



Paediatric drug development: The impact of evolving regulations[☆]



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ABSTRACT

Children deserve medicines that are adapted to their needs. The need to include children in drug development has been recognised increasingly over the past few decades. Legal and regulatory frameworks are well established in the EU and US. The amount of work done to study medicines for children is significantly greater than it was 10 years go. Proof-of-concept has been demonstrated for all segments of the paediatric drug development pipeline. It is now time to examine how the practice of developing medicines for children has evolved within those frameworks and to determine how that work should be generalised. This review describes the development of medicines for children and critically appraises the work that has been done within those frameworks. Significant effort is needed to realize the potential provided by the current regulatory framework. Using the work programme of the Global Research in Paediatrics (GRiP) Network of Excellence as a template we outline current work and future growing points.

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1. Introduction

Everyone deserves medicines that meet their needs. All medicines need to be given at the correct dose, with an acceptable risk benefit profile. Medicines should be of good pharmaceutical quality with legally enforceable quality assurance of all aspects of their development and use.

In the past children were largely denied access to appropriate medicines that meet these criteria. Historically, children have not received medicines that have been rigorously evaluated and have been given medicines designed for adults. When medicines are adapted for children this is often done informally and in the absence of evidence, using measures such as cutting pills in half [1]. In the past decade significant attention and effort have been directed to overcome the gaps in medicines provided to children. A clear expectation that children will have medicines that meet their needs is now established.

Legislative and regulatory frameworks to underpin the expectation that children will be given the medicines they deserve are now established in two major jurisdictions (EU and USA). These frameworks are no longer “new” ways of doing things. The outlines of how to provide appropriate medicines to children are well established. The drug development community needs to work within those outlines. Future work needs to optimize the existing frameworks and develop the best ways to work within those frameworks.

2. Background: children need adapted medicines and specific approaches to drug development

Children differ from adults in a number of ways that are relevant to the development and use of medicines. These differences include the ways in which medicines are adsorbed, distributed, metabolized and excreted by the body (pharmacokinetics) and what medicines do to the body (pharmacodynamics) [2]. Children are often unable to take the dosage forms that are designed for adults. For example, tablets that allow for adult doses may need to be split before being given to younger children, based on an undemonstrated assumption that the distribution of the active substance within the tablet is uniform. The effects of such manipulations are poorly documented [1]. In the past, and unfortunately still today, a large proportion of medicines were given to children in an “off label” manner, or even without a license/marketing authorisation [3]. Clinical practice was defined by extrapolating data

from adults without testing medicines in children [3]. The data used to do this were not necessarily gathered from adults being treated for the same indication (or the same disease). There could be little evidence derived from pharmacokinetic, dose finding, or formulation studies properly conducted in the paediatric population. Inadequate testing can expose children to a direct risk of under or overdosing and a delayed risk of long term adverse effects.

Moreover diseases in children are often different from their adult equivalents. The processes underlying growth and development might lead to a different effect and response to drug unseen in adults. Particularly, children at various ages might be exposed to different risk/benefit ratios. Thus, children are not small adults. Indeed, pharmacologically speaking infants are not small children. Important medicines need to be tested in each target population [3].

In the past market forces alone were not a sufficient incentive for adequate research and development of paediatric medicines. Paediatric development has depended to a considerable extent on the pharmaceutical company's product strategy with respect to the adult population. For many companies adults represent the most economically attractive market. Paediatric strategies are often driven by the incentives relating to adult markets rather than the needs of children. Exceptions to this generalisation include vaccines and medicines for indications only found in children. Regulatory and scientific international collaborations are needed because they can favour global paediatric development programmes, and consequently make paediatric research more effective, efficient, ethical and quality well conducted. Recently, it has become widely recognised that children and young people and their parents and caregivers must be at the heart of research planning and conduct. Regulators such as the European Medicines Agency (EMA) developed frameworks for the involvement of children and young people in their work [4].

3. Legislative and regulatory frameworks

Children have been often referred to as “therapeutic orphans” who are exposed to avoidable risks while missing out on therapeutic advances [5]. Children have suffered from a lack of testing and authorisation of medicines for their use, despite the fact that the pharmaceutical legislative framework, ensuring the high standards of safety, quality and efficacy of medicinal products for use in adults, was developed primarily in response to past “drug disasters”, mainly involving children (e.g. sulphanilamide and thalidomide tragedies), reviewed in [3].

The adoption of paediatric regulatory initiatives in the US and then in Europe has significantly changed the worldwide legislative frameworks.

3.1. ICH

The first joint paediatric regulatory action was taken in the context of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), an organisation working on the harmonisation of pharmaceutical regulatory requirements between the EU, Japan and the US in July 2000 with the adoption of the ICH E11 guideline [6]. The goals were to encourage and facilitate timely paediatric drug development internationally and to provide an outline of critical issues in paediatric drug development and approaches to the safe, efficient and ethical study of medicines. The ICH E11 guideline became a valuable instrument in designing paediatric clinical research worldwide; however, the guideline is a recommendation, not a mandatory requirement, thus it had practically no effect on paediatric submissions in Europe and worldwide: for example, between 1995 and 2005, 44% of the 243 medicines authorised by the EMA had a potential paediatric use but no data available [7]. Due to advances in the knowledge and understanding of paediatric medicine development an update of this guideline is necessary and some initial work has been started in this context.

3.2. US FDA regulatory initiatives

The first regulatory initiatives based mainly on a voluntary process were launched successfully by the US FDA in the 1990s and early 2000s, and afterwards amended and reauthorized in 2007 as related sections of the Food and Drug Administration Amendments Act (FDAAA). Title III or the Pediatric Medical Device Safety and Improvement Act, Title IV or Pediatric Research Equity Act (PREA) and Title V or the Best Pharmaceuticals for Children Act (BPCA) all affirmed the priority of appropriate development of products intended for use in children. Title V of FDAAA (BPCA) codified a voluntary process initially included in the Prescription Drug User Fee Act of 1997 then subsequently renewed in the BPCA of 2002 where FDA would define the pharmaceutical products which needed paediatric studies based on perceived public health impact, outline the necessary studies, and issue a Paediatric Written Request to Sponsors. If the Product Sponsor submitted studies responding to the Paediatric Written Request, six additional months of marketing exclusivity were granted. The BPCA provision of FDAAA renewed the exclusivity incentives, strengthened a process for research into off patent medicines involving government contracts for paediatric studies, and mandated public disclosure of the study results. PREA extended the mandate programme to perform studies in children for products developed for adults that meet certain criteria based on public health impact. The provisions of BPCA and PREA have recently been made permanent with the Food and Drug Administration Safety and Innovation Act (FDASIA) [8]. FDASIA has reconfirmed the PREA principle of an expectation for a paediatric study plan (PSP) for products that are the subject of a marketing application if the application relates to a new active pharmaceutical ingredient, a new formulation, a new indication or a new dosing regimen or route of administration [9]. As in the past, mechanisms for requesting waivers or deferrals for some or all paediatric age groups are included.

