

Similar but Different

With more paediatric-specific studies occurring worldwide, it is important that sponsors are aware of the differences in the regulations governing the development of medicines for children in the US and Europe, especially regarding the approval process and timing, and keep these differences in mind when planning their studies

The US was ahead of Europe in recognising the need for legislation to ensure that pharmaceuticals are developed for, and tested in, the paediatric population. Paediatric exclusivity provisions were established in 1997 as part of the Food and Drug Administration Modernization Act (FDAMA), and in 2002 the Best Pharmaceuticals for Children Act (BPACA) was introduced followed by the Pediatric Research Equity Act (PREA) in 2003. The legislation was aimed at increasing the numbers of clinical studies conducted in children in order to provide adequate information for product labelling in the paediatric population. In return, the pharmaceutical companies developing medicines for children could obtain additional market exclusivity for their product and recoup the additional investment required to perform paediatric studies.

In Europe, the Paediatric Regulation (EC 1901/2006 Medicinal Products for Paediatric Use) only came into force in January 2007. However, due to the rigid timelines and strictly regulated processes for the submission and evaluation of paediatric investigation plans (PIPs), this regulation has probably posed more of a challenge to the global pharmaceutical industry than the established requirements in the US. In particular, it has become difficult to develop a practicable clinical programme for paediatrics (including timelines for studies in children) which will satisfy both the Paediatric Committee (PDCO) in Europe and their counterpart assessors at the FDA.

Pediatric Research Equity Act – US Paediatric Regulation

The Pediatric Research Equity Act (PREA) was reauthorised in 2007, and the Act stipulates that all new drug applications (NDAs) as well as biologics licensing applications (BLAs) for a new active ingredient, indication, dosage form, dosing regimen, or route of administration must contain a paediatric assessment unless the applicant has obtained either a waiver or a deferral of the assessment until after approval has been granted in adults. Complying with PREA is an essential part of any drug development plan, and applicants are encouraged to start thinking about their paediatric assessments and appropriate study programmes early in development.

The amount of clinical data required for the paediatric assessment will depend on the type of application, the available knowledge on the use of similar products in adult and paediatric populations, and the disease or condition being treated. In some cases, if the course of the disease and the effects of the drug are judged to be sufficiently similar in adults and paediatrics, the FDA may decide that the paediatric effectiveness can be extrapolated from clinical studies conducted in adults, and additional paediatric data may be limited to pharmacokinetics studies. Extrapolation may also be possible between different paediatric populations, and a study may therefore not be needed in each age group.

Since there is an ethical argument for confirming the safety and effectiveness of a drug in the adult patient population prior to conducting studies in children,

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applicants can request a deferral for conducting their paediatric studies until a specified date after the drug has been approved for use in adults. A deferral can be granted on one of the following grounds:

- The drug or biological product is ready for approval for use in adults before paediatric studies are complete
- Paediatric studies should be delayed until additional safety or effectiveness data have been collected
- There is another appropriate reason for deferral

In order to obtain a deferral the applicant must provide:

- Certification of the grounds for deferring the assessments
- A description of the planned or ongoing studies
- Evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time
- The timeline for the completion of such studies

A request for a deferral should be submitted during Phase 2 or early Phase 3; if a deferral is not granted, the sponsor then has sufficient time to conduct the necessary paediatric studies and submit in the NDA. For drugs intended to treat life-threatening or severely debilitating

Table 1: Conditions for PREA waivers	
Partial or full waiver	Partial waiver
<p>The necessary clinical studies are impossible or highly impractical (for example, the number of patients is too small or the patients are geographically dispersed)</p> <p>There is strong evidence to suggest that the drug or biological product would be ineffective or unsafe in specified paediatric age groups or in all paediatric age groups</p> <p>The drug or biological product does not represent a meaningful therapeutic benefit over existing therapies for paediatric patients and is not likely to be used in a substantial number of paediatric patients</p>	<p>The applicant demonstrates that reasonable attempts to produce a paediatric formulation necessary for a particular age group have failed. The waiver shall cover only the paediatric groups requiring that formulation</p>

illnesses, discussions should take place at the IND stage. Once dates are established by the FDA for initiating studies and submitting final study reports, sponsors are expected to comply with the dates as outlined in a product’s approval letter. These dates are generally negotiated with the Review Division prior to issuance of the approval letter.

In addition, applicants can request waivers either for the entire paediatric population (full waivers) or for certain age groups (partial waivers). The FDA will grant a full or partial waiver of the paediatric assessment if the conditions in Table 1 are met. Applications for waivers must clearly present the feasibility and scientific rationale justifying the applicant’s request.

