



## CURRENT EUROPEAN REGULATION PERSPECTIVE ON PEDIATRIC CLINICAL TRIALS

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### ABSTRACT

Evidence based medicine and healthcare constitutes the pillars of optimal medical care. However there are deficits in understanding the quality and efficacy of pediatric therapies, as prime criteria study of regulation required for conducting pediatric clinical trials. Many efficacy data's are anecdotal. It is evident that over 50% of medicines used in children are not licensed for use in pediatric population. The extrapolation of adults data on medicinal products for pediatric population is basically considered inappropriate. Evidently it was considered that it is difficult to conduct clinical trials in pediatric population taking ethical consideration and recruitment issues, the present study focuses on the regulation of pediatric clinical trial in UK.

**KEYWORDS:** Clinical trial, pediatric drug regulation, off labelled drugs, pediatric investigation plan.

### INTRODUCTION TO OFF LABELLED DRUGS <sup>[1]</sup>

Efficacy of the pediatric drug is generally determined by the extrapolation of the adult's clinical trial data and that drugs are consider as a off labelled drugs. Until recently it was considered that it is difficult to perform clinical trials in pediatric patient because of the ethical consideration. Doses for the pediatric population are often determined from adult dosage. Pharmacokinetic differences are there in children and adult. Absorption, distribution, metabolism, and excretion of the drugs are different in pediatric population as compare to the adult. Many inadequately documented drugs are used in pediatric population. There has been a lack of pediatric trials and this will leads to the limited documentation with respect to many approved drugs. Paracetamol is one of the example of off label drug use (age/weight) in a premature infant, other examples are diclofenac sodium used for abdominal pain (indication) in pediatric population. Adrenaline (rout of administration) given to the pediatric population through inhalational rout rather than intravenous route, pediatric specific information is not available on morphine, lack of pediatric data's are there on codeine and this codeine is used as a analgesic in pediatric patient.

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sometimes children also received drugs that do not have approval of drugs regulatory authority and pediatricians prescribed non approved drugs because of there is no available approved drugs or drug strength or formulation suitable for children. In many children hospital the majority of pediatric patient in hospital receiving at least one drug which is off label or unapproved drug. Many risks and adverse drug reaction are also associated with use of the off label drugs and unapproved drugs. Children have same rights as adults to receive effective and safe drugs, i.e. well tested, appropriate route of administration, correct dose, right indication, right period of time, with adequate and correct information and medical surveillance. Critically ill neonates and infants have higher exposure to the off labelled drugs and hence they require clinical trial. Use of these off labelled drugs in pediatric patient is major public health concern. Hence Clinical trials for such drugs is essentially required and should meet every aspects of drug treatment in pediatric patient i.e. occurrences of ADR and all other drug related problem should be documented in clinical practice. Pediatric clinical trial in older drugs is also needed particularly for most commonly used drugs in pediatric population, i.e. analgesic and cardiovascular drugs.

#### EXTRAPOLATION FROM THE ADULT'S CLINICAL TRIAL <sup>[2]</sup>

US Food and Drug Administration (FDA) put a proposal in 1994, based on extrapolation of efficacy determine from adults clinical trial to the Pediatric

population, to maximize the use of the data obtained from the adult's clinical trial and other data when designing Pediatric drug-development programs. Extrapolating efficacy from data obtained from adults clinical trial or other data to the Pediatric population can make more efficient Pediatric drug development and help to increase the number of approvals of the drugs for pediatric use. Extrapolation has been extensively used by FDA since 1997 when issuing written requests (WR) for studies in pediatric population. There is no any simple formula to determine whether there is sufficient proof to support the judgment to extrapolate efficacy to the population of pediatric. The judgment should be based on a body of evidence that takes into account the scientific information of all aspects of the disease and its natural history in the adult and populations of pediatric and the interactions between developmental changes and the disease and responses to therapy, experience with other drugs in the same class and for the same indication, and the validity of the Pediatric efficacy end points. When there is assurance regarding the scientific basis for extrapolation of adult's data, there is greater possibility of successful new Pediatric labeling. In addition, the relatively high failure rate of controlled studies of efficacy emphasizes the importance of incorporating verified scientific approaches and Pediatric expertise in the development of successful protocol of Pediatrics study. Extrapolation of efficacy from the adults clinical trial data to the Pediatric population has helpful to make best use of the available information to increase the efficiency of Pediatric drug-development programs while maintaining the goal of increasing the number of safe effective approval of medicines for use in Pediatric population on the basis of scientifically robust data.

