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Chapter 12

# Clinical Trials in Paediatrics — Regulatory and Methodological Aspects

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Additional information is available at the end of the chapter

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## 1. Introduction

Until very recently, decisions about the medical treatment of children with acute or chronic health conditions were based on the results of research conducted almost exclusively in adults. Although differences in treatment effects between young and adult patients are well known (e.g. regarding mechanism of action and metabolism), there were less clinical trials (CTs) than needed to adequately evaluate the effects of new medicines in children. This was mainly due to:

- the lack of appropriate rules for the conduct of paediatric CTs, especially with regard to ethical considerations;
- the lack of an adequate methodology enabling to provide powered evidences while taking into account the paediatric specificities [1];
- the lack of economic interest of the industrial developers due to the limited market offered by children.

Starting from 1994, Food and Drug Administration (FDA) adopts different measures to promote, incentive or oblige to conduct paediatric trials. More recently, for effect of the Paediatric Regulation (EC) No 1901/2006 [2] requiring a sound scientific evidence for treatment benefits in children and adolescents, the conduct of CTs testing medications for their use in children and adolescents becomes mandatory in the European Union (EU).

Despite the high number,,(more than 1000) of Paediatric Investigation Plans (PIPs) applied to receive an opinion by the Paediatric Committee (PDCO) at the European Medicines Agency

(EMA) since the Regulation entry into force very few advancements have been done in terms of new studies, new trials and new paediatric approved medicines on the market. [3]. At the same time, looking at the American side, we can observe that the implementation of the existing rules has been and are still strongly problematic and under debate, allowing to recent modifications of rules and guidelines.

The aim of this chapter is to describe the requisites for implementing paediatric CTs in compliance with the principles of good clinical practice (Good Clinical Practice, GCP), and with the regulatory standards in order to be part of an agreed PIP in EU or of a Pediatric Study Plan (PSP) in the United States (U.S.).

It will include the following topics:

**1.** Paediatric trial regulatory aspects

*Currently covered by the CTs Directive 2001/20/EC* [4], *rules on paediatric trials are changing for effect of the recently approved CT Regulation that will enter into force by 2016* [5]. *The transition phase and the new context deriving by this transition will be considered in this chapter mainly in terms of a) trial authorisation, b) rules and competencies of Ethics Committees, c) consent and assent from parents and children, d) children privacy and confidentiality.*

**2.** Paediatric Plans and paediatric trials methodology

*The traditional drug development approaches do not satisfy the requirements of research in the paediatric population. In particular, in paediatrics the following issues are challenging: large population needed for Randomised Controlled Trials (RCTs), randomisation procedure, placebo use, validate paediatric endpoint, appropriate outcomes, long-term effects evaluations, etc.*

*In the last years, the main activities performed at scientific and regulatory levels to cover these gaps have been aimed to identify innovative methods of research to overcome the existing paediatric limitations.*

**3.** Paediatric trial incentives and main results of the existing legislation

*By many years the U.S. legislation provides financial incentives to study medicines in children. This has produced a significant increase in the number of paediatric trials conducted since 1997. The EU paediatric medicines Regulation, which was adopted in 2007* [2] *is also based on a series of incentives and requirements and will lead to a further stimulation of paediatric drug development. This chapter explores the distribution and other characteristics of recently conducted paediatric trials in EU and US also providing a comparison between the two areas.*

## 2. Paediatric trial regulatory aspects

### 2.1. The legislative framework to promote paediatric medicines and research

To overcome the lack of paediatric trials, many initiatives have been promoted both in U.S. and in Europe.

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The first rule came from FDA in 1994 [1]. It was an attempt to use existing data (may be extrapolated from adults) and additional pharmacokinetic (PK), pharmacodynamic (PD), and safety studies, if the course of the disease and the response to the drug are similar in children and adults. The 1994 law did not impose a general requirement to the manufacturers to carry out studies when existing information was not sufficient and was not successful to obtain its aim.

In 1997, for the first time, the FDA Modernisation Act [6] introduced incentives for conducting paediatric studies on drugs for which exclusivity or patent protection exists, while off-patent drugs were excluded. At that time it was not accepted that FDA would mandate timing and other paediatric studies provisions to the manufacturers.

Today, the current U.S. regulatory framework includes:

- The Best Pharmaceuticals for Children Act **(BPCA)** [7], that provides incentives for drug companies to conduct (after FDA Written Request) paediatric studies by granting additional six months of marketing exclusivity.
- The Paediatric Research Equity Act (**PREA**) [8] that requires drug companies to study their products in children under certain circumstances. When paediatric studies are required, they must be conducted with the same drug and for the same use for which they were approved in adults.[1]

Noticeably, BPCA provided mechanisms for studying on- and off-patent drugs and to test off-patent drugs by:

- Identifying and prioritising drugs which need to be studied;
- Developing study requests in collaboration with experts at National Institutes of Health (NIH), FDA and other organisations;
- Conducting studies on priority drugs after manufacturers decline to do so.

On the other hand, under the **PREA** as originally enacted, a proposed timeline and plan for the submission of paediatric studies were not required to be submitted during the New Drug Application (NDA).By July 9th 2012, for the first time PREA includes a provision that requires manufacturers to submit a Pediatric Study Plan **(PSP)** early in the drug development process. Pediatric Review Committee (PeRC) is a consultative body which reviews all activities under PREA (the same committee is in charge for the activities foreseen under BPCA).

A similar intervention in the EU arrived almost 10 years later. In fact, the EU Paediatric Regulation [2] entered into force in January 2007. After the Paediatric Regulation approval, relevant changes have been implemented not only in Europe but also in the U.S.

The main pillars of the EU Paediatric Regulation are:

- to set up a new Committee at EMA named the Paediatric Committee (PDCO);

1 More details at: Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

- to rule a new type of Marketing Authorisation, the Paediatric Use Marketing Authorisation (PUMA) only accessible to off-patent drugs;
- to introduce the obligation for the manufacturers to apply for a PIP early in the drug developmental process;
- the obligation to conduct the paediatric studies in compliance with an approved PIP that can also include waiver (exemption to conduct any paediatric studies) or deferral (the right for the manufacturer to delay the paediatric study respect to the adults MA);
- to state that dedicated incentives should be provided under the European Research Framework to develop off-patent drugs if included in a 'Priority List' published by the PDCO-EMA

### 2.2. The current regulatory framework for approving clinical trials

The introduction of specific rules devoted to implement the paediatric research in the paediatric population allowed an increased attention to the CT approval and conduct.

For many years, the traditional approach to diagnosis and treatment has been based on symptoms and signs, which reflect, in the majority of the cases, the patient phenotype. Accordingly, trials have been conducted by grouping patients into broad groups with similar symptoms. Pharmaceutical and biotechnology companies have developed medicines for these broad populations, and the regulatory assessment of risk and benefit has been based on the average clinical response across these groups. This model has been strongly regulated with the aim of performing ethically and methodologically well-conducted CTs.