3.3. EU regulatory initiatives

The need to include children in drug development was implicitly included in European legislation for some time [10]. These measures did not provide the information needed for the majority of medicines [11–14]. At the end of 2006, an EU Paediatric Regulation (Reg 1901/2006/EU and Reg 1902/2006/EU) was adopted with a similar scope and a different implementation mechanism than the US legislation.

Like the US legislation, the goals focus on improving children's health through advancements in research and on providing a new framework for an efficacious and safe use of paediatric drugs. Similar to the system in place under FDASIA, the EU Paediatric Regulation is expected to lead to faster and more profound changes since paediatric development has become mandatory for all new "unauthorised" drugs under development and for any variations of patented authorised medicines, unless a waiver is granted.

An important contrast between the framework in the EU and the USA is the timing of the paediatric development plan. The European PIP should be agreed at the end of Phase 1 while the American PSP should be agreed at the end of Phase 2. The theoretical advantages for early engagement are often outweighed by the fact that studies included in PIPs are deferred for considerable periods. Global development would benefit from a harmonised approach across the two jurisdictions.

Even if it brings higher requirements to industry, the Paediatric Regulation retains the principle of rewards (an extra 6 months of patent protection, i.e. extension of the duration of its Supplementary Protection Certificate [SPC]), for unauthorised and/or patented medicines and an extra two years of market exclusivity for orphan medicinal products; it requires agreement with the Paediatric Committee (PDCO) on the paediatric development and compliance with the agreed paediatric investigation plan (PIP) before applying for the marketing authorisation for all unauthorised and/or patented medicines, including type II MA variations; interestingly, the paediatric development is required to cover all paediatric age subsets, from neonates to the adolescent, in all paediatric and adult conditions, with an age-appropriate formulation. In some cases, studies can be deferred until after the studies in adults have been conducted. This ensures that research in children is done only when it is safe and ethical to do so. On the other hand the uncritical use of deferrals can lead to unnecessary delays. In some conditions the benefit–risk balance is in favour of conducting studies in children and neonates early in the adult development programme. Deferral can also mean that paediatric studies are planned after patent expiry which may be a risk for companies or lead to the studies not being done. Even when studies are deferred, the PIP has to include details of the paediatric studies and their timelines. Moreover, as some diseases do not affect children (for example Parkinson's disease), a PIP is not required and it can be waived.

Finally the Paediatric Regulation has also established a new type of marketing authorisation (not foreseen by the US legislation), called the Paediatric Use Marketing Authorisation (PUMA), intended to stimulate the development of off-patent products for use in the paediatric population (most of these compounds are widely used daily in children of all age groups and mostly not adequately tested in this population). PUMA guarantees a 10 (8 + 2) year data protection.

3.4. Other legislations

Very few legislative and regulatory initiatives have been undertaken in countries other than USA and Europe. In *Canada*, a 6 month extension for data protection is granted to innovator companies providing evidence to support a paediatric label indication. In *Japan*, there is no comprehensive legislation to provide incentives and mandate development of paediatric medicines. In 2010, a programme was introduced as part of the new drug development promotion scheme: a price premium for promotion of new medicines, and creation and resolution of unapproved/off label medicines. As of February 2011 the development of 60 unapproved medicines and 122 off-label indications has been requested by the Ministry of Health, Labour and Welfare (MHLW). In *Australia*, despite many paediatric specific medicine initiatives through professional and government advisory bodies, formal legislative and regulatory reforms addressing paediatric medicines are still missing [15].

Finally, WHO launched an initiative ‘*Making Medicines Child Size*’ in 2008 to issue a list of essential medicines for children, advocating the paediatric development of and access to appropriate quality medicines especially for emerging countries: <http://tinyurl.com/82knoar>.

The next sections present a review of the impact of the US and EU legislation. The focus is on publications associated with the FDA and EMA, with some other papers cited when appropriate.

4. The achievements and impact of legislation in US and EU

Each of the major jurisdictions had reviews of progress during 2011–12.

In EU this included a report from the European Commission about the impact of the Paediatric Regulation during the five years after its implementation [16]. This was informed by a report from the EMA [17] and supported by a consultation with stakeholders [18]. Five years is enough to look at process but not impact. An impact assessment of 10 years after the implementation of the EU legislation is planned; this will include economic aspects. A similar exercise was conducted in the US. The Institute of Medicine examined the impact of American legislation [19]. The data presented in those reviews is based on data routinely collected by the regulators. This was supplemented by interpretative work by members of the agency and expert assessors. A number of general reviews have been published [3,7,20–23]. Book length descriptions of the issues in paediatric drug development include a summary of key aspects of drug development [24] and an overview of regulatory aspects [25].

Some of the data about the impact of regulations are comparable across jurisdictions. Other aspects of the reports are complementary. In either case the literature provides an important opportunity to look at the impact of legislation in a semi-quantitative way. A full impact assessment will require health economic data and will only be possible once the legislation has had the chance to influence the life cycle of a considerable number of medicines. In essence, the “regulatory revolution” seen in the past decade has demonstrated proof of concept that it is possible to develop medicines for children in a way that benefits children and meets the needs of all relevant stakeholders. The following sections indicate which aspects of that concept have been proven and which aspects need further development. The impact and achievement of each element of the regulatory frameworks are considered in turn.