Best Pharmaceuticals for Children Act (BPCA) – WRs and Paediatric Exclusivity

A product that qualifies for exclusivity can benefit from an additional six-month marketing exclusivity period, which is either added to the market exclusivity granted at the time of approval or to the product’s patent expiry – whichever is later. However, the hurdles for obtaining paediatric

exclusivity are generally higher than those required in PREA commitments, and agreement on exactly which paediatric studies are necessary requires close interaction with the Reviewing Division at FDA throughout the process. The document upon which exclusivity is based is the Written Request (WR) issued by the FDA, which defines the paediatric studies required to be performed by the applicant for exclusivity to be granted.

The FDA generally uses the Proposed Paediatric Study Request (PPSR) to develop the WR, but may incorporate information from other sources. The PPSR should include details for FDA’s consideration such as:

- Study objectives
- Indications to be studied
- Number of patients and age groups to be studied
- Study endpoints
- Drug specific safety concerns for monitoring
- Potential labelling

- Statistical information
- Timeline for study(s) and report(s)

Once a WR is issued to a sponsor, revisions are possible, but must be negotiated and agreed with FDA in advance of amendments to the studies.

It is important to note that responding to a WR does not necessarily mean that the results of the studies must be positive. If a study fulfils the WR, but did not show efficacy in paediatric patients or reveal safety issues, exclusivity can still be granted and the product’s labelling will reflect the information from these studies.

Timing and planning of paediatric studies are crucial, especially when the goal is to obtain exclusivity, since the studies need to be completed in time to allow for FDA review and prior to expiration of market exclusivity/patent protection. Final study reports must be submitted at least six months prior to exclusivity or patent expiration.

It is common for applicants to want their PREA study(s) to also satisfy the requirements for exclusivity. In general, the studies required by the FDA to satisfy PREA are not as extensive or challenging to conduct as those required for exclusivity. For instance, studies to satisfy PREA may include only pharmacokinetic and safety studies, while exclusivity studies often need to be blinded, comparator studies investigating efficacy and safety in a variety of age groups. Communication between the sponsor’s regulatory representative and the Reviewing Division is the key to a successful paediatric plan, whether a sponsor is satisfying the requirements of PREA or

