plan for a medicine can be modified at a later stage as knowledge increases. Modifications can also be made if the applicant encounters such difficulties with the implementation of a PIP, which render it unworkable or no longer appropriate.

The Agency also develops standard PIPs to help applicants obtain the agreement for PIPs on specific types or classes of medicines. Adhering to the principles and key binding elements contained in a standard PIP will facilitate the PIP approval process.

The PDCO may grant PIP deferrals for some medicines. These allow an applicant to delay development of the medicine in children until, for instance, there is enough information to demonstrate its effectiveness and safety in adults. Even when studies are deferred, the PIP will include details of the paediatric studies and their timelines.[106]

The PDCO may also grant waivers when development of a medicine in children is not needed or is not appropriate, such as for diseases that only affect the adult population.

After assessing an application for a PIP, deferral, waiver or modification, the PDCO formulates an opinion, which is notified to the applicant. The applicant is then able to request a re-examination of the opinion, if it wishes. Once the Committee has issued its final opinion, after re-examination if requested, the Agency adopts a decision.

The Agency makes all opinions and decisions on PIPs, deferrals and waivers public, after deletion of information of a commercially confidential nature.

Applicants can also request scientific advice from EMA in preparation of a PIP, which is free of charge for questions relating to the development of paediatric medicines. They can also follow up a PIP with scientific advice, for example on combined adult and paediatric development in light of the PIP requirements. EMA discourages applicants to submit scientific advice and an PIP applications in parallel.

Applicants must follow agreed PIPs exactly. Once the plan is complete, the EMA or the medicines authorities in Member States check that companies comply with the agreed measures listed in each PIP.

These checks are necessary before the applicant can apply for a MA or a change to an existing MA.

Medicines authorised across the EU with the results of studies from a paediatric investigation plan included in the product information are eligible for an extension of their supplementary protection certificate by six months. This is the case even when the studies' results are negative. For orphan medicines, the incentive is an additional two years of market exclusivity.

Scientific advice and protocol assistance at the Agency are free of charge for questions relating to the development of paediatric medicines.

Medicines developed specifically for children that are already authorised but are not protected by a patent or supplementary protection certificate are eligible for a PUMA. If a PUMA is granted, the product will benefit from 10 years of market protection as an incentive.[107]

According to EMA's report to the European Commission (2017)on companies and products that have benefited from any of the rewards and incentives in the Paediatric Regulation and on the companies that have failed to comply with any of the obligations in this regulation, in total, 261 PIPs were scheduled to finish by 30 June 2017; of those, 150 (57%) were completed; of the remaining 111 that have not been completed, 31 do not have a valid justification (example: a modification to amend the date of completion is pending/ongoing or development has been discontinued).[22]

5.2. Paediatric medicines for rare diseases: Orphan Medicines

According to EMA, there is about 30 million people living in the EU suffering from a rare disease, collectively they affect about 6-8% of the human population.[108] So, when we talk about paediatric diseases, we cannot exclude rare diseases since many of them are diagnosed during that age range and about 80% affect children. A rare disease is now known as a disease who affects fewer than 1 in 2000 people in Europe and fewer than 200,000 people in the United States of America.[109–111]

Curiously, paediatric and orphan drugs have many features in common, especially obstacles to their development as we speak of small populations.

Since they affect a small population, heterogeneous and widely dispersed, it is more difficult to enroll enough patients in clinical studies and pharmaceutical company shows a scarce interest in this field for the low return they may have.

Moreover, considering the high incidence and prevalence during the childhood, the ethical issue is predominant in this field. And additional challenges may result from the frequently progressive, life-limiting or life-threatening nature of these diseases.[88]

Regulation works best in areas where the needs of adult and paediatric patients overlap. Especially, in diseases that are rare and unique to children and which in many cases are equally supported through the orphan legislation, major therapeutic advances often failed to materialize yet.

Therefore, and before proposing any amendments, the Commission intends to take a closer look at the combined effects of the Orphan and Paediatric Regulation through a joined evaluation of those two legal instruments aimed at supporting medicine development in subpopulations of

particular need. Given the weaknesses identified in the 10-year Report to the EC on Paediatric Medicines, about the orphan reward, which is primarily geared to non-patented products and has no built-in flexibility to allow companies to maintain orphan status by opting for the supplementary protection certificate reward. This is often relate to paediatric diseases that qualify as orphan condition, only such combined effort will guarantee to adjust the right parameters, if required.[22]

Recently, on 17 June 2019, the EC's organised a conference on Medicines for rare diseases and children, untitled "Medicines for rare diseases and children: learning from the past, looking to the future", aiming to discuss suggestions and ideas on the evaluation of both EU Regulations on Orphan Medicinal Products and Paediatric Medicines.[112]
Were discussed, among other themes, the need to expand research and the compilation and sharing of data in order to accelerate the process from research and development to the patient. As well as the need for incentives that support real innovation in the orphan therapeutic background and better agreements that a reward is proportionate including a better coordination and identification of priorities.[112]

Progress has been made since the Regulations came into force. However, only some 5% of identified rare diseases have so far been addressed under the Orphan Regulation. The pharmaceutical industry claims that without incentives the development of new treatments for rare diseases will slow down. Some weaknesses have also been identified as regards the Paediatric Regulation: these mainly relate to the incentives provided for the development of these medicines. The general effectiveness of the system to address unmet needs and achieve availability and equal patient access across the EU can also be improved.[112]

6. DISCUSSION

The evolution of innovative technologies in the paediatric pharmacology and preclinical phase of drug development will give an impulse to both development of new medicines for children and paediatric clinical research. The consciousness about the limited application of the innovative technologies in the paediatric drug development process and the limited availability of safer and efficacious drugs for children has led, over the last years, to the onset of initiatives and collaborative efforts in this field.