4.1. Overview

There has been a significant increase in the number of medicines with information relating to children. The FDA examined a source frequently used by US clinicians to support prescribing, the Physician’s Desk Reference [26]. In 1999, 20% of new medical entities relevant to paediatrics had paediatric information while between 2002 and 2008 41% had paediatric information. In 1973 this publication had paediatric information on 22% of products and in 2009 the figure was 46% [26].

The regulatory frameworks have improved our understanding of a number of medicines used in children. This is illustrated by an FDA report on labeling changes relating to children made between 1998 and 2005. Of 108 products (some with more than one labeling change), 23 had dosing changes or new PK data, 34 had new information about safety, 19 had information about a lack of efficacy in at least some conditions while 77 broadened the age range for on-label use and 12 had a new formulation. Of 16 case studies examining pharmacokinetics, five had lower clearance than expected on the basis of body weight, four had higher than expected clearance and four had clearance that reflected weight [27].

4.2. Paediatric development plans

Here we describe paediatric plans (a generic term to cover EU paediatric investigation plans, PIPs, and US paediatric study plans, PSPs).

In the US, between July 1998 and September 2011, the FDA approved 500 labeling changes of which 453 were related to studies requested under BPCA or required under PREA.

Between the implementation of the EU Paediatric Regulation and the end of 2011, the PDCO had made decisions about 682 PIPs and 29 PIPs had been completed. Of these, 24 led to new paediatric indications (for 24 medicines) and 77 for new formulations. Another 5 PIPs were completed but the information did not support the use in children. This information can be included in the product information and indicated that the PIP process can lead to decisions not to use medicines in children. To date there has been one successful application for a Paediatric Use Marketing Authorisation (PUMA).

The main incentive under the regulation is a 6 month extension of the Supplementary Protection Certificate by the National Patent Offices. This has been granted in at least one Member State for 11 medicines.

It is clear that children were neglected during drug development in the past. The EMA has estimated that before the Paediatric Regulation came into force 34% of medicine authorisations included a paediatric indication, 23% of medicines were not useful for children and 43% of medicines could be relevant to children but data relating to children were not included in the materials submitted to support a Marketing Authorization. As of the end of 2011 30% of applications for medicine development had been deemed not relevant to children (through the grant of a waiver by the PDCO). The remaining new medicines are now all included in PIPs. There has been a significant expansion in the scope of research about medicines for children.

4.3. Neonates

One example of the way legislation can promote much needed research is the inclusion of neonates in drug development plans. Neonates are particularly vulnerable and more likely to have developmentally mediated differences in drug disposition and effects. As of the end of 2011, 395 opinions from PDCO were potentially relevant to neonates (not products related to allergens or products with a full waiver in the paediatric age group). Of these, 60 (15%) PIPs submitted by companies included studies on neonates with a waiver sought in the other cases. The PDCO added measures for neonates to 50 PIPs (13%) meaning that 110 (28%) of potentially relevant PIPs included studies in neonates. The studies included in PIPs were tailored to specific features of the indication in neonates. For example, of 110 PIPs involving neonates, 47 (43%) included controlled trials of safety and efficacy and 57% of neonatal plans relied on extrapolation of efficacy from older age groups. 58 neonatal PIPs (53%) included PK (PD) and tolerability studies and 24 (22%) included non-controlled safety and efficacy studies (PIPs can include more than one type of study). In contrast, the FDA reports that between 1998 and 2010 there were 365 labeling changes relating to children. These included 23 (6%) that involved studies recruiting neonates. The predominant neonatal condition which was affected by labeling change was infection, changes were also made to medicines relevant to neonatal gastroenterology, cardiology and anaesthesia [19]. The relative neglect of neonates since the initiation of regulatory initiatives targeting children has been highlighted by a study of FDA databases [28].

The needs of neonates are not being met. This may be due to a lack of new medicines that can be influenced by regulatory processes. Neonatal markets are relatively small and “legacy” medicines are widely used and cheap so that companies may not have sufficient incentives to develop new medicines for existing indications. On the other hand, a large number of waivers have been allowed by the PDCO and FDA has not been able to consider neonatal data sets for many proposed labeling changes. The waiver pathway was intended to avoid unnecessary research. When applied to neonates it suggests that companies and the PDCO believe that the benefit–risk balance of many medicines is unfavourable. It is possible that these decisions are more risk averse than they need to be. A lack of information about medicines is more likely to be harmful

than well-conducted studies about medicines that are likely to be beneficial.

4.4. Off patent medicines

In the EU the Regulation provided funding to support research into off patent medicines through Framework Programme 7. To date, 19 projects involving at least 24 off patent medicines have been funded. In the US work on/off patent medicines is funded by the NIH and administered through the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), through a Pediatric Trials Network. Both jurisdictions have processes to prioritise research into off patent medicines. In Europe this is done by the EMA and PDCO [29].

The EMA has also published lists of needs relating to medicines in children [30].

In the US this is done by the NICHD with consultation by the FDA, subject matter experts and the public [31].

4.5. Extrapolation

There is an ethical requirement to minimize the number of studies in children and the number of children recruited to studies. Children are not able to consent for themselves and in many cases can be more vulnerable to the effects of studies than people in older age groups. One way to meet this requirement is to extrapolate from data about the drug and the condition from older age groups. This approach is outlined in regulatory guidance, for example ICH E11 [6]. A baseline for the use of extrapolation in the development of medicines for children is provided by a review of updates to drug status provided by 95 EPARs between 1995 and 2007. These authors concluded that 66% of the studies were required, 22% could have been done more appropriately if all relevant data had been used to develop a well-designed extrapolation study and 12% of studies were judged to be unnecessary [32].

The use of extrapolation studies has been reviewed by the FDA who was able to use extrapolation (partial or complete) in a majority of studies [33].

When the 210 PIP opinions given by the PDCO until January 2010 were reviewed, it was found that 47 (22%) of opinions included modeling and simulation. Some of this was for bridging and other cases were designed to optimize the development process, for example through dose selection. FDA has reported case studies of modeling in paediatric PK dosing [34] and other contexts [35].