#### **PEDIATRIC CLINICAL TRIAL: <sup>[3]</sup>**

Many treatments which are prescribed by physician for children have not been effectively tested in children, sometimes these results into harmful treatments being given and useful treatments being withheld. There is an equal right of children to participate in Pediatric clinical trials have not always been recognized. The need for Pediatric clinical trial has been increasingly recognized by the scientific community, this leads to the new rules and regulation in some countries for Pediatric clinical trials and adult clinical trials before drug approval is given. Clinical Trials in Pediatric population are more challenging as compare to the adult's clinical trial. Small numbers of children are entering in the clinical trials because many conditions are rare in children, and decisions are taken by parents about participation in the trial on behalf of their child.

#### **A. THE IMPORTANCE OF CLINICAL TRIALS IN CHILDREN :**

Pediatric clinical trials have resulted in considerable improvements in their health care. There are some examples in that a very famous example is childhood acute lymphoblastic leukaemia, in which the 5-year survival improved from 25% to more than 70% as a result

of multi centre pediatric clinical trials. Since there are few Pediatric trials but unfortunately the list of improvements in child health resulting from Pediatric clinical trials is not long and is limited to some childhood diseases. Therefore, many ineffective and even harmful treatments are given to children before they have been appropriately assessed in randomized Pediatric clinical trials, and other useful treatments have had a delayed introduction into practice. In the absence of specific Pediatric clinical trial based data in children, clinicians are forced to extrapolate from results of clinical trial studies in adults. Because of the differences in pharmacokinetic, some adverse effect of the drug is also differ in Pediatric population e.g. the adverse effects to medications such as thalidomide (phocomelia in the unborn child), tetracycline (staining of the teeth), chloramphenicol (the grey baby syndrome), and aspirin (Reye's syndrome in children with viral infections) are specific to children.

#### **B. BENEFITS OF TRIAL PARTICIPATION**

Participants in randomised controlled trials (RCTs) in Pediatric population are having many benefits, including entrance of new treatments that might not be routinely available. Subjects who assigned to placebo from them outcomes having similar to or better than eligible non-participants. Participants or trial subject have lower mortality, fewer clinical events, and lower complication rates than similar patients those are treated outside RCTs.

#### **C. RISKS OF TRIAL PARTICIPATION**

Along with benefits of the participation in Pediatric clinical trial, risks and inconveniences are also there. Potential risks specific to Pediatric population, that are not usually of concern as compare to the studies in adults, i.e. discomfort, inconvenience, pain, fear, separation from parents or familiar surroundings, effects on growing or developing organs, and size or volume of biological samples. In therapeutic research higher degrees of ethically permissible risk are allowed as compare to nontherapeutic research. In therapeutic research, children Parents are prepared to take greater risks in trials that address the treatment of their child's condition, because they assume that it will improve their child's illness. Recruitment issues are quite different for Pediatric clinical trial as compare to adult clinical trials. The recruitment of children is thought to be more difficult as compare to adults. The small number of trial subjects are available, and the major disincentive for the pharmaceutical industry to fund trial in children are, the higher fixed and marginal costs and the market size is often small at the end of an expensive research. This is the most common excuses for failure to do Pediatric studies. the difficulty of finding enough patients to participate, the complex ethical issues associated with studying children, and inadequate numbers of quality Pediatric pharmacology investigators, this all things makes difficult to do Pediatric study.