In Europe several guidelines, directives and regulations have been released, including Directives 2005/28/EC [9] and 2001/20/EC [4], GCP Guidelines (CPMP/ICH/135/95) [10], Reg. (EC) No 726/2004 [11]. In particular, Directive 2001/20/EC has established specific provisions regarding the conduct of CTs on human subjects involving medicinal products and recognises GCP principles. As internationally agreed and in accordance with GCP [10], a CT may not commence in EU if an Ethics Committee has not approved the study. The Directive 2001/20/EC also introduced the concept of "Competent Authority", adding the legal obligation to obtain an "authorisation" in addition to the positive opinion of the Ethic Committee.

However, the above mentioned provisions in Europe have never considered the paediatric specificity until the approval of the CT Directive. In fact, the main novelty of the Directive has been represented by the introduction of a dedicated article (art. 4) that refers to differences in the ethical and methodological approaches between paediatric and adult trials and provides the basis for including paediatric trials in the developmental process of adult drugs. Moreover, following the approval of the Paediatric Regulation, destined to increase the number of paediatric trials, the art. 4 of Directive 2001/20/EC was considered insufficient to protect children involved in a trial [12]. The '*Ethical Recommendations on paediatric trials*' issued in 2008 by the EU Commission [13], represent the more advanced regulatory framework for paediatric research in Europe.

In U.S. the ethics framework for approval of CTs is quite similar. Every CT must be approved and monitored by an **Institutional Review Board** (IRB) to make sure the risks are as low as

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possible and potential benefits are valuable. An IRB is an independent committee of physicians, statisticians, community advocates, and others people ensuring that a clinical trial is ethical and the rights of study participants are protected. All institutions that conduct or support biomedical research involving people must, have an IRB that initially approves and periodically reviews the research.

In the U.S. legislation, details on how to conduct trials in the paediatric population are included into Subpart D (401-409) of the '*Code of Federal Regulations TITLE 45 PUBLIC WELFARE, PART 46 PROTECTION OF HUMAN SUBJECTS':* Additional Protections for Children Involved as Subjects in Research [14]. In the code different provisions are identified on the basis of the risk level of the trial such as: 1- Research not involving greater than minimal risk; 2- Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual subjects; 3- Research involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield general knowledge about the subject's disorder or condition.

In addition, research that presents a reasonable opportunity to advance the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children can be also approved under special conditions.

A great relevance is given to the procedures to obtain the children assent. The permission to include a child in the trial is given by both parents in case of researches involving greater than minimal risk, and by only one parent if only a minimal risk is concerned.

### *2.2.1. What is changing in the regulatory framework*

After its entry into force, the EU Directive 2001/20/EC has been the object of many concerns and debates leading to a new legislative process aimed to change and consolidate a EU framework by the means of a *Regulation*[2] instead of a *Directive*. In line with different reports and publications [15] the main problems dealing with the Directive were:

**1.** *The need for harmonisation of aspects and procedures aimed at providing ethical protection*

In contrast with the U.S. where only one Federal rule applies, in Europe Directive 2001/20/EC, given its 'non-binding' nature, needed to be implemented by all the different Member States (MSs). Therefore, the harmonisation of ethical issues and the authorisation procedures in different countries were faced but not solved in the context of Directive 2001/20/EC, and this holds true in the case of paediatric trials [16]. In addition, Directive 2001/20/EC does not provide information on how competent authorities and Ethics Committees of each MS should act in case of multi-centre and multi-national studies, while these studies prevail among the trials aimed to a MA approval.

**2.** *The increased burden of administrative and authoritative procedures causing delay in conducting clinical trials in Europe*

2*Regulation, unlike Directive, supersedes national laws and it is directly implemented throughout Europe without the need for transposition into national laws.*

The main cause for the decreasing number of trials conducted in Europe and for the increasing of costs is due to the double obligation to obtain an "authorisation" from the Ethic Committees and the Concerned Authorities to be repeated in all the concerned member states. As reported in the EC Explanatory Memorandum preparing a new Regulation [15]: *'The number of applications for clinical trials fell by 25% from 2007 to 2011. For non-commercial sponsors, the increase in administrative requirements due to the Directive 2001/20/EC has led to a 98% increase in administrative costs; the insurance fees have increased by 800% for industry sponsors; the average delay for launching a clinical trial has increased by 90%, to 152 days'.*

From 2016, with the application of the new EU Regulation on CTs (Regulation 536/2014) [5], a unique central procedure will be applied to be carried out through a single EU CT portal, where an homogeneous submission package (valid for all MSs) will be submitted in order to obtain the CT authorisation. The centralised submission will include also the ethical assessment, both for adults and paediatric trials.

Noticeable, the principal duty of the centralised assessment will consist in confirming or not the nature of trial that could be 'interventional' 'low-risk interventional' or 'non-interventional'.

The category of 'non-interventional trial is a novelty in the EU context and is based on a recognised 'minimal risk' of the trial (e.g. only limited procedures added to the current therapy) to which a lower level of requirements (including insurance coverage) is needed.

A "Reporting Member State", in charge to draw up an "assessment report" and the release of the authorisation, will be proposed by the sponsor corresponding to the country where it intends to carry out the Clinical Trial Application (CTA) at first. In case of multi-national trials, the other involved MSs follow a simplified procedure of assessment focused on national and ethical aspects (e.g. informed consent, recruitment of subjects, data protection, suitability of investigators and trial sites, mechanisms of insurance compensation collection of biological samples, submission fees, arrangements for rewarding/compensating investigators and subjects) for their own territory compliance.

In case of paediatric trials, for effect of a large consultation process and after relevant amendments provided by different stakeholders, in particular by the Paediatric Research Networks (such as EnPREMA[3], TEDDY[4] and GRiP[5]), the new Regulation represents a potential positive step in the process to increase the number and the quality of paediatric trials.

In more details, the Regulation states that:

- The application should refer to the PDCO opinions and related approved PIPs: The Reporting MS shall assess the application with regard to the relevance of the CT, including PDCO' opinions on PIPs.

3 EnPREMA is the Network of the existing Paediatric Network, stated in the Paediatric Regulation and set up at EMA

4 TEDDY is a European Network of Excellence for Paediatric Clinical Research. For more information, http://www.teddyoung.net/

5 GRiP amendments are available here http://www.grip-network.org/index.php/sfPropelFileStorage/download/name/GRiP+on+CT+regulation.pdf

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- As stated in the Paediatric Regulation [2], all paediatric studies should be registered in the EU register of CTs, including studies that are part of an agreed PIP and carried out in third countries.

With regards to the preparation of submission documents, besides the rules applying for every type of trials, issues specifically dealing with paediatrics have been established as follow:

- the cover letter shall indicate the reference to trial population (minors), and a statement that the trial is part of an agreed PIP.
- the link to the Decision of the Agency on its website must be indicated in order to demonstrate that at the time of the Ethic Committee application, the Agency will have already issued the Decision about the PIP;
- the protocol shall include a justification for including minors and detail the procedures for inclusion of single subjects;
- the summary of the results of the CT shall include paediatric regulatory details (information whether the CT is a part of a PIP).