The complexities of assessing whether extrapolation is required are provided by Piana et al. [32]. Further work is needed to provide a systematic approach to extrapolation. Central to extrapolation is the exposure/response relationship (E/R) which needs to be developed in adults if bridging is to be done [32]. EMA has stimulated discussion about this. One approach is to consider when extrapolation is possible and useful [36]. This can be extended by examining which data is useful in a range of scenarios [37]. At the time of writing EMA is examining the best approaches to extrapolation in drug development and, after a public consultation, has released a “Concept paper on extrapolation of efficacy and safety in medicine development” (EMA/129698/2012), aimed at developing a framework for an explicit and systematic approach which sets out when, to what extent, and how extrapolation can be applied and which includes many examples for paediatric development. [38].

4.6. Timing

The progress of paediatric plans is difficult to assess using publicly available data. Some types of plans have to submit annual progress reports in the EU. Up to the end of 2011 the EMA had received 91 of these annual reports. Among these reports, 21 reported delays with recruitment, 11 reported delays with ethics or regulatory approvals, 6 had concerns with safety and 3 with efficacy. A review of the progress

of paediatric studies required under the US PREA legislation showed that up to “78% of drug studies and 54% of studies on biological products (such as vaccines) were either not completed or were finished late”, compared to their due date in 2007 ([39] citing Dr Fraterelli). This topic is specifically addressed in the FDASIA of 2012 with enhanced tracking requirements.

Most of these delays are due to avoidable, organizational issues. Recruitment can be optimized through well-organised clinical research networks with strong performance management. Adequate recruitment requires appropriate targets that can only be set accurately in the light of good feasibility data. Feasibility data should inform the development of paediatric plans as well as individual protocols. Issues with ethics and other regulatory groups often stem from lack of awareness of the relevant procedures. Previous experience of these procedures can shorten trial setup times considerably. The need to “reinvent the wheel” slows down many sponsors when they address paediatric studies for the first time. An effective way to address recruitment and regulatory issues is to use pre-existing clinical research networks that provide reusable infrastructure and generic expertise. The development of competent and efficient clinical research networks is a priority if the potential of the regulatory environment is to be realized.

4.7. Modifications

By the end of 2011, when 513 PIP opinions had been given, there had been 315 opinions about modifications to PIPs. A sample of 100 modifications was examined. Timelines were changed in 59 of 100 modifications, of which 31 were changes of less than 1 year and 28 were changes of more than one year. Delays were reported in 61% of these reports. Changes to dosing recommendations were found in 9% of the modifications and changes to inclusion criteria and secondary outcomes were found in 9% of the modifications.

4.8. Preclinical

The European Regulation includes consideration of animal studies. A guideline has been issued by the EMA [40] and reviewed in [41].

The experience of the EMA pre clinical working group has been described [42] using a sample of 97 PIPs submitted between November 2008 and May 2010. Juvenile animal studies were planned, or had been completed, by the applicant in 33% of the 97 PIPs. The non-clinical working party recommended additional studies in 26% of the cases. Triggers for juvenile animal studies included a target population aged less than 2 years. The EMA had particular concerns about whether reactions would be reversible and potential effects on the reproductive system that would only be apparent after puberty and in later life [42]. A review has examined PIP decisions between 2007 and 2009 [43]. In total 50 of 205 (24%) of PIPs included juvenile animal studies. The number of proposed studies was 87 with 60 of them (69%) involving juvenile rats.

The FDA reported some illustrative case studies of the value of studies in juvenile animals [44]. Over time there was a tendency to reduce the use of two species in juvenile testing and use of study designs that examined specific questions about toxicity that had been raised by adult studies (human and animal) or mechanisms that are specific to children. These examples include more targeted safety information, and novel signals. This provided a rationale for setting the lower age limit for paediatric use in some cases. In other cases, the findings were reassuring and potential safety issues could be de-emphasized in subsequent development [44].

4.9. Use of existing data

Article 45 of the European Paediatric Regulation prompted marketing authorisation holders to share studies with the EMA. More than

18,000 studies (completed before the entry into force of the Paediatric Regulation) were submitted, covering c.1000 active substances. The National Competent Authorities (NCAs) have shared the assessment of these studies. By the end of 2011, 149 active substances had been reviewed, leading to changes in 65 Summaries of Product Characteristics (SmPCs; labeling information).

Meanwhile, up to September 2011, 318 studies (completed after the entry into force of the Paediatric Regulation) have been submitted (Article 46) and 25 assessment reports for nationally authorised medicines have been published.

Articles 45 and 46 of the EU Paediatric Regulation resulted to be a valid tool for gathering fragmented and sparse considerable amount of paediatric information that existed at company level, and for recommending and implementing changes to the SmPCs of authorised products. However, there still remains reluctance by marketing authorisation holders to start this update process on a voluntary basis.

4.10. Collaboration between regulators

Joint working between regulators has been increasing since the foundation of a Paediatric Cluster by members of the paediatric medicines team at the EMA and the Office of Paediatric Therapeutics at the FDA. This allows discussion of paediatric plans as well as general issues in regulatory science. The Japanese and Canadian agencies are also involved in these discussions. The EMA, the FDA and the NICHD are members of the World Health Organization's Paediatric Medicines Regulators' Network (PmRN): <http://tinyurl.com/7177pbs> and the FP7 Network of Excellence, Global Research in Paediatrics (GRiP): <http://tinyurl.com/ozv863z>.

4.11. Links between regulators and investigators

The EU Regulation included a unique provision to set up a network of paediatric clinical research networks that support clinical trials of investigational medicinal products. The European Network for Paediatric Medicines Research at the European Medicines Agency (EnprEMA) was established in 2009. EnprEMA allows a dialogue between PDCO and networks [45]. Networks represent investigators and have been accredited using the criteria developed by networks and summarised on the EnprEMA website [46]. EnprEMA bridges between industry and networks to find centres. It has also supported the development of model PIPs and is promoting participation in clinical trials. It is clear that there are a lot of good practices among paediatric clinical research networks, which need to be disseminated. Regulators have collaborated with investigators to develop guidelines for trials and summarise regulatory issues in a number of therapeutic areas including Hepatitis C [47], obesity [48] and psychopharmacology [49–51]. There has been some collaboration between regulators, researchers and industry to develop a shared understanding of rational drug development: <http://tinyurl.com/qge5bkg>.

Examples include products for specific immunotherapy of allergens [52]. Overall, this fits with the claims of regulators to have a proactive attitude [53].

