

# Challenges of paediatric drug development and impact of paediatric legislation

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## Abstract

Medical writers are increasingly involved in designing and documenting overall plans in paediatric drug development, e.g. EU PIPs (Paediatric Investigation Plans) and individual components, e.g. protocols and study reports. It is essential to differentiate between the overall process and the individual components that together constitute paediatric drug development. Paediatric drug development does not mirror the development of drugs for adults. Drugs are developed by commercial companies. Paediatric drug development was triggered by laws dating back to 1997 (USA) and 2007 (EU) to give children better access to pharmaceutical progress. The active players are the regulatory authorities, the respective company, and the professionals involved in the planning and execution of defined development activities. For companies, participation is partially voluntary in the USA but compulsory in Europe. Key elements are assessing epidemiology and existing therapies in children, and all elements of adult drug development adapted to children's different anatomy, metabolism, and developmental stage. Paediatric drug development might include, for example, developing liquid formulations for children (vs. tablets), doing studies in juvenile animals, and paediatric clinical studies. Most key components of the paediatric drug development plan are negotiated between authority and company, and executed by paediatricians, clinical pharmacologists, and others.

**Keywords:** Paediatric drug development, Paediatric Investigation Plans, Pediatric legislation

## Introduction

With few exceptions, paediatric drug development does not mirror adult drug development. Some companies do develop drugs for children, e.g. vaccine developers or companies targeting rare

paediatric diseases. In general, drug development is market-driven by companies competing in the business world. Paediatric drug development is funded by an industry that develops predominantly adult medicines. In the USA in 1997 the FDAMA (FDA Modernization Act) offered 6 months patent extension in return for voluntary drug research in children. This was complemented in 2003 by the mandatory PREA (Pediatric Research Equity Act).<sup>1</sup> These laws are required to be re-authorized every 5 years, the next re-authorization being due in summer 2012. The EU paediatric regulation, in force since 2007, added new momentum to the development of drugs for children.<sup>2,3</sup> This legislation is intended to ensure that children are considered within the process of development of drugs for adults. This is relatively straightforward where a disease exists both in adults and in children, and is more complex when this is not so, but where a drug might have another use in children, e.g. ibuprofen for persistent arterial duct in newborns. Specifically, targeted paediatric drug development would require a different framework.

## US pediatric legislation and background factors

Fig. 1 is a showcard from 1918 with a drug labelled for adults and children. Fig. 2, from slightly earlier, is for a product advertised for children only. These labels show only limited comparability with today's labels, which describe only the proven properties of the respective medicine. It was different in 1918. Dr Arnold's cough killer contained morphine. It certainly suppressed cough, but it could also kill children. These drugs were on-label, but in these days the label could claim anything. The manufacturer didn't have to prove these claims.

In the USA, it is only since 1962 that drug manufacturers have had to prove the efficacy and safety of their medicines. Only since then have modern drug



Figure 1: Lung tonic for coughs, colds, and chest trouble, suitable for children and adults. Showcard 1918. Source: [www.wellcomecollection.org](http://www.wellcomecollection.org).



Figure 2: Dr Seth Arnold's Cough Killer. Colour trade advertisement, 1800s. Like many nineteenth-century over-the-counter medicines, much of its effect was due to the fact that it contained a narcotic drug or hallucinogen, in this case morphine, a derivative of opium. People were unwittingly being exposed to habit-forming drugs, something the American Medical Association started investigating about this time. It compiled a list of dangerous 'nostrums' in May 1909, including alcohol, opium and its derivatives, morphine and codeine, cocaine, chloral, and cannabis. Legislation followed eventually.

Source: [www.wellcomecollection.org](http://www.wellcomecollection.org).

labels existed. One consequence of the US Kefauver-Harris amendments (1962) was that, to avoid litigation, manufacturers introduced disclaimers that the respective medicine had not been tested in children.<sup>4</sup> Since then much has been learned about children and medicines. Clinical pharmacology has evolved as a science, with paediatric clinical pharmacology as a sub-

specialty,<sup>5,6</sup> adding to our understanding of the maturation of organ systems, children's metabolic pathways, absorption, and excretion.<sup>7</sup> Generations of hospital clinical pharmacologists have spent considerable time procuring hand-made paediatric formulations. Paediatric clinical pharmacology evolved by investigating drugs that were already on the market. The 1997 US legislation encouraged the generation of 'some' paediatric data – at a time when for many drugs no paediatric data were available at all.