Finally, some important requirements, already stated in previous non-mandatory documents, such as the need for paediatric expertise or advice in Ethics Committees, become mandatory, such as the involvement of minors in the informed consent procedure according to their age and mental maturity. The table below shows the comparison between EU and U.S. rules on specific key topics of paediatric trials.

| **TOPICS** | **Europe (Regulation 536/2014)** | **U.S. (Subpart D (401-409) - Code of Federal Regulations title 45-46)** |
|---|---|---|
| **Trial authorisation/ approval** | The Reporting Member State and other MSs involved authorise the trial. The assessment includes the Ethics Committees review. The reporting Member State shall assess the application with regard to the relevance of the clinical trial, including PDCO' opinions on PIPs. | An Institutional Review Board (IRB) approves and monitors the trial. |
| **Ethics Committee rules and competencies** | Experts in paediatric research are members of Ethics Committees reviewing the protocol. Alternatively the Ethics Committees take advice from external experts on clinical, ethical and psychosocial issues in the field of paediatrics. | IRBs are also allowed to invite individuals with special expertise or knowledge to provide consultation and information on individual protocols, where needed. |

| TOPICS | Europe<br>(Regulation 536/2014) | U.S.<br>(Subpart D (401-409) - Code of Federal Regulations title 45-46) |
|---|---|---|
| **Research involving neonates** | No specific rules. All rules intended to paediatric research apply. Research on non viable or of uncertain viability neonates are not cited. | Specific rules apply to neonates: a) non viable, b) of uncertain viability, c) viable (general rules apply). |
| **Risk/Benefit** | No specific rules for paediatric population. | Each IRB shall approve only Paediatric Research not involving greater than minimal risk or involving greater than minimal risk if:<br>- presenting the prospect of direct benefit to the individual subjects<br>- likely to yield general knowledge about the subject's disorder or condition (if minimal risk increase)<br>- research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (under special conditions). |
| **Minimal Risk definition** | Minimal risk could be defined as the probability of harm or discomfort not greater than that ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. | Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (this rule is not a specific paediatric rule). |
| **Consent and assent from parents and children** | Informed consent of the parents or legal representative. Assent of the children, that are entitled to receive information according their age and maturity.<br>No minimum age is defined for providing assent.<br>Need to obtain the consent if the subject reaches the age of legal competence during the trial | Parents (both or only one, according the level of risk) or guardians provide permission before children can be enrolled in research. Researchers must seek a child's assent unless the IRB determines that the children to be involved are not capable of providing assent, given their age, maturity, and psychological state.<br>The regulations do not describe the information that must be provided to children but rely on IRBs to use their discretion in judging assent provisions. |
| **Children privacy and confidentiality** | No specific rules for children issued in Reg. 536/2014 (as well as in the Privacy Directive 95/46/EC) | Children confidentiality and privacy is not mentioned in FDA code. |

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| TOPICS | Europe (Regulation 536/2014) | U.S. (Subpart D (401-409) - Code of Federal Regulations title 45-46) |
|---|---|---|
| | The only reference is present in the EC Ethical Recommendation,2008 | FDA regulation (50.25(a)(5)) states that in seeking parents' informed consent, (5) a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained (including the possibility of FDA inspection) must be provided. However, this point is not cited with reference to children's assent. |

**Table 1.** EU and U.S. regulations on paediatric research

## 3. Paediatric plans and paediatric trials methodology

### 3.1. Paediatric plans

As detailed before, both EU and U.S. legislation currently require that a developmental plan (i.e. the PIP in EU and the PSP in U.S.) is approved by the responsible Official Bodies before the paediatric studies will start.

PSP is required for each drug or biological product that includes a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration (including a biosimilar product that has not been determined to be interchangeable with the reference product).

FDA strongly regulates the timing to which the **PSP** should be presented (not later than 60 calendar days after the date of the end-of-phase 2 meeting or equivalent timing if the meeting would not have place. A PSP should include;"(i) an outline of the paediatric study or studies that the sponsor plans to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); (ii) any request for a deferral, partial waiver, or waiver if applicable, along with any supporting information; and (iii) other information specified in the regulations"

In EU the Paediatric Regulation [2] requires **PIPs** to be submitted to the Agency early, wherever possible and the PIPs should:

- include a description of the studies and of the measures to adapt the medicineformulation to make its use more acceptable in children, such as use of a liquid formulation rather than large tablets;
- cover the needs of all age groups of children, from birth to adolescence;
- define the timing of studies in children compared to adults[6].

The table below describes the main measures included in the EMA-PDCO and FDA guidance.

| TOPICS | EMA provisions (PIP)[17] | FDA provisions (PSP) [18] |
|---|---|---|
| **WHO** | The sponsor of a 'product not yet authorised' (that NOT includes variations) (art.7).<br>The sponsor of a marketed patented drug willing to introduce variations (art. 8).<br>The sponsor (even different from the MAH) willing to develop a paediatric study on an old off-patent drug (art. 30. This is voluntary and lead to a PUMA). | The sponsor of a 'new active ingredient' (that includes variations) (this is an obligation under PREA). |
| **WHEN** | Early, wherever possible (in time for studies to be conducted in the paediatric population, where appropriate, before MAAs are submitted).<br>PDCO requires: "not later than upon completion of the human PK studies and initial tolerability studies, or the initiation of the adult phase-II studies (proof-of-concept studies), but before pivotal trials or confirmatory (phase-III) trials are initiated.<br>Applications during confirmatory or phase-III trials in adults, or after starting CTs in children, are likely to be considered unjustified. | Not later than 60 calendar days after the date of the end-of-phase 2 meeting (special rules apply according with the FDA meetings timing).<br>For products for life-threatening diseases, at the end-of-phase 1 meetings. |
| **which AGE TO COVER** | All the paediatric population's groups (birth to 18 years). | All relevant paediatric populations (birth to 16 years). |
| **CONTENTS** | **Administrative and product information** also including:<br>- A.5: Regulatory information on CTs related to the condition (EAA).<br>A.6: Marketing authorisation status of the medicinal product.<br>A.7: Advice from any regulatory authorities.<br>A.8: Orphan drug status in the EEA. | n.a. |
| | Overview of the **Disease Condition** in the Paediatric Population:<br>- pathophysiology of the disease, | Overview of the **Disease Condition** in the Pediatric Population:<br>- pathophysiology of the disease, |