In the United States, links between regulators and investigators are direct and indirect. Direct linkage is through advisory committees that meet with regulators to provide input. Examples include a Paediatric Advisory Committee and subspecialty focused Paediatric Oncology Subcommittee that reports to the Oncological Drugs Advisory Committee. In addition, investigators and regulators meet through ad hoc meetings about specific products. Paediatric device development is supported through a consortium supported by the FDA Office of Orphan Drug Products and all product types can be supported by individual programme grants through the same office.

Indirect linkages occur through the NIH with a joint NIH–FDA initiative to periodically develop a priority list plus NIH support of a Paediatric

Trials Network to generate data primarily in response to Written Requests for off patent medications.

4.12. Growth points in regulatory science

Regulatory science can be defined as “the science of developing new tools, standards, and approaches to assess the safety, efficacy, quality, and performance of products requiring approval by national or supranational competent authorities” (adapted from <http://www.fda.gov/ScienceResearch/SpecialTopics/>). This section summarises a selection of aspects of regulatory science which have been stimulated by the legislation.

Regulators can provide unique insight into the utility of different aspects of trial design by examining studies from more than one development programme. For example Sun et al. reported that enrichment for subjects with long lasting migraine attacks did not overcome the high placebo response rates seen in migraine trials, while the non-randomisation of patients who had an early placebo response was successful for at least one drug [54]. Benjamin et al. examined paediatric trials of antihypertensive and found that trials were more likely to show an effect if they compared large differences in doses, used paediatric formulations and used diastolic rather than systolic blood pressure as the primary outcome [55]. Smith et al. examined safety in placebo groups of trials of antihypertensives [56]. Ten trials submitted to FDA between 1998 and 2005 included a total of 1707 children in placebo arms. There was no difference in AE rates. There were only 5 SAEs in the 10 trials. None were related to the study drug and there was only one among the participants allocated to placebo. These are useful data in discussions about the role of placebos in trials that recruit children [56].

One way to maximise the value of recruiting children to trials is through pooling data across drug development programmes. A good example of this from within the FDA is a systematic review of 110 controlled clinical trials of long acting beta agonists including 60,954 participants [57]. Adverse outcomes associated with long acting beta agonists were more common in children than in adults. Allocation to regular inhaled steroids appeared to mitigate the risk associated with long acting beta agonists [57]. In addition to providing a specific message for clinicians and investigators, this study shows proof of principle for regulator led meta-analysis. FDA has contributed to similar studies, e.g. reporting the incidence of cough in children receiving angiotensin converting enzyme inhibitors or angiotensin receptor blockers [58]. Another study identified racial differences in response to antihypertensives [59]. Regulators are not sufficiently resourced to pool studies comprehensively. Many clinical researchers would welcome the opportunity to be part of such studies, with appropriate safeguards about confidentiality and conflicts of interest. Systematic reviews and spontaneous reports from a National Competent Authority have been used to develop proportionate pharmacovigilance in trials [60]. A major challenge is the routine use of proprietary data standards by regulated industry, the absence of consistent terminology and outcome definitions, and the subsequent need to map and convert individual data sets to a common analytic data set for each meta-analysis.

4.13. Pharmaceutical quality

The European Regulation includes specific requirements for companies to develop age appropriate formulations. EMA reports that PIPs have included relevant work. There have been a lot of discussions about the safety of excipients and about how formulations will be adapted to ensure that they are relevant to the needs of children. The Formulations Working Group of the PDCO analysed 84 PIPs. A total of 125 pharmaceutical forms were proposed in these PIPs, of which 102 (82%) led to discussions of excipients. These discussions related to the justification of excipients, the dosage of excipients and the potential to avoid excipients through alternative formulations. Testing for palatability and acceptability was requested in 50% of the proposed dosage

forms. Practical issues (manipulations, small volumes etc.) were problematic for 23% of the formulations.

The EMA has recently published a guideline for pharmaceutical development in children [61]. This work is supported by Paediatric Formulation Initiatives in the US [62] and EU [63]. Excipients are discussed elsewhere in this issue.

4.14. Guidelines

A number of guidelines and recommendations have been published.

The EMA maintains a webpage for paediatric guidelines [64]. A number of workshops have been held: <http://tinyurl.com/qge5bkg>. Some standard PIPs have been developed [65]. The FDA database of guidelines can also be consulted [66].

4.15. Support for companies

The PDCO has contributed to Scientific Advice about 70 times a year. The FDA offers presubmission meetings with the relevant review division. In both cases, these procedures offer valuable opportunities to streamline the regulatory process.

Moreover, EMA regularly organises workshops, not binding for PDCO, on topics related to paediatrics aimed at providing general guidance for paediatric development: <http://tinyurl.com/qge5bkg>.

4.16. Economic return

There can be a significant economic return from the US incentives for paediatric drug development. In one study 9 programmes that were submitted for 6 months of additional exclusivity as a result of studies in children, “paediatric exclusivity”, reflecting a range of therapeutic areas between 2002 and 2004 were selected for detailed economic evaluation. Among the 9 programmes net economic return of the 6 months of paediatric exclusivity ranged from – \$8.9 million to \$507.9 million and the net return to cost ratio ranged from – 0.68 to 73.63 [67]. A subsequent study examined 9 orally administered antihypertensive agents. For these agents, the net economic return to cost varied between 4 and 64.7, with an average of 17 [68]. Thus for at least some agents an additional 6 months of exclusivity can be profitable. It has been argued that the regulatory frameworks may not be economic for small to medium sized enterprises (SMEs) working with medicines that are not blockbusters [49].

One important goal of the EU is to support small and medium sized enterprises (SMEs). The Paediatric Regulation included provisions for industry, including SMEs, with fee exemptions, deferrals and reductions. The EMA has developed an SME office. By the end of 2009, more than 170 SMEs had benefitted from regulatory assistance with 130 requests for scientific advice. Fee reductions to that date had totalled €6.9 million [69].

4.17. Summary of achievements

The culture of drug development has changed following the implementation of legislation in the EU and US. Regulators, industry and investigators have developed a system that routinely delivers development plans to guide research and product label changes to guide clinical practice.