## EU paediatric legislation: a new approach

The EU paediatric legislation came into force in 2007.<sup>2,3,8</sup> It parallels the US legislation, but its scope is radically increased. Marketing Authorization Applications (MAAs) for any new drug must be submitted with a Paediatric Investigation Plan (PIP) approved by the EMA Paediatric Committee (PDCO), unless the EMA confirms in writing the applicability of a class waiver. Generics are exempt, orphan drugs are not. The EMA CHMP (Committee for Medicinal Products for Human Use) approves new drugs, but the PDCO can block a submission. EMA will not validate a submission without an approved PIP. The PDCO is composed of 33 members plus another 33 alternates. Each member state is represented by one member and one alternate; additional members represent the CHMP, professional paediatric healthcarers' organizations, and patient organizations. The PDCO decides about PIPs, waivers (no development in children) and deferrals (later execution of studies).

The PIP must cover all age groups as defined by ICH E 11: preterm newborns (<36 weeks gestational age), newborns (0–27 days), infants and toddlers (1–23 months), children (2–11 years), and adolescents (12–17 years).<sup>9</sup> It should be submitted at the end of human pharmacokinetics (PK), interpreted by EMA as the end of phase 1, i.e. before proof of concept. It must include plans for preclinical testing, e.g. juvenile animal studies; formulation(s), e.g. intravenous for preterm newborns, liquids for infants and young children; clinical pharmacology for dosing; and clinical trials.

## Development strategy for drugs for children

Drug developers must do their paediatric homework. Within the framework of EU and US legislation, the essential questions are as follows. Does the targeted disease exist in children? From which age onwards? Are the mechanisms of drug and disease comparable enough between adults and

children to allow extrapolation of efficacy? Which dose should be used at which age? What clinical trials are needed? What special formulation(s) are needed? Are studies in juvenile animals of value? The company team will know the adult disease, but for children additional external expertise will be required. The best approach is to reach tentative conclusions within the company, and then to challenge them with a group of external paediatric specialists face-to-face. The PIP is then written. Usually, the first round of 'paediatric negotiations' is with EMA PDCO and negotiations with the FDA come later. If the company's approach is scientifically sound it will be easier to convince the regulatory authorities. EMA PDCO will also ask for paediatric drug development in rare and very rare diseases.

### PIP or paediatric Plan

The PIP life cycle has three phases: preparation; submission and negotiation; execution and modification(s). The PIP submission begins with a letter of intent 2 months before PIP submission (template on the EMA paediatric website<sup>10</sup>). EMA will communicate the names of three key people: the EMA paediatric coordinator, the PDCO rapporteur, and the PDCO peer reviewer. The 20 EMA paediatric coordinators serve as a procedural and administrative link between the applicant and the PDCO. They also help with teleconferences and give procedural advice.

There is no official PIP template, but the 'EMA/PDCO summary report template with internal guidance text'<sup>11</sup> is used by most applicants. The PIP, application form, clinical study form, and a cover letter must be sent to the EMA coordinator and the PDCO rapporteur and peer reviewer by post or courier and via Eudralink. Once the submission is validated, the entire documentation must be sent as a CD-ROM and via Eudralink to all PDCO members and alternates. References are required as PDF files on the CD-ROM. To meet deadlines, receipt via Eudralink is accepted.

The PIP negotiation procedure consists of two 60-day blocks. The PDCO day 30 discussion is documented by a report. The day 60 discussion results in a list of requested modifications, and a clock stop starts. Once the requests for modification have been considered, a response document should be sent to EMA together with the modified PIP. The PDCO will discuss this at day 90, and issue a new list of requested modifications. Last amendments take place between days 90 and 120. For remaining questions an oral explanation may be requested at day 120. If the PDCO is satisfied with the modified PIP content, it issues a positive opinion. If not, the

applicant can choose between a negative opinion, re-examination, or PIP withdrawal. The applicant can also sue at the European Court of Justice. So far, one company has sued and lost both in the first instance and in the main trial.<sup>12,13</sup>

After the PIP is agreed upon, clinical trials and other measures in children begin according to the committed timelines. This can include requests for modification. In EMA's estimation, the average PIP requires 3–5 modifications.<sup>14</sup>