6 EMA website: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000293.jsp&mid=WC0b01ac0580025b91

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| TOPICS | EMA provisions (PIP)[17] | FDA provisions (PSP) [18] |
|---|---|---|
| | - diagnosis,<br>- currently available treatments and/or prevention<br>- incidence and prevalence of the disease. | - diagnosis,<br>-currently available treatments and/or prevention<br>- incidence and prevalence of the disease. |
| | Overview of the **Drug or Biological Product:**<br>- mechanism of action<br>- potential therapeutic benefits<br>- Other possible therapeutic uses of the drug | Overview of the **Drug or Biological Product:**<br>- mechanism of action<br>- potential therapeutic benefits<br>- Other possible therapeutic uses of the drug |
| | **Extrapolation** could include:<br>- efficacy from adults to children or from older to younger children,<br>- safety information from adults to children can also be included,<br>- modelling of PK and/or PD if used for decision-making. | Overview of Planned **extrapolation** to Specific Paediatric Populations:<br>- any plans to extrapolate efficacy from adult or from one paediatric age group to another including neonates,<br>- extrapolation for other drugs in the same class, can be considered as supportive information, |
| | **Request for Drug-specific waivers (global or partial):**<br>The requirement to submit a PIP shall be waived for specific medicinal products or classes of medicinal products that:<br>are likely to be ineffective or unsafe in part or all of the paediatric population;<br>are intended for conditions that occur only in adult populations;<br>do not represent a significant therapeutic benefit over existing treatments for paediatric patients. | **Request for Drug-Specific Waiver(s):**<br>(a) Necessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed).<br>(b) There is evidence strongly suggesting that the drug or biological product would be ineffective or unsafe in all paediatric age groups.<br>(c) The drug or biological product (1) does not represent a meaningful therapeutic benefit and (2) is not likely to be used in a substantial number of paediatric patients<br>Partial waiver provision also apply:<br>-if attempts to produce a paediatric formulation failed<br>- for a specific age group. |
| | Planned **Nonclinical and Clinical Studies and timeline** | **Planned Nonclinical and Clinical Studies and timeline** |
| | **Paediatric Formulation Development** | **Pediatric Formulation Development** |

**Table 2.** Main provision to apply for PIP and PSP

Considering the two described systems, we noted some interesting differences. In particular, while the EU Paediatric Regulation covers all the paediatric medicines (in-patent, off-patent, under development) and deserves incentives only to the off-patent drugs, in U.S. two different

regimens apply for: a) medicines to be granted a paediatric exclusivity after a solicited request (Written Request) as stated in BPCA, and b) medicines for which a PSP is mandatory under PREA. Noticeably, the medicines that are under PREA can also be granted a Written Request, allowing to receive a paediatric exclusivity (see also Fig.1).

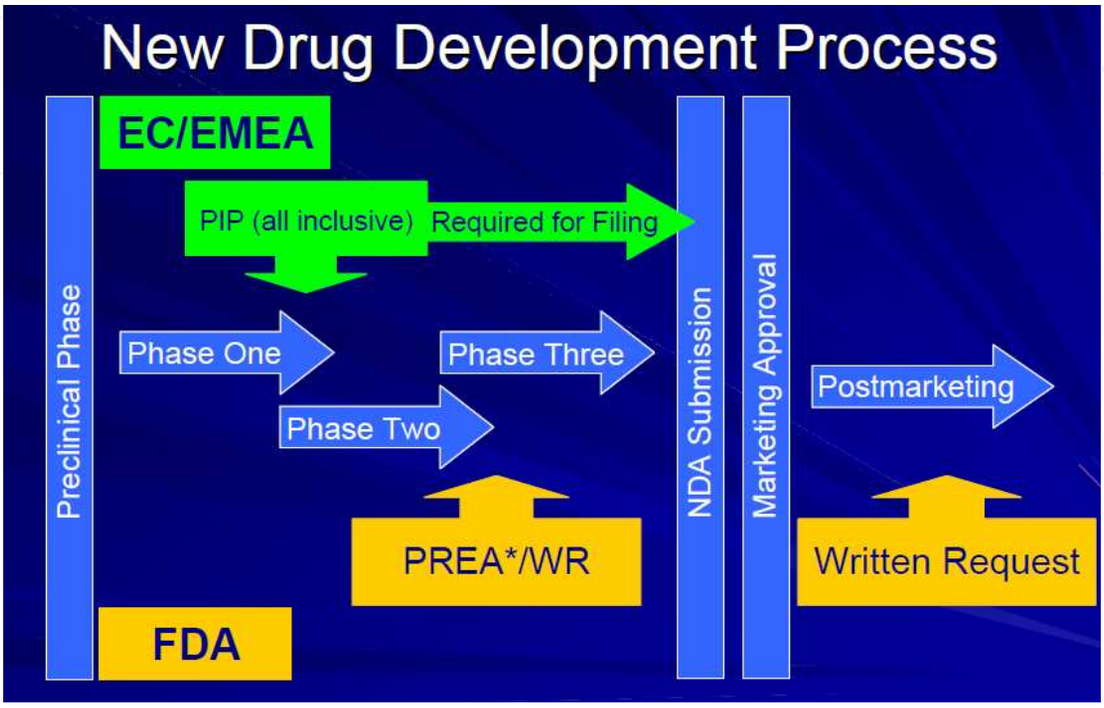


**Figure 1.** Paediatric drug regulatory process in EU and U.S. (source: FDA and EMA Paediatric Regulatory Process: J Temek, MD, FDA website)

Moreover, the paediatric developmental plan procedures of the two Agencies are not completely aligned mainly due to the different regulatory status provided by the different regulations and the different approaches of the two Committees. In particular:

- In EU, unlike in the U.S., a MAA (Marketing Authorisation Application) (equivalent to NDA in U.S.) must contain the results of the paediatric studies conducted in compliance with the agreed PIP (or waiver or deferral). In lack of this, the MA cannot be granted.
- In EU, the paediatric product development is requested earlier in the regulatory process than in U.S.
- In EU, the PDCO, the counter part to the PeRC in the U.S, unlike the PeRC, makes binding decisions.
- FDA "feasibility " criteria for waivers do not exist in the EU legislation. Thus, a study may be required in EU but waived in the U.S. under PREA.
- FDA may request or grant paediatric studies under BPCA, using the voluntary financial incentive, even during the PSP process, while in Europe patented drugs do not have access to financial incentives.

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- Finally, unlike the U.S., the EU does not have a public process whereby paediatric focused post-marketing safety reviews are presented to an Advisory Committee.

These differences still represent an obstacle to a prompt development of paediatric drugs in a global context. An intensive work aimed at merging the paediatric efforts at the two levels is highly required and desirable. To this aim, currently a process of 'Information Exchange' is in place to discuss product-specific paediatric development issues and general scientific/regulatory/safety issues. The Japan Pharmaceuticals and Medical Devices Act (PMDA) has recently joined this initiative as observer.

### 3.2. Paediatric trials methodology

#### *3.2.1. The ICH-E11 guideline*

Before specific paediatric legislations were in place, regulators, companies and clinicians were well aware that the current methodological approach, based on well-designed RCTs, could result difficult to apply in selected cases such as the paediatric population.

In particular, in paediatrics the following issues are challenging large population available for RCTs, randomisation procedure, placebo use, availability of validate paediatric endpoints, appropriate outcomes, long-term effects evaluations, etc.

The ICH-E11 Guideline, issued in 2000 at international level [19], has represented the main international reference for paediatric CTs and the methodological standard to perform paediatric CTs scientifically correct, and ethical in the same time. It still represents the only standard acceptable by the Regulatory Authorities.