There is more attention to the needs of children than there was in the past. There is more attention to formulations, extrapolation and off patent medicines than there was in the past. The data from the agencies and others provides encouraging markers about the process. There have been significant advances in regulatory science as evidenced by the ongoing publication of guidance documents.

5. Problems and lessons learned

Stakeholders have identified a number of issues and points for further process development. These include:

- Industry, regulators, investigators and advocates for children and young people need to work closely during the development of paediatric development plans.
 - This is particularly important when a large number of molecules are under development for a high impact condition with a small patient group (e.g. Type 2 Diabetes and Hepatitis C, pulmonary hypertension, arterial hypertension, and HIV infection).
- Although there has been progress with including neonates in drug development there is still a way to go [70–72]. In part, this reflects the limitations of incentives and poor market signals for this age group. There remains a market failure for research in neonates. In older age groups the legislation has shown that it is possible to overcome market failure.
- The therapeutic areas covered by studies conducted under the legislation reflect the adult needs rather than children's needs [16,19]. It has been suggested that there is a need to measure PIPs against a benchmark of paediatric needs. However, it may be difficult to identify a suitable benchmark.
- Long term safety and effectiveness remain under studied. New EU pharmacovigilance legislation as well as incorporation of relevant assessments in longitudinal studies in children may help. The FDASIA also addresses this point.
- The US Government and EU have made significant investment in research about off patent medicines. In Europe PUMA has stimulated research through EU funding but so far has not made much difference to licensing.

5.1. Conduct of development plans

Some development plans are easier than others. The IoM report considered the case study of treatments for HIV infection, bacterial conjunctivitis and gastro-oesophageal reflux (GOR) in neonates. Successful drug development was associated with (1) clarity and agreement about the nature of the condition to be studied; (2) valid, reliable, and practical methods to diagnose the condition and account for the heterogeneity of the population; and (3) valid and reliable endpoints for studies of response or efficacy [19]. As further examples, FDA has reported factors associated with successful trials in migraine [54]. The EMA has described development programmes for pain [70].

Delays occur in paediatric drug development. These are most frequently due to recruitment. This may be improved by better feasibility. The ideal approach is to design the drug development programme around a realistic assessment of the number of patients available for research. Networks can contribute to this but this process needs to be formalized. The second important cause of delays is regulatory process. This needs more harmonisation. The burden of regulation needs to be minimised. Many large pharmaceutical companies have strong paediatric teams. Greater understanding of paediatric drug development and regulatory processes is needed particularly among small companies and academic investigators. It is noteworthy that concerns about safety and efficacy of medicines were relatively rare causes of delay, reported in less than 5% of plans available for assessment (see Section 5.5 above). This preliminary evidence that fears about exposing children to medicines during the development of the medicine may be unfounded. Other causes for studies not achieving their full potential noted in the IoM report include a lack of dose ranging studies to guide efficacy trials. The agencies are working on this problem including the intelligent application of simulation and modeling.

5.2. Use of existing data

It is clear that companies have rarely used existing data to update labels. It is striking that of the 18,000 studies reported to the EMA under Article 45 of the regulation, very few are of sufficient quality to support changes to labels. This raises important questions about the ability of investigators (in industry and clinical settings) to design and conduct studies. This situation needs to improve. The following observation is striking: “It is disappointing, and perhaps surprising for the [EMA's Paediatric] Committee, that many healthcare professionals do not recognise the need for evidence based paediatric prescribing, achieved through the conduct of paediatric clinical trials [73]”. The EMA PDCCO considers that this unexpected hurdle should be addressed by all stakeholders. Indeed, ICH E11 notes that the “responsibility is shared by companies, regulatory authorities, health professionals, and society as a whole”.

5.3. Application of findings

New data about pediatric medicines has not been diffused adequately. For example, between 1998 and 2004 253 studies were submitted to the FDA to support pediatric exclusivity, only 113 (45%) were published in the peer reviewed literature [74]. Safety data is under represented in publications [75]. This indicates a need to develop knowledge translation processes to ensure the effective implementation of the information that is gathered during drug development.

Hoppu et al. examined the impact of changes in marketing authorisations in the EU and US on medicines available in other regions of the world. They describe the situation as a “hostage” environment in which children across the world contribute to research that is reflected in prescribing information in the EU and US but not in all the countries that contribute to the research [15].

5.4. Waivers

One reason for unmet needs is the way the waiver system has been applied. Both PREA and the EU Regulation only required studies in children when drugs were developed for adult indications and when the indication was the same in children and adults. In addition, when drugs are developed for indications only seen in children then development is required. However, there has been a loophole. When drugs are developed for adult indications but the drugs can be applied in other conditions in children, development is not required. This has led to some significant clinical needs being ignored. Waivers from paediatric development need to be based on whether a drug has any application in children. EMA is looking for ways to correct this problem [76]. In the US, the incentive programme under BPCA can still apply but it remains voluntary.

5.5. Ethics

Some of the ethical issues in paediatric drug development need continued discussion. In February 2008, the European Commission released an updated recommendation on ethical aspects of clinical trials involving children to tackle the weakness of the existing rules by integrating principles contained in other various international ethical/legal sources with the aim of ensuring the protection of subjects involved in biomedical research, while recognizing the importance of benefits derived from research [77]. However, there is always a need to balance interests of the individual with benefits of more knowledge. This discussion needs to be rooted in the specifics of each development programme. There is no escaping dialogue between families, investigators, regulators, industry and Ethics Committees as early as possible and frequently during the planning and implementation of development plans. One particular sticking point in discussions has been the choice of comparator when the standard of care involves off label use of a medicine.

In Europe, at least, Ethics Committees are not well positioned to deal with studies needed under the Paediatric Regulation [78]. Issues identified by Ethics Committees following the introduction of the European Regulation included a need for more expertise in evaluating clinical trial protocols, particularly inclusion and exclusion criteria, difficulty in understanding measures to minimize pain and discomfort among children participating in trials and complexity in evaluating consent/assent and the risk/benefit balance of trials [78].

5.6. Animals

The utility of studies in juvenile animals during paediatric drug development has been discussed in a number of reviews [41,42,79–83].

Given the confidentiality that surrounds these studies it is difficult to make a systematic assessment of the contribution to drug development by research involving juvenile animals. A survey within industry included 82 development programmes from 11 companies through to 2009 [79].