Figure 1: BPCA Written Request process

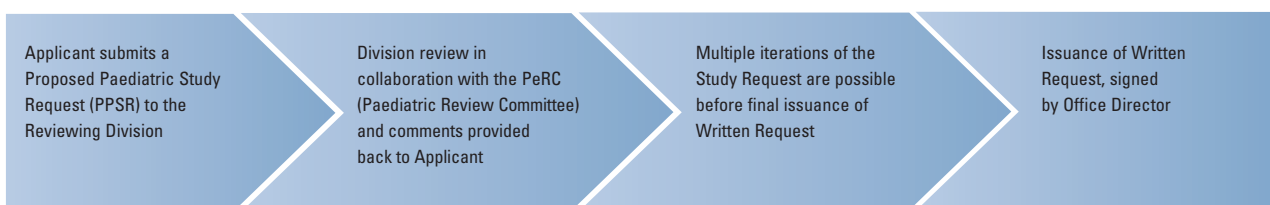


Table 2: Comparison of paediatric regulations in the US and EU

	US paediatric legislation	US reference source	EU paediatric regulation	EU reference source
Legislation	Governed by two separate laws: <ul style="list-style-type: none"> • PREA requiring paediatric studies • BPCA providing for additional market exclusivity 		Governed by one unified regulatory provision: <ul style="list-style-type: none"> • Regulation 1901/2006/EC is applicable throughout the EU • Incentives and rewards for performing paediatric studies are regulated by PIP requirement(s) 	
Reviewing/approving governance	<ul style="list-style-type: none"> • Review of paediatric development plans is conducted by the specific division for the disease area being studied • Approval for Paediatric Study Requests issued by FDA, as well as all deferrals and waivers for paediatric studies, is done by an internal but centralised FDA Paediatric Committee 	FDA Amendments Act of 2007 (FDAAA) <ol style="list-style-type: none"> 1. Internal review committee – memorandum establishing paediatric review committee 2. BPCA, 4 January, 2002 (Public Law No 107-109) 	<ul style="list-style-type: none"> • All PIPs are reviewed and approved by the Paediatric Committee of the EMA 	Article in 1901/2006/EC, Chapter 2, Article 3, 4, 5, 6
Regulatory scientific consultations	<ul style="list-style-type: none"> • All scientific advice is provided for free by FDA 	FDA Modernization Act – see Section 111	<ul style="list-style-type: none"> • For paediatric studies, scientific advice is available for free from the EMA 	Article in 1901/2006/EC Chapter 5 Article 26
Timing	<ul style="list-style-type: none"> • PREA stipulates that a Paediatric Development Plan must be submitted prior to or at the time of the NDA submission • FDA may make a WR or accept a proposal for a WR for any drug that conforms to the stipulations of section 505A of the Federal Food, Drug and Cosmetic Act or the Amendments Act of 2007 • Amendments to WRs are possible, with FDA agreement obtained prior to commencement of clinical studies 	BPCA and paediatric exclusivity Guidance for industry: qualifying for paediatric exclusivity under Section 505A	<ul style="list-style-type: none"> • PIP submission recommended after completion of pharmacokinetic studies in adults • The PIP must have received a positive opinion prior to submission of a Marketing Authorisation Application (MAA) • PIPs can be amended but modifications require approval 	Article in 1901/2006/EC, Chapter 3, Article 16 Article in 1901/2006/EC, Chapter 1, Article 7, 8 Article in 1901/2006/EC, Chapter 3, Article 22
Exclusivity awards	<ul style="list-style-type: none"> • BPCA provides for six months of additional marketing exclusivity if studies in paediatric patients are completed in accordance with a WR issued by FDA, but only as an extension of other granted exclusivity • Under certain conditions, paediatric exclusivity may be granted to a product without remaining exclusivity IF the supplemental application itself qualifies for a new exclusivity period under the Drug Price Competition and Patent Term Restoration Act (Waxman-Hatch Amendments) • Paediatric exclusivity does not accrue only to the product that was studied in the paediatric population. It attaches to all the applicant's formulations, dosage forms and indications for products with existing marketing exclusivity or patent life that contains the same active moiety 	FDAAA – Title IV: Pediatric Research Equity Act of 2007 (PREA) Sec 401,402, 403,404 and Title V: Sec. 501,502,503	<ul style="list-style-type: none"> • Six months of patent extension is granted for paediatric studies that have been performed as described in the PIP • One year patent extension for products that have demonstrated a significant clinical paediatric benefit for an approved indication • Two years of additional marketing exclusivity are granted for orphan products for which paediatric studies are conducted as described in the PIP 	Article in 1901/2006/EC, Title V, Article 36, 37, 38
Off-patent drugs policies	<ul style="list-style-type: none"> • No additional exclusivity is available for developing off-patent drugs for use in children 	The Pediatric Exclusivity Provision – January 2001 Status Report to Congress 2005 FDA Science Forum Poster Abstract: H-13	<ul style="list-style-type: none"> • Eight years of data protection and 10 years of market exclusivity is available for off-patent drugs granted a PUMA 	Article in 1901/2006/EC, Chapter 2, Article 30, 31
Financial considerations	<ul style="list-style-type: none"> • Research grants are available for paediatric drug development 	Grants and funding opportunities at the National Institutes of Health	<ul style="list-style-type: none"> • Funding is available from the EU Community Framework Programme for paediatric drug development • Financial and other incentives are also available in certain member states 	Article in 1901/2006/EC, Title V, Article 39, 40

the more challenging studies typically needed for exclusivity.

The Paediatric Investigation Plan (PIP) – EU Paediatric Regulation

Although the Paediatric Regulation (EC 1901/2006 Medicinal products for paediatric use) is in many ways similar to the US regulations that preceded it, the European legislation allows less flexibility and requires a Paediatric Investigation Plan (PIP) to be prepared at an earlier stage during product development. As in the US, there are incentives (in the form of additional patent protection) that are available to companies investing in paediatric studies. It is also possible to apply for a Paediatric Use Marketing Authorisation (PUMA) for new formulations of substances no longer protected by a patent.

An approved PIP is mandatory for marketing authorisation applications for new substances and for applications

for new indications for patent protected authorised products. The PIP has to be approved by the PDCO of the European Medicines Agency (EMA), or a waiver or deferral has to be granted, otherwise an application for marketing authorisation in the EU will not be validated. The requirement for a PIP is independent of whether the applicant intends to apply for an indication for use of the product in children.

The PIP defines the clinical studies to be conducted in children and is binding once agreed, which means that the studies defined in the PIP, including the protocol design, number of patients and the study timelines cannot be changed without approval of a PIP modification by the PDCO.