The guideline milestones are:

- Paediatric patients should be given medicines that are properly evaluated for their use in the intended population.
- Product development programs should include paediatric studies when paediatric use is anticipated.
- Development of appropriated products in paediatric patients should be timely and, often requires the development of paediatric formulations.
- The rights of paediatric participants should be protected and they should be shielded from undue risks.
- Responsibility should be shared among companies, regulatory authorities, health professionals and society as a whole.
- Marketing Authorisation Holders (MAHs), and competent authorities/medicine regulatory agencies are the two major stakeholders responsible for medicine safety at the time of authorisation.

The approach to the clinical programme needs to be clearly addressed with the regulatory authorities at an early stage and then periodically during the development process. To this aim, the guideline has provided specific indications on trial characteristics, including:

- when initiating a paediatric program for a medicinal product (need of a medicinal products, therapeutic benefits, lack of alternatives);
- timing of initiation of paediatric studies during medicinal product development (need that preliminary safety/tolerability data are known in adults);
- types of studies (PK, PK/PD, efficacy, safety); according to the principle to avoid unnecessary studies in all paediatric age groups, large efficacy studies should be considered only when extrapolation of results from adults (or from older children to younger) is not feasible; on the contrary, PK studies and short and long term safety evaluations are always required.
- age categories: five paediatric ages have been identified from neonates to adolescents and each paediatric group should be given medicines that have been appropriately evaluated for their use;
- special rules for ethic approval of paediatric clinical investigation (including children right to be informed and privacy).

*3.2.2. The ICH-E11 modification process*

Currently, a revision of the ICH-E11 guideline is ongoing. It derives by the relevant changes occurred in the last years, both at scientific and regulatory levels. **Innovative methods of research are in progress** to overcome the existing paediatric studies limitations and are having a profound impact on the assessment procedures at the regulatory agencies level. The main novelties in the field are:

- use of innovative PK/PD methodologies for dosing and efficacy extrapolation exercises [20];
- use of population PK PD (pop PKPD) models to assess different clinical scenarios without exposing children to any risk to explore new drug [21];
- use of alternative statistical approaches to reduce the size of the experimental population and the number of the trials needed in the clinical phase [22].

The updated E11 Guideline as proposed in August 2014, aims to include the new scientific and technical knowledge advances in paediatric drug development in a new regulatory guidance. To this aim, an addendum to the ICH Topic E11 guideline will be finalised by November 2015 with the following revised topics:

- Timing of paediatric development: need for more harmonisation and clarity to guide the developers of paediatric medicines; it is proposed to focus on the multi-national/multi-regional status of many paediatric trials for which the requirements of multiple regulatory authorities should be satisfied.
- Age classification and paediatric subsets including neonates: there is the need for better understanding the developmental process in paediatric subsets, especially neonates and infants.
- Ethical considerations in paediatric studies: there is the need for enhance the ethical considerations in paediatric studies.

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- Types of studies and methodology of CTs: the advances in paediatric CTs design and conduct should be incorporated in the ICH-E11 guidance including: innovative study designs, development of clinical outcome assessments, development of validated age-appropriate clinical endpoints and surrogate markers (biomarkers), specific scales for measuring outcomes particularly in case of younger age groups,
- Common rules to apply appropriate principles for extrapolation of data (from adult to paediatric populations or older children or different indication). This last point could possibly lead both the Agencies to agree a Paediatric Algorithm firstly proposed at FDA level and still now not regularly adopted at EMA level.
- Formulation challenges in paediatric drug development: need for developing specific comprehensive guidance on formulation development for children.

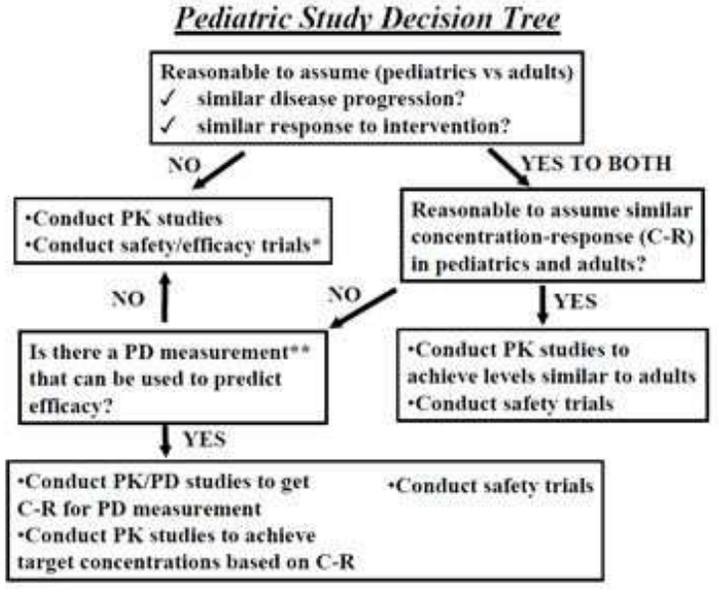


**Figure 2.** Paediatric Study decision tree for bridging efficacy data in an adult population to a paediatric population (source: FDA)

## 4. Paediatric trial incentives and main results of the existing legislation

As stated before, important changes both in U.S. and EU legislations both imposed the pharmaceutical industry to study medicines in children, with the aim to increase the number of paediatric trials to be conducted, to reduce the existing gap. A comparison between the two regulations in terms of impact on paediatric trials is difficult, because of the existing differences on requirements and incentives provided in the two contexts, as well as the very limited amount of published data on the regulations results. As a general finding, it seems that public funding provisions and active strategies both in Europe and US have a strong relevance in improving the current situation through the conduction of studies in children and adolescent in the world.

### 4.1. Impact of paediatric regulation on paediatric trials

In Europe, the most recent available document summarising the main results of the Paediatric Regulation has been released by the EC covering the period 2007-2012. It provides relevant information on PIPs and paediatric trials approved in Europe. It states that:

By the end of 2012, the Agency had agreed 600 PIPs (more than 1.000 presented). Of these, 453 were for medicines that were not yet authorised in the EU (Article 7), while the remaining ones are related to new indications for patent-protected products (Article 8) or PUMA (Article 30).These plans cover a broad range of therapeutic areas, as shown in the figure below and all the paediatric ages including neonates.