## REGULATION OF PEDIATRIC CLINICAL TRIAL<sup>[4]</sup>

The pediatric regulation in Europe was proceed by the ICH guidance 11 for conducting studies in the pediatric population it also obligates pharmaceutical manufacturers to conduct clinical studies in children in accordance with an agreed pediatric investigation plan (PIP), in return for six-month patent protection.<sup>[5]</sup>European commission has been introduced the PIP to help insure that medicines for children are included in the main stream drug development process in Europe rather than as an optional extra. After the introduction of the regulation 1901/2006 medicinal product for pediatric use, it is now mandatory for all pharmaceutical companies to submit the PIP to the pediatric committee (PDCO) at EMEA (European medicinal agency) most probably at around the end of the first phase of the testing of the new medicinal product in adult. PIP should be submitted early during the development of the pediatric drugs before the studies to be conducted in the pediatric population, and before marketing authorization applications are submitted. PIP applications can submit during or even before initial PK studies in adult. PIP ensures that the useful data obtained through the study in the children. For ensure the quality, safety and efficacy of pediatric drug, PIP is mainly required. PIP reflects the development plan in clinical non - clinical and technical aspects including timeline and covers all existing or planned (adult) indication and dosage form (including specific age appropriate pediatric formulation or route of administration if necessary). The PIP clearly defines timing of studies in children relative to adults, including deferrals until completion of studies in adult to ensure that studies in children are conducted only when it is safe and ethical to do so.

### PAEDIATRIC COMMITTEE (PDCO)<sup>[5]</sup>

It Established in July 2007. All members are appointed for the period of 3 years, and it is renewable. 33 members are there in the PDCO.

- 5 CHMP (committee for medicinal products for human use) members,
- one expert from each of the 22 Member States not already represented by a CHMP member
- 3 representatives of patients' associations
- 3 health care professional representatives
- Nearly all of the current PDCO members are pediatricians

### PIP INCLUDES {8}

1. Defines timing of study in children compared to adults.
2. It covers the need of study in all age group of children, from birth to adolescence.
3. The formulation which is going to use in children is more acceptable. i.e liquid formulation rather than tablet.

4. PIP covers description of the study.

In some cases the study in the Pediatric population can be deferred until after the study in the adult have been conducted to ensure that study in children is safe and ethical. There are some diseases that not affect the children (for example Parkinson's disease) so the development of the medicine for this type of disease not requires the study in children so PIP will be waived.

### STRUCTURE OF THE PIP<sup>[5]</sup>

**Part A:** Administrative and product information

**Part B:** Overall development of the medicinal product including information on the

Conditions

- Information on the target disease/ condition
- Information on the product mode of action
- Significant therapeutic benefit/therapeutic need

**Part C:** Applications for product specific waivers

**Part D:** Pediatric investigation plan

- Existing data in adult and children
- Details of proposed studies (ongoing or future)
- Proposed timelines

**Part E:** Applications for deferrals

**Part F:** Annexes (references)

Pediatric investigation plan also contains,

#### 1. Existing Data/Overall Strategy Proposed for the Paediatric Development

- Paediatric Investigation Plan indication
- Selected paediatric subset(s)
- Information on the existing quality, non-clinical and clinical data, including existing data in adults and completed studies in children

#### 2. Quality Aspects

Strategy in relation to quality aspects

- Outline of each of the planned and/or ongoing studies and steps in the pharmaceutical development

#### 3. Non-clinical Aspects

- Strategy in relation to non-clinical aspects
- Overall Summary Table of non-clinical studies
- Synopsis/outline of protocol of each of the planned and/or ongoing non-clinical studies

#### 4. Clinical Aspects

- Strategy in relation to clinical aspects
- Overall Summary Table of clinical studies