In the USA, for compliance with PREA, the FDA requires a paediatric assessment at the end of the phase 2 meeting, and a Paediatric Plan (PP) at submission. The PP will be reviewed during the approval procedure. For a reward of 6 months patent prolongation, the company can negotiate a written request to investigate the drug for use in children in another indication.<sup>15</sup>

### Clinical trials in children

In the last century, the prevailing opinion was that it would be unethical to expose children to clinical trials. Today mainstream thinking is that it is unethical and more dangerous to treat children with drugs that have never been properly investigated in children. Nevertheless, a skeptical attitude remains. The parents' position also depends on the seriousness of the disease. Almost all children with cancer participate in clinical trials. Thanks to decades of research the diagnosis of acute lymphatic leukaemia in a child is today no longer a death sentence, although still a horror; 80–90% of children survive thanks to cytostatic and other medications developed for adult cancer treatment decades ago.

Phase 1 studies in healthy children are not allowed. However, children receiving treatment can have experimental drugs as add-ons, allowing PK and pharmacodynamics measurements. Clinical trials in children are always more demanding than those in adults. Children are always part of a family, and the clinical investigator must be aware of this. Parents will often visit together with other children. If the study centre is shabby, the study personnel unfriendly, or the scheduled visits too rigid, the parent will not return.

From a legal point of view, parents have to sign the informed consent. The question of whether this should be one or both parents is a nightmare: the requirements are different in each country. From around school-age onwards, children themselves have to be informed and should, as a symbolic act, also sign an assent.

The physical clinical trials are performed by clinicians. There are now many paediatric research



networks in Europe, partially coordinated by the EMA under the European Network for Paediatric Research (Enpr-EMA).<sup>16</sup>

### Other operational challenges

Paediatric clinical trials must be approved by an ethics committee and must be registered with the authorities. Approval by ethics committees has evolved into a major hurdle because many ethics committee members are not experienced in paediatrics and often lack any knowledge of pediatric legislation. There are many more challenges, such as laboratory issues, how much blood can be taken and how often blood can be taken, and the need for adequately trained study personnel.<sup>17</sup>

### Outlook

Paediatric drug development is expensive. The EU gives a reward of 6 months patent extension through a supplementary protection certificate (SPC) but this comes at the end of patent life, while the additional development costs must be paid earlier. A company that has developed a drug up to proof of concept will not abandon it because it has to submit a PIP. EMA classified melanoma as a juvenile disease in view of the incidence of 1.7/100,000 in 15–19 year olds, quoting US Surveillance, Epidemiology, and End Results (SEER) Carcinoma Statistics.<sup>18</sup> However, of the group cited, two-fifths are adults (18- or 19-year-olds). The number of juvenile melanoma patients is probably half of the cited number. In 2011, two companies got a melanoma PIP approved.<sup>19,20</sup> There will come a point where companies will stop investing in therapeutic areas where PDCO demands turn the potential profitability of future drugs around. A possible example might be epilepsy: one new epilepsy compound ended up with 16 trials or measures in the sub-diseases: paediatric epilepsy syndromes; neonatal seizures; epilepsy with partial onset seizures; idiopathic generalized epilepsy with primary generalized tonic clonic seizures.<sup>21</sup>

The pharmaceutical industry was not proactive during the years preceding the EU regulation. The focus was on requesting more months SPC prolongation. During these years, better solutions could have been found. Today, each company is faced with an established EMA paediatric structure. Even if requests are unbalanced, there is little a company can do. The EU paediatric regulation is due for a first review in 2013 and a second one in 2018.

Both sides are learning and will continue to learn. Companies learn during the PIP procedure, the EMA

adapts and individuals learn. The degree of detail in each PIP will be less in the future, as EMA representatives announced at the DIA/EFGCP/EMA paediatric conference in autumn 2011.<sup>22</sup> This will reduce the workload on both sides. Consideration of children is now an essential part of drug development, and this will not go away. The future will show whether the research-based pharmaceutical industry will find a way to switch to a proactive approach. Let's imagine an independent European institute that would work out binding recommendations for each drug, financed by the pharmaceutical industry, with regulators, industry and clinicians on the board of directors. This would probably cost a fraction of what all companies together invested into the more than 1000 PIPs submitted so far. For the moment, each company must negotiate a programme from which children will benefit and that allows the company to survive. Much of this workload is borne by medical writers.

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