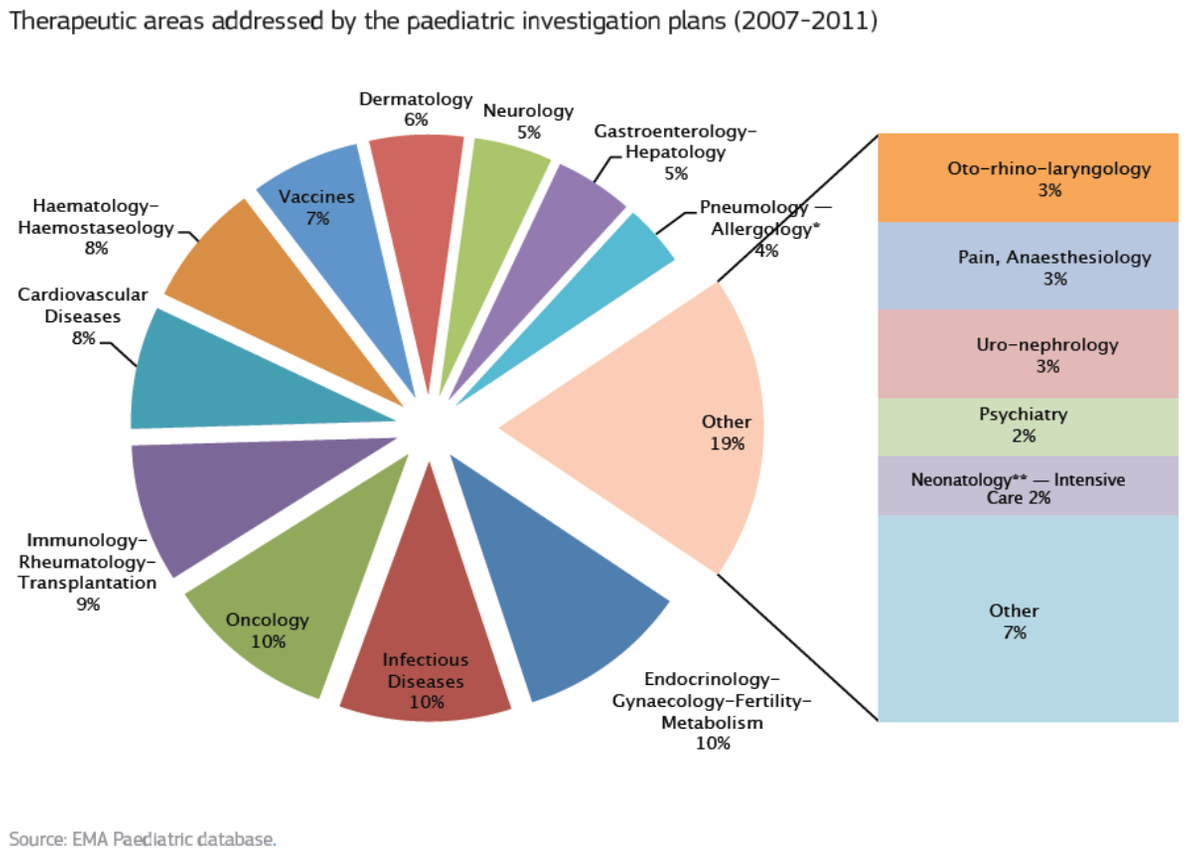


**Figure 3.** Therapeutic areas addressed by the PIPs (2007-2011).[7]

Regarding the number of paediatric trials, the reference derived by the official source EudraCT[8] demonstrates that the number of trials in children did not increase after the approval of the Regulation but remained stable between 2006 and 2012, corresponding to an average of 350 trials per year. However, until recently EudraCT was limited to paediatric trials com-

7 Progress Report on the Paediatric Regulation COM (2013) 443 Final

8 EUDRACT is the EU register of all (ongoing, completed, prematurely terminated) trials with medicinal products taking place in the European Union and those studying medicines for paediatric use contained in an agreed PIP carried out in third countries.

mencing in the EU, while data on paediatric trials that are part of a PIP and conducted outside the EU have only become available since spring 2011.

| | 2005 | 2006 | 2007 | 2008 | 2009 | 2010 | 2011 | 2012 |
|---|---|---|---|---|---|---|---|---|
| Paediatric trials (number) | 254 | 316 | 355 | 342 | 404 | 379 | 334 | 332 |
| Paediatric trials that are part of an agreed PIP* | 2 | 1 | 2 | 6 | 16 | 30 | 76 | 76 |
| Proportion of paediatric trials that are part of an agreed PIP among paediatric trials* | 1 % | 0 % | 1 % | 2 % | 4 % | 8 % | 23 % | 23 % |
| Total number of trials (adults and/or children) | 3 350 | 3 979 | 4 749 | 4 512 | 4 445 | 4 026 | 3 809 | 3 698 |
| Proportion of paediatric trials of all trials | 8 % | 8 % | 7 % | 8 % | 9 % | 10 % | 9 % | 9 % |

Source: EudraCT Data Warehouse using a predefined query on 6 March 2013 and counting the first authorised trial only, in the case of more than one Member State.

**Table 3.** Paediatric Clinical Trials by year of authorisation.

Of the total number of trials conducted in the last years after the approval of the Paediatric Regulation, only a few have been included in the Marketing Authorisation documentation, in order to obtain a paediatric indication.

In particular, data from TEDDY-EPMD[9], a database including information on the paediatric medicines approved by EMA, demonstrate that, after the implementation of the Paediatric Regulation, on a total of almost 70 new active substances approved for children by EMA, 33 applications include a paediatric plan (all available in 'COM (2013) 443 Final' at www.ema.europa.eu). Additional 12 medicines received a paediatric indication using results of the existing studies after reviewing all the studies at central level (art.45-46 of the Paediatric Regulation) (26).

### 4.2. Impact of FDA rules on paediatric trials

Between the 1998 and 2011the FDA issued ~340 Written Requests for new paediatric studies, today 533 labelling changes associated with BPCA and PREA acts have been approved (BPCA only = 161; BPCA + PREA = 73; PREA only = 249; Rule = 49; None = 1), which is significantly higher if compared to the number of labelling changes approved in Europe.

On the basis of these data, according to Lynn Yao it is possible to affirm that: 'Before BPCA and PREA became law, more than 80% of the drugs approved for adult use were being used

9 www.teddyoung.net

in children, even though their safety and effectiveness had not been established in children. Today that number has been reduced to about 50%. (http://blogs.fda.gov/fdavoice/index).

| **With New Pediatric Studies** | **N°484** |
|---|---|
| PK | 122 |
| Efficacy | 133 |
| Safety | 281 |
| With no New Pediatric Studies | N°49 |
| TOTAL | N°533 |

**Table 4.** FDA- New Pediatric Labelling Information Database (1998-2014)

An analysis performed on 174 CTs completed for Pediatric Exclusivity published in May 2010 [23], demonstrated that the U.S. is the most frequent site for conducting CTs, followed by Europe. However, 65% of paediatric trials were conducted in at least 1 country outside the U.S. and 11% did not include any sites in the U.S. Fifty-four countries were represented, and 38% of trials enrolled patients in more than 1 site located in a developing/transition country.