Applicant should notify the agency about the intent for the PIP by using the form for the letter of intent. The letter of intent can be send to the EMEA. Applicants those are fail to comply with the Pediatric regulation for example late submission of PIP, agency reports yearly to the European commission about those applicants.<sup>[6]</sup> According to Article 16 of Directive 1901/2006, "the pediatric investigation plan or the application for waiver shall be submitted with a request for agreement, except in

duly justified cases, not later than upon completion of the human pharmacokinetic studies in adults.” The proposed pediatric development must therefore be integrated into the product clinical development plan at a very early stage and at the latest, upon completion of the ‘proof of concept’ study in adults. {9} Applicant has to submit an application as one electronic copy on CD or DVD accompanied by a cover letter. In the cover letter applicant has to mention that the application is for a PIP or a request for a modification of agreed PIP. In cover letter applicant has to mention the PIP number, and should also declared about the electronic versions

(WORD and PDF) are identical. Finally the applicant should mention in the cover letter that the ‘check-sum’ number received when the electronic application template form is saved. When submitting the document, the applicant has to group that document into one or more compressed (zip) file. Each zip file should not exceed 40Mb. Applicant will be informed of the names of the assigned rapporteur and peer reviewers as soon as they have been nominated and this will take approximately two months before the planned start date of the procedure. The agency will appoint its pediatric coordinator after receipt of the full application. {8}

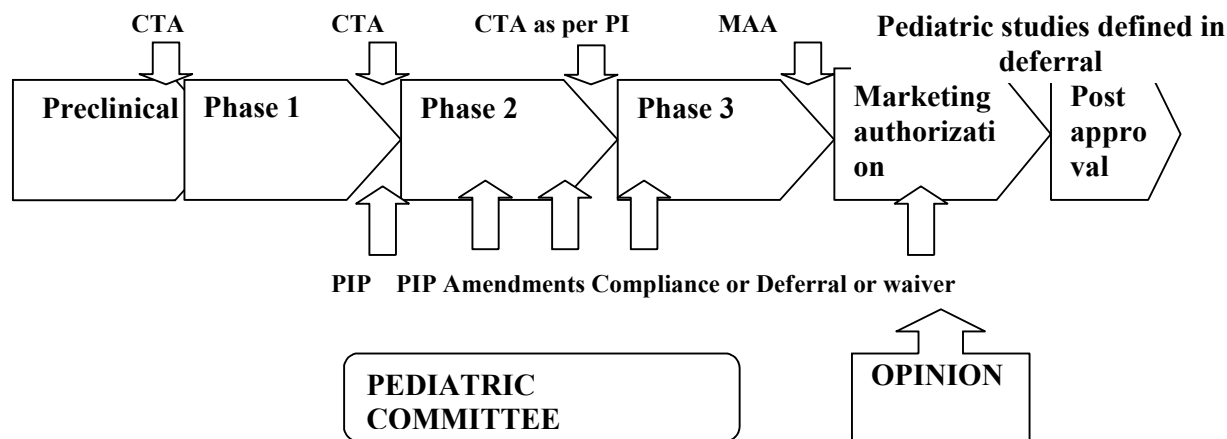


Figure 1: Timing of PIP development and PDCO consultation

ASSESSMENT OF PIP :{10}

Assessment of the PIP is carried out by the EMA (scientific administrators). The Paediatric Coordinator acts as the interface between companies and PDCO. PDCO members and alternatives share the work.

Designated Rapporteur and Peer Reviewer both review and comment on the Summary Report, (Day 30) then present to PDCO (Day 60). Other Members comment on it during and after discussion (verbally or in writing). They Achieve consensus or vote if necessary and Experts also invited if necessary.