Children represent a particular group of vulnerable subjects and therefore should be protected and preserved by the risks that a clinical research can entail, for their safety and ethics. However, it's known that higher risks in term of major toxicity or reduced efficacy can result by the administration of drugs not properly tested and developed for them. Despite this, the off-label drug administration is still common worldwide in the paediatric population and children have been considered for years as the therapeutic orphans due to the well-known lack of medicines specifically targeted for them. Furthermore, the vast progresses and developments reached in the pharmaceutical field have not been applied to the paediatric population at the same extent of the adults.

The gap in the availability of proper medicines for children can be traced back to ethical, practical and economic reasons. As discussed in this dissertation, the main practical reasons can be associated with the differences existing in the diseases affecting children compared to adults, as well as in the different physiology itself of the children compared to adults, the low number of patients affected, the need to take into account different age groups and the need to make available appropriate formulations. Moreover, the ethical concerns make more difficult to obtain the parents' consent. In addition, the pharmaceutical companies are not interested in this small market, since they cannot predict an adequate economic return. Besides, more challenges have to be faced when considering paediatric rare diseases. Complex etiology, small affected population and subsequently small market size, high cost, and possibly low return on investment led to a large gap between basic research and patient unmet needs for rare disease drug discovery.[88]

Many initiatives have been taken over the years, also at institutional levels, to promote a respectable research in the paediatric field, in order to involve children and at the same time preserve them by unnecessary risks. Only increasing our understanding about human development processes and about how these processes impact on the onset and progression of diseases will able us to develop specific medicines targeted for children. The awareness of these processes will allow us to transfer in the paediatrics all the advancements and innovative

technologies nowadays available in the adults' pharmacological research. Thus, more efforts are needed in terms of capitals, human resources, and technological expertise to speed up both the preclinical and clinical drug development in children and make available to children new medicines and appropriate treatments.

7. CONCLUSION

One of the most important milestones in the history of EU Drug Regulation has been the recognition that medicines given to children must meet the criteria of quality, safety and efficacy as required for adult-approved medicines. This means that medicines must be targeted for child-specific "marketing authorisations" for full access to new therapeutic innovations.

Medicinal products administered to children should preferably have a child-specific marketing authorisation for real access to therapeutic innovations. This implies the obligation to comply with quality, safety and efficacy criteria as for adult medicines. Thus, clinical research in paediatrics is evolving from an additional niche, treated in the final stages of drug development, to an integrated part of drug development.

The implementation of the European Paediatric Medicines Regulation and its objectives has contributed to a significant improvement in European children's access to "best" medicines, specifically tailored to their reality. There are currently significant changes in the development of medicines in paediatrics with the aim of improving children's access to therapeutic innovation and ensuring high quality research in this population.

The European Regulation for Paediatric Medicinal Products requires pharmaceutical companies to consider paediatric needs in their drug development projects. The Paediatric Committee ensures that the final decision considers studies of significant value in this population, established in a Paediatric Research Plan.
Since the implementation of the Regulation and after five years, more than 3000 Paediatric drug development proposals have been evaluated. The results of the implementation of the Regulation are positive and promising, although an analysis of its impact is still premature.[17,113]

It is a complex process that moves around the scientific, research and regulatory areas and is expected to ensure the success and development of safe and effective medicines for children. Ten years after the entry into force of this Regulation, there is now widespread anticipation of the need to conduct appropriate clinical trials and develop appropriate formulations for the paediatric population.
Clinical research in paediatrics has evolved towards a reasonable compromise between ethics and the need for pharmacokinetic and pharmacodynamic information that leads to rational therapeutic practice in paediatrics. It is therefore indispensable that research in the field of paediatric pharmacology is truly considered.

With these very promising regulatory measures, children are expected to have easier access to therapeutic innovations that are treated with effective, appropriate and risk-free medicines. It is clear to all that paediatric health is a primary objective, both socially and in defence of the rights of the child, and deserves increased attention. Thus, a real gain in public health benefits is also anticipated, resulting in decreased child morbidity and mortality.[17]

The ideal paediatric formulation should have flexible dosage increments and minimal excipients, be palatable, safe and easy to administer, and be stable with regard to light, humidity, and heat. Nevertheless, a significant number of drug formulations are unsuitable for children, which leads to unsafe off-label and unauthorised use of adult medicines. Recent initiatives promoting paediatric drug development have made some initial progress in the neglected area of paediatric formulations. Most efforts have focused on age-appropriate oral solid preparations, which enable dose flexibility, easier administration, and better acceptance in children. Despite these advances, the new paediatric formulations are still only a small part of the full therapeutic arsenal needed to serve all paediatric patients.[9]

It's required a continuous prioritization process that focuses on unmet public health issues and ensures that drug development supports with the true clinical needs in children.
A future research on paediatric formulations could potentially benefit from existing or innovative technologies under development in adults. Practice-based evidence on the impact of novel formulations, generated by health care professionals and caregivers, could provide further support for the development of paediatric medicines with clear clinical advantages. Novel experimental treatments of adult cancers, infections, and asthma have used nanoparticle-targeted therapy, novel smart polymer-based drug delivery systems, new chemical entities, and remote triggering devices. These treatments may have significant applications in children, and the identification of appropriate animal models for paediatric preclinical studies should be a research priority.[9,64]

To reach these goals, it is essential that there is a committed collaboration between stakeholders that extends across disciplines and geographic regions. Moreover, this collaboration should have the innovative potential to further shape the paediatric drug development agenda and thus to close the adult–child medicine gap.[8]

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