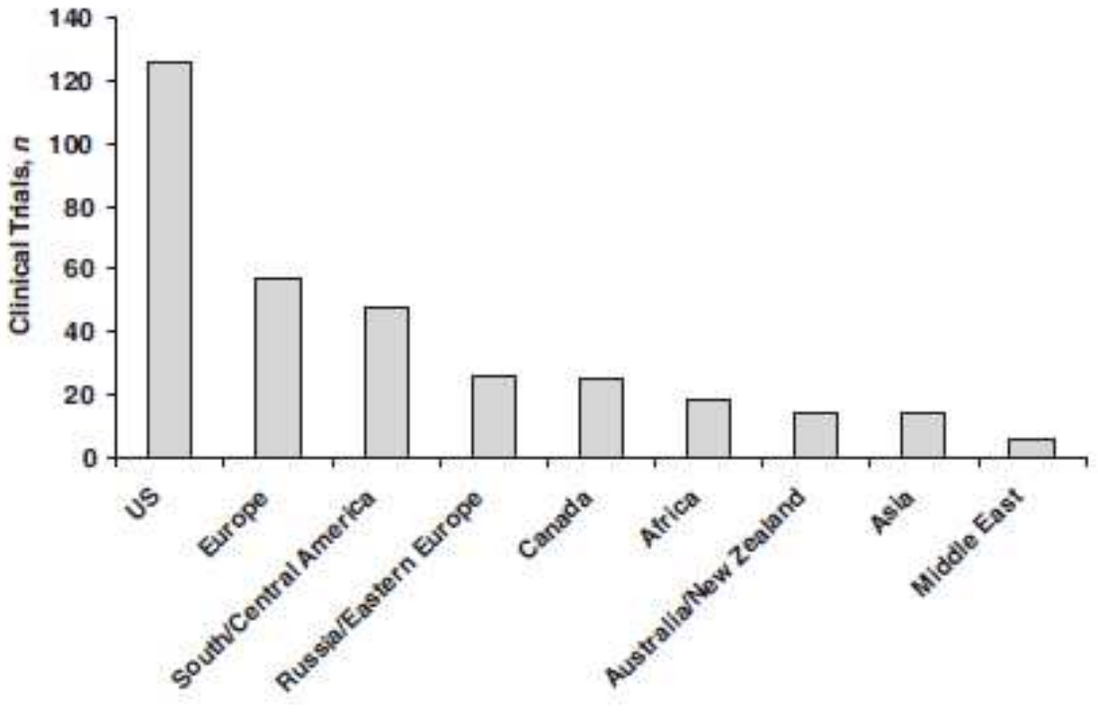


**Figure 4.** Location of 174 trials included in BPCA act.

Under these programs, ~436 separate studies that enrolled ~56,000 children were performed over a 5-years period. An example of results achieved by public incentives to paediatric research is provided by an extensive study evaluating outcomes of BPCA procedures granted

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from 2002 to 2007 [24]. This study, analysing 99 Written Request[10] applications submitted to FDA, reports that:

- 257 paediatric CTs (average 2.6 trials per application) have been conducted, covering approximately 60 indications. The most commonly studied indications were bacterial infections;
- the paediatric trials enrolled at least 46,000 subjects in 5,850 clinical centres;
- all paediatric ages have been addressed, but most of patients were aged 12-17 years old;
- in contrast with the sponsors' trend to shift the location of adult trials away from the country, the U.S. remains the dominant location for paediatric trials (54%), although most paediatric drug programmes are global;
- The trials were distributed across more than 60 countries and the EU contributed 11% of the centres and 7% of patients

### 4.3. Funded studies for paediatric medicines in EU and US

Both in EU and in U.S., funding is devoted to better support paediatric drugs development. Initiatives in this direction are justified under many points of view such as:

Relatively few trials specifically studying the younger age groups, (neonates, infants and toddlers) were approved. In fact it has been demonstrated [23] that from 1998 through 2010, only 23 (6 percent) of the 365 labelling changes, after the submission of new paediatric studies, included the addition of information from studies with neonates.

The most commonly studied indications do not necessarily reflect greatest paediatric therapeutic needs but closely matched the distribution of these drugs over the adult market, and not the drug utilization by children [23].

Off-label drugs are poorly studied. Neither the financial benefit for the pharmaceutical companies in USA, neither the new MA, the PUMA, ad hoc created in EU, demonstrated to be attractive for the commercial sponsors.

Strategies have put in place to overcome this limitation mainly based on funding ad hoc studies and promoting non-commercial, research-driven paediatric trial. Positive examples of these strategies in EU and in US are described below.

**1.** *FP7 Research Framework provisions to develop off-patent drugs currently used off-label in children*

The EU supports research into paediatric medicinal products through its multi-annual Framework Programme for Research and Technological Development.

According to article 40 of the Regulation, the European Research Framework Programs should reserve funds to support PUMAs in case of off-patent drugs recognised as of high therapeutic interest for children and included in a 'Priority List' (PL) adopted, on annual basis, by the EMA (European Medicines Agency) through its Paediatric Committee.

10 A Written Request may be initiated by FDA or in response to a Proposed Pediatric Study Request (PPSR).

In the last 6 years such EC funds have been delivered through the Seventh Framework Programme for Research (FP7-FRP). In particular, with reference to HEALTH-(2007-2013) Programme area, five calls for proposal have been released with reference to the topic 4.2-1 'to develop off-patent medicinal products for the paediatric population'.

From 2007 to 2013, 20 projects were granted with funds. The total amount awarded to these projects is 98.6 million Euros.

The twenty approved projects are investigating a total of 24 active substances, in 10 therapeutic areas (see tab. 5). In particular a total of 71 studies have been funded, involving almost 400 investigational sites in EU and non-EU countries, 246 partners of whom 51 are private companies and around 7000 children (representing 23% of all the paediatric patients included in clinical trials in Europe from 2007 to 2011) were recruited. Eighty percent of the projects include studies to develop new age-appropriate formulations or dosage form and all paediatric subgroups are represented in the clinical trials with particular reference to preterm and/or term newborns.

| Project | Active Substance(S) | Addressed paediatric indication(s) | Therapeutic area |
|---|---|---|---|
| TINN | Ciprofloxacin*<br>Fluconazole | treatment of infections in preterm and term newborns | Infections |
| TINN2 | Azithromycin | treatment of infections in preterm and term newborns | |
| NeoMero | Meropenem | treatment of late-onset sepsis in neonates and infants aged <3 months<br>treatment of bacterial meningitis in neonates and infants aged <3 months | |
| NeoVanc | Vancomycin | treatment of late onset bacterial sepsis caused by vancomycin susceptible bacteria in neonates and infants aged under three months | |
| NeoOpioid | Morphine<br>Fentanyl | treatment of acute pain | Pain |
| GAPP | Gabapentin | treatment of chronic pain | |
| Loulla & Philla | Methotrexate*<br>6-Mercaptopurine* | treatment of Acute Lymphoblastic Leukemia | Malignant neoplasms |
| 03K | Cyclophosphamide<br>Temozolomide | treatment of paediatric malignancies | |
| EPOC | Doxorubicin* | treatment of childhood cancer | |
| HIP trial | Dopamine | management of hypotension in preterm newborns | Cardiology |
| NeoCirc | Dobutamine | treatment of systemic hypotension in infants | |
| LENA | Enalapril | cardiac failure in children | |

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| Project | Active Substance(S) | Addressed paediatric indication(s) | Therapeutic area |
|---|---|---|---|
| NEMO | Bumetanide | treatment of neonatal seizures in babies with hypoxic ischemic encephalopathy | Neurology |
| KIEKIDS | Ethosuximide | treatment of absence and myoclonic epilepsy | |
| TAIN | Hydrocortisone* | treatment of adrenal insufficiency in neonates and infants | Endocrinology |
| METFIZZ | Metformin | treatment of polycystic ovary syndrome | |
| CloSed | Clonidine* | Sedation in intensive care | Intensive care/ anaesthesiology |
| DEEP | Deferiprone* | treatment of chronic iron overload | Haematology |
| PERS | Risperidone | treatment of conduct disorder<br>treatment of schizophrenia | Child & adolescent psychiatry |
| NEuroSIS | Budesonide* | prevention of bronchopulmonary dysplasia | Respiratory and cardiovascular disorders |

* received an Orphan Drug designation (four in the same indication addressed by the project)

**Table 5.** FP7 approved projects in Europe ([25]

These data demonstrated that paediatric studies receiving support from the EU institutions are attractive even outside Europe and also for the private companies engaged in view of the final PUMA approval.