Key points include the need to continue developing studies focused on specific questions relevant to children, rather than apply standard toxicology designs to juvenile animals, and the need for consistent advice between regulatory authorities (supported by early engagement between sponsors, regulators and investigators). The scope of work involving juvenile animals may change with the development of: greater understanding of postnatal adaptation in all species; greater understanding of correlations between species; microsampling toxicokinetic methodologies and post-marketing surveillance in humans. It may be possible to reduce testing of drugs in the same class once the developmental safety profile has been established in one example of that class.

5.7. Impact of the legislation

It is difficult to identify the effects of the legislation on medicine utilization (or even prescriptions) due to problems with the data that is available. A more developed picture of the situation would require extra data to be collected by health care systems, industry and regulators. It is not clear where the resources to do this can be found.

Some pediatric development plans have been submitted to regulators that are relatively late in the life cycle of the drug. From the perspective of the regulators, these delays appear to result from misunderstanding the needs of and opportunities provided by legislation. Some authors argue that the situation would be improved if the EU and US harmonise their requirements.

The IoM report suggested that administrative burdens need to be reduced while the transparency of decisions and justifications for decisions needs to be increased [19]. Access to data is important for systematic reviews [84].

The regulatory initiatives have led to drug development programmes that incur significant costs. It will be important to justify those costs. The primary justification for these initiatives has been the improvements in child health that will follow from greater availability of medicines with a marketing authorisation. It is important to assess whether the legislation is having the intended effects.

A direct evaluation of the impact of efforts to improve the availability of medicines with a marketing authorisation can be envisaged. The most direct approach would be to identify clinical needs that were not addressed before the advent of the legislation and determine the extent to which those needs are met after the legislation was introduced, with a sufficient delay to allow drug development and market penetration. A cost utility analysis would be required for each clinical need. Each clinical need would require specific assessments of health status among children to be captured at baseline and after sufficient time for the legislation to have an effect. This requires that relevant measures of health status were available and utilized in the decade before 2005 and will be reapplied to a similar population in the decade after 2015. Accurate costing data for the drug development programme would be needed.

These constraints are not trivial. In practice it may be possible to identify a few informative case studies but the direct approach is unlikely to be sufficient to make a definitive evaluation of the direct public health impact of the legislation.

In the context of imperfect information indirect measures will be needed. Process metrics will be valuable. A number of process metrics have been summarised in Section 4 of this review. One important metric is the proportion of prescriptions that are supported by adequate labeling information. Baseline data is available for some clinical areas in many settings [85].

The legislation supports a company to obtain a marketing authorisation or labeling update for a specific medicine for a specific indication. This step is only one part of the link between medicines and child health. Once a marketing authorisation has been approved a number of steps that are required before the medicine can have the intended effect. These include: obtaining patent and other benefits under the legislation; influencing health care reimbursers to allow the medicine to be used; influencing prescribers to prescribe the medicine; and ensuring sufficient adherence for the medicine to have an effect. Successful application of the legislation will therefore need a number of “downstream” events to fall into place. An apparent lack of effect may reflect downstream issues rather than problems with the legislation.

A further consideration is the framework used for the evaluation of the legislation. Monetary cost is one frame of reference but is not the only one. Patient preference is important. In addition there is a moral dimension. The regulatory changes that followed the sulphanilamide or thalidomide disasters were not based on financial calculation. The problems spoke for themselves.

In summary, an assessment of the impact of the legislation on child health should be multimodal. When specific case studies of success or failure can be identified they should be evaluated in detail. Process metrics will be important. A narrative approach that takes account of attrition during and after drug development will be informative. It should be recognised that a rigorous assessment will be costly. The data necessary for the evaluation of the legislation is not the same as the data needed for the implementation of the legislation. There will need to be a balance between the rigor and cost of the evaluation. Groundwork to support an evaluation could include gathering selected baseline data and debating the terms of reference for the evaluation.

6. Work by networks and investigators to apply the framework for drug development in children

Efficient drug development requires close working between regulators, industry and investigators. As noted, investigators work best in clinical research networks. The European Commission has funded a Network of Excellence to bring together networks and the EMA to optimise drug development in children. This network, Global Research in Paediatrics, GRiP, is working on a number of themes <http://tinyurl.com/ozv863z>.

6.1. Education and training

The people involved in medicine development need to have appropriate knowledge and skills about the scientific and regulatory standards and expectations. This includes children and young people, their parents and families. Generic training to support patient and public involvement is available: EuPATI: <http://tinyurl.com/c5yxk5e>.

Professionals also need education and training. This can be generic, such as Good Clinical Practice (GCP). There is a need to address the specific issues that arise during research with children. GRiP is addressing these issues with a palette of training opportunities. These include a 1 or 2 day road show that is designed to introduce the issues to professionals involved in children’s medicine research. GRiP is also organising a Masters course in Pharmacology and Clinical Trials in Children.

This will be supplemented by specific tools to support the evaluation of medicines in children.

6.2. Post-marketing surveillance

The formal evaluation of medicines, usually before an indication is granted, is limited in scope and does not include enough children to identify the nature or extent of important concerns with the safety of medicines. Post-marketing surveillance is an essential part of the lifecycle of medicines. A large amount of information is captured in routine clinical databases and can contribute to post-marketing surveillance. One important challenge is unlocking this information and making it available for analysis. GRiP is working on approaches to linking clinical databases. This work includes software that can bridge between proprietary database structures and governance systems that allow data to be shared while respecting legal and other requirements.

6.3. Interoperability & infrastructure

Medicine evaluation currently involves many people doing the same thing in different ways. The drug development community needs to ensure that study assessments yield comparable data and that data can be shared. This requires attention to shared terminology. GRiP is working with a range of study teams to develop shared terminology for clinical studies. This will allow consistent assessments and data sharing. In addition, many study procedures have been optimized in some settings and provide useful templates for work more generally.

Infrastructure is another issue to be taken into account and in this sense, some attempts have been made by the European Network of Paediatric Research set-up at the EMA (Enpr-EMA) and expected to facilitate capacity building and bringing together national and European networks, investigators and centres with specific expertise in design and conduct of paediatric studies: <http://tinyurl.com/pwnlgqt>.