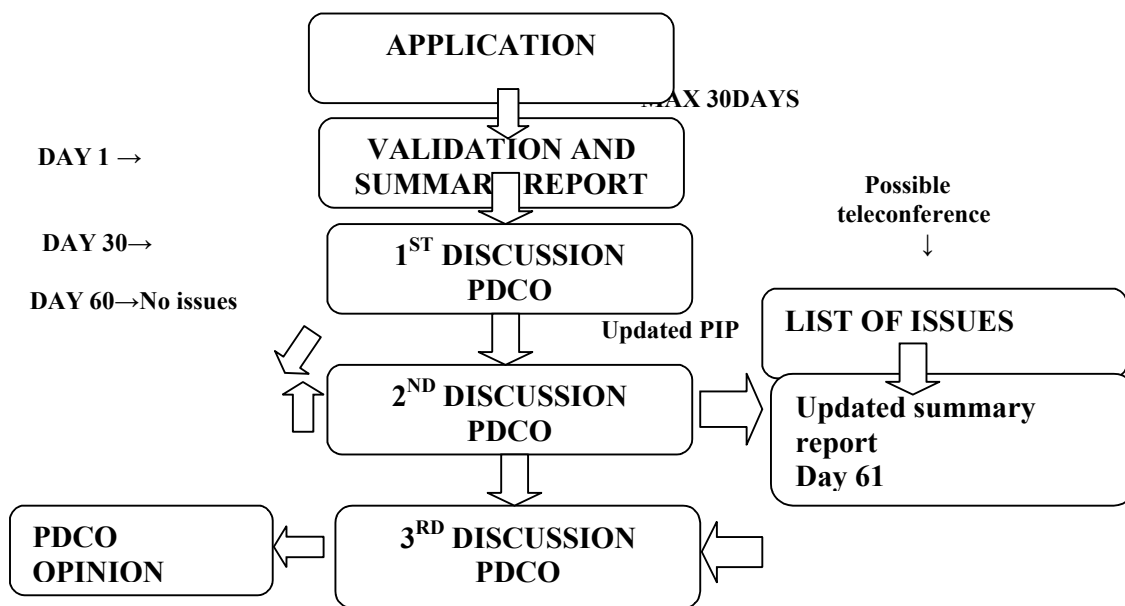


Figure 2: Overview of PIP procedure

Teleconference with the applicant is also carried out on any issue. Oral explanation meetings are also possible. If major changes occurs during day 30 and day 60, these major issues are difficult to clarify during procedure. Important issues should be clarified prior to day 61(difficult to solve major issues between day 61 and 120 even with a face to face meeting. On between 90 to 120 days final PDCO position and issues communicated to the applicant. And they give last chance for clarification in oral explanation. In these 90 to 120 days there is no possibility of submission of additional or modified documents. A compliance check is performed to verify that all the measures agreed in a PIP and reflected in the EMA decision have been conducted in accordance with the decision, including the agreed timelines. To avoid delays, compliance check should be initiated by applicant prior to submission (30 or 60 day procedure) once final clinical trial report is available. Request to modify agreed PIP may be needed prior to compliance check. If non-compliance is found then the MAA will not be validated.

### CONCLUSION

This study emphasize a need for pediatric clinical studies as well as compilation of existing clinical experience and scattered evidence, particularly for drug treatment pediatric population. A large number of medicines used in pediatric population have not been tested on pediatric population and hence they are used as **off label or unlicensed**. This absence of suitable authorized medicinal products to treat conditions in children is an issue that has been of concern for some time, and one that is increasingly coming to the fore. Children have often had to accept medicines and treatments based on what is known to work in adults. As a society, we should not agree to this "hand-me-down" approach. To improve clinical care of children, researchers should conduct more studies focused on

children's health and developing treatments, drugs specific to children.

### ACKNOWLEDGEMENT

The authors are profoundly thankful to Dr. K. Pundarikakshudu, Director of L. J. Institute of Pharmacy, Ahmadabad, India for providing all the facilities, guidance's and encouragement to carry out the research work.

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#### How to cite this article:

Ketan Mishra\*, Jignesh Shah, Dilip Maheshwari\*: Current European regulation perspective on pediatric clinical trials, 6(1): 2311 - 2315. (2015)

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