Furthermore, to date, 22% of the planned enrolment for these trials is completed, that is in contrast with the reported low recruitment capacity and difficulties with the conduct of paediatric trials in Europe.

**2.** *The Pediatric Trials Network (PTN)*

Sponsored by the Eunice Kennedy Shriver National Institute of Child Health and by the Human Development (NICHD), the Pediatric Trials Network (PTN) is an alliance of clinical research sites located around the United States that are cooperating in the design and conduct of paediatric CTs. PTN relates to BPCA since funds are devoted to develop research driven studies in the area where the investments of private companies are very limited and the FDA incentives resulted insufficient.

As European Consortia, the PTN is studying the formulation, dosing, efficacy, and safety of drugs used in paediatric patients. In keeping with the goals of the Best Pharmaceuticals for Children Act, data collected from PTN trials will help regulators to revise drug labels for safer and more effective use in infants and children.

Currently 20 PTN trials are in progress, the results of 4 of them have been published. Noticeably, 3 active substances funded within PTN are also funded under EU FP7 projects. The list of the projects is available on the FDA website and results are continuously updated.

| Trial | Status |
|---|---|
| Metronidazole | Enrolment and analysis completed, clinical study report submitted to FDA, results published |
| TAPE | Enrolment completed in less than 2 months, results published |
| Acyclovir | Enrolment complete, analysis in progress, results published |
| Hydroxyurea | Enrolment completed |
| POPS | Enrolment ongoing |
| Lisinopril PK | Database locked; analyses in progress |
| Midazolam | Data analysis in progress |
| Ampicillin | Results published |
| Obesity informatics | Analysis in progress |
| Anti-staph trio | Enrolment ongoing |
| Sildenafil | Enrolment ongoing, interim PK analysis |
| Clindamycin obesity | Enrolment ongoing |
| Fluconazole safety | Meta-analysis ongoing |
| Midazolam obesity | Protocol in development |
| Acyclovir phase II | Protocol complete, opening sites |
| Pantoprazole | Enrolment ongoing |
| Pediatrix meta-analysis | Protocol complete, analysis ongoing |
| Antibiotic safety (SCAMP) | Protocol complete, selecting sites |
| Diuretic safety | Protocol complete, opening sites |
| Methadone pharmacokinetics | Enrolment ongoing |

**Table 6.** PTN trials

Taking into account these results, we consider that the problems issued by paediatric drug development are only partially solved. Regulations are now quite similar both with reference to the requirements and the incentives provided but profound differences still exist in the practical application.

The U.S. remains the dominant location for paediatric trials but the balance may change in the future. EU results in increasing the numbers of paediatric approved drugs are still disappointing but in EU the number of studies in specific categories (neonates) and of projects responding to real therapeutic need (off-label) is higher than in US. However the approved drugs in this category still remain very few (on a total of 533 labelling changes in U.S. only 19 off-patent drugs have been the object of a FDA Written Request while in EU only 2 PUMA have been granted till now).

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## 5. Conclusive remarks

Despite many regulatory provisions have globally focused, in EU and in US, the attention on the paediatric themes, some significant issues have to be further improved in order to fill in the existing gaps. Some of the most relevant criticisms are summarised below.

1. Especially in EU, it has been recognised that paediatric development strategy is still often perceived as a regulatory obligation, more than an integral part of the whole medicinal development process [26].

2. Paediatric provisions demonstrated not to be able to specifically address the paediatric needs. For example, in Europe most of the therapeutic needs periodically identified by expert groups at EMA/PDCO are still uncovered by PIPs and/or PUMAs. In the U.S. there is a discrepancy between the drug prescription pattern in children and the drugs granted paediatric exclusivity. Actually, the majority of drugs granted paediatric exclusivity is rarely used by children and drugs frequently used by children are underrepresented in the paediatric studies aimed to obtain exclusivity [27].

3. The field of neonatology is quite critical. In Europe, the number of neonates included in clinical trials substantially increasedafter the Paed. Reg. entered into force [3]. However many neonatal therapeutic needs recognised by EMA/PDCO are still unmet [28]. Similarly, in the U.S. only a small percentage (6%) of the labelling changes involving the submission of new paediatric studies included the addition of information from studies with neonates [29].

4. With reference to the availability of drug formulations suitable for children, a lack of age-appropriate formulations, in terms of safety of excipients, palatability, acceptability, dosing flexibility, accuracy and practical handling still exists [3]. In U.S., a public-funded Pediatric Formulations Platform[11] is trying to fill this gap but no similar initiatives have been identified in Europe.

5. Deferral measures have been introduced in both regions to avoid delays, provoked by paediatric development, to the availability of drugs for adults. As a negative counterpart, deferrals are deeply impairing paediatric drug development: 63% of new medicines intended for both adults and children have a deferral in the agreed PIP [3]. In the U.S, despite nearly all (98%) of the rationales for deferrals were consistent with the law, the amount of deferred studies delayed and/or pending is relevant (78%). It has been estimated that the number of pending studies grew by 50%, while the number of delayed studied increased by more than 80% [30].

6. Another example of criticism in paediatric drugs availability deals with rare diseases: both in EU and in the U.S, very few medicinal products for rare diseases affecting children have a paediatric indication[12]. As a consequence, in the U.S. (but not in EU), specific orphan

11 http://bpca.nichd.nih.gov/collaborativeefforts/initiatives/pages/index.aspx

12 data deriving from EuOrphan, a database of EU and U.S. orphan drugs hosted by Gianni Benzi Foundation

programs for paediatrics have been recently proposed (Rare Pediatric Disease Priority Review Voucher Program). The first voucher was awarded under this program in February 2014, but it is still too early to measure the impact.

7. Finally, a lack of appropriate measures to incentive paediatric research has been observed especially in EU. As already mentioned, the PUMA has been unsuccessful until now and, despite the positive results achieved by the projects for the development of off-patent drugs, the specific funding programme setup from 2007 to 2013 under the EU Seventh Framework Programme has not been renewed in Horizon 2020.

On the basis of these few considerations, EU and U.S. regulators should continue to discuss coordinated approaches and to share results.

In particular, these efforts should be concentrate to minimize unnecessary paediatric trials and to optimize trial design, so that the limited paediatric populations available are enrolled only in ethically implemented, scientifically important trials.

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