6.4. New methods

“Conventional” approaches to medicine development may be sub-optimal for some novel therapies in some age groups [86]. There is a need to develop medicines as efficiently and quickly as possible, particularly for serious conditions affecting children [87]. This requires a range of methodologies that can be used as the situation requires. These considerations apply to children, even more than adults. GRiP is evaluating a range of novel methodologies to facilitate the rational selection of methodologies in the contemporary landscape for therapeutic development.

6.5. Formulations

Children deserve age-appropriate formulations. Formulation development is a relatively poorly developed area. It lies at the interface between hypothesis-driven research and technology. The current need is to build up capacity and share expertise. GRiP is working to establish and maintain an International Paediatric Formulation Knowledge Platform; provide formulation education for scientists and clinicians; and facilitate global paediatric formulation research worldwide.

6.6. Neonates

Neonatology has traditionally been a research rich specialty. That research has not been linked to the work required to obtain marketing authorisations of medicines for newborn babies. GRiP is undertaking underpinning work to facilitate links between research activity and therapeutic development.

The effects of medicines may not be apparent immediately, particularly in neonates. Medicines may influence developmental processes that underpin physiological or psychological function that is only

manifested years after a medicine is given. Medicines may have benefits or harms during infancy, which are not translated into important outcomes later in life [88,89]. Interventions may have benefits or harms that are only apparent in later life [90]. Long-term follow-up can provide reassurance about concerns derived from studies of animals [91]. One approach to these issues is to insist that all neonatal drug developments include follow-up until outcomes can be reliably ascertained. For neurocognitive outcomes this will be at school age or older [92]. For renal, cardiovascular or pulmonary outcomes this may be into adulthood [93,94]. Short-term benefits may be sufficient to justify a marketing authorisation so that long-term follow-up may not be appropriate in all cases. Conditional authorisation will be a useful mechanism. In any case drug development plans can only be developed in the light of the state of the art. The understanding of development, and its assessment, may change over time. Definitive judgments about licensing/marketing authorisation need to relate to the state of the art when the programme was planned. The market (reimburseurs and prescribers) is the best place to decide whether the medicine should be used in the light of the information available at the time of use.

When long-term outcomes are necessary for marketing authorisation or post-marketing surveillance, one approach is to ensure that neonates are tracked in sufficient detail to allow long-term surveillance. The costs of tracking and generic assessments should be borne by health care systems since long-term follow-up of sick neonates has generic value: long-term follow-up informs service delivery as well as drug development. When specific risks can be foreseen on the basis of known biology or preclinical/clinical drug development then additional, specific assessment of these anticipated harms could be organised by research networks and paid for by whoever will benefit from the information (e.g. sponsor). It is important to remember that neonatal markets have limited financial value and it is important to avoid pricing innovators out of the market. The recovery of costs associated with long-term surveillance requires careful negotiation and is likely to require arrangements that share risk between health care systems and pharmaceutical companies. The costs and effort for families and clinicians will be minimised by agreement about the content and timing of assessments. Standardised outcome assessments will also allow pooling of data which will maximise the value of information gained during research.

6.7. General issues

A common approach underlines much of this work. Assessment is followed by evaluation leading to the development of deliverables. Assessment includes the design of a research question that is used to conduct an environmental scan and/or a systematic review. Evaluation involves combining the results of the assessment phase with novel

work by GRiP partners. This leads to iterative refinement of draft outputs. The drafts are influenced by appraisals, Delphi processes, surveys and application to real world situations as appropriate. The material is then presented as deliverables. The aim is to provide materials that are fit for purpose, targeted for specific needs while avoiding duplicate effort. GRiP developed a general inquiry approach that involves sequential surveys of publications and individuals to generate a description of the current status of a topic. The current status is then subject to a gap analysis for what key data or concepts are barriers or lacking. Following identification of knowledge gaps, small studies are designed specifically to address the gaps. Subsequently, the gap-filling data are reintegrated into the larger summary status and the whole is analysed again by subject matter experts (See Fig. 1).

The diverse components of GRiP all address a common aim: to develop an infrastructure matrix that facilitates the development of appropriate medicines for children. The GRiP network provides a strong model for the integration of these efforts. Another commonality relates to the challenges inherent in the implementation of that matrix. Developing medicines requires coordination between regulators, industry, patients and investigators. A challenge for investigators is aligning their work to the expectations of regulators and industry. This involves working to the stringency required for regulatory processes. Many clinical investigators are used to working to academic standards or the standards required to influence their peers. These standards are different from the standards required for regulatory approval. Regulatory standards are informed by a long history of therapeutic disasters and the potential for commercial pressures to influence the design and interpretation of studies [3]. These influences translate into greater rigor and stringency in the regulatory approach than other approaches to research about medicine in children. The GRiP project, and other projects funded by the European Commission will raise the awareness of the requirements for regulatory approval of medicines for children [95]. This will have spin off effects by exposing clinical researchers to a range of designs and higher standards for data collection and analysis. Increased rigor in studies that are not aimed at regulatory submissions will reduce the risk of bias and increase the utility of studies about medicines for children.

7. Conclusions

The time is ripe for a concerted effort to improve the therapies available for children. After decades of effort the regulatory frameworks for the rational development of medicines for children were put in place in recent years. These frameworks have now been road tested and can be used with confidence. GRiP and other initiatives are defining how to make the most of the opportunities provided by the established frameworks for paediatric drug development.

Conflicts of interest

M.A. Turner is the Chair of the European Network for Paediatric Research at the European Medicines Agency (EnprEMA).

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A Knowledge Advancement Process

1. Initial Assessment Phase
 - 1.1. Research Topic Identification
 - 1.2. Environmental Scan
 - 1.3. Systematic Review
2. Evaluation Phase
 - 2.1. Draft knowledge summary
 - 2.2. Gap Analysis
 - 2.3. Consultation with stakeholders and subject matter experts
3. Experimental or Simulation Phase
 - 3.1. Generate new data if needed and feasible
4. Consensus Phase
 - 4.1. Second draft incorporating consultation and new data
 - 4.2. Conference or dissemination to select individuals and organizations
5. Final draft
 - 5.1. Dissemination and Knowledge Transfer

Fig. 1. A knowledge advancement process.

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