The PIP has to include all subsets of the paediatric population:

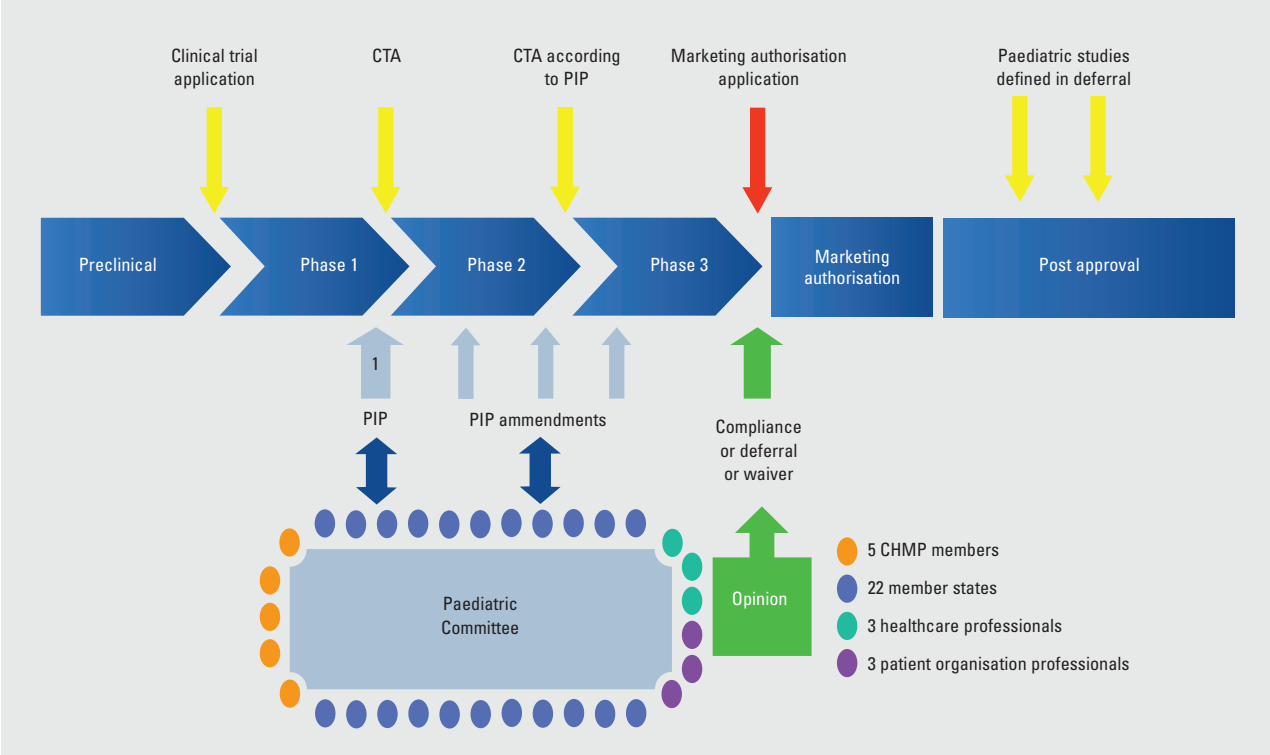
- Preterm newborn infants
- Term newborn infants (0 to 27 days)

- Infants and toddlers (28 days to 23 months)
- Children (2 to 11 years)
- Adolescents (12 to 18 years)

The PIP also has to cover existing and new indications, different pharmaceutical forms and routes of administration. Assessment of a PIP is according to fixed timelines, which are determined by the dates of the PDCO monthly meetings. The PIP requires careful preparation and input from many different departments (clinical and preclinical development, regulatory affairs, marketing and patent experts) and can take nearly a year to obtain a final PDCO opinion.

According to Article 16 of Directive 1901/2006, “the paediatric 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

Figure 2: Timing of PIP Development and PDCO consultation



human pharmacokinetic studies in adults.”The proposed paediatric 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. Generally this is considerably earlier than the stage at which consideration of PREA requirements are necessary in the US.

Since the results of later stage clinical trials in adults can require changes to the proposed paediatric studies approved in the initial PIP, it is customary for several PIP modifications to be required during the course of product development. This must be taken into account in the overall submission timelines. Submission of a modification to an approved PIP also follows fixed timelines, requiring two months and results in a revised PDCO opinion.

Analogous to the PREA legislation, a deferral or waiver of paediatric clinical studies can be requested as part of the PIP. However, deferral of studies until after the approval of the marketing authorisation is generally more

restrictive than in the US. A request for a deferral must be submitted with the PIP and must be justified on scientific, technical or public health grounds. A deferral will be granted by the PDCO:

- If it is appropriate to perform studies in adults prior to initiating studies in children
- In order prevent a delay in the availability of new medicinal products to the adult population

The PDCO opinion on the agreed PIP specifies the time limits for initiating and completing the deferred paediatric studies and may not necessarily coincide with PREA commitments agreed with the FDA. If medical need is identified, the PDCO can request shortening of the deferral requested or deny deferral due to the need for availability of the product in children.

As in the US, applicants can request waivers in their PIP either for the entire paediatric population (full waivers) or for certain age groups (partial waivers). However, the grounds for waivers are

more restrictive than in PREA, as a waiver will be only granted by the PDCO if one of the following applies:

- Product is ineffective or unsafe in part or all of the paediatric population
- Disease or condition only occurs in adults
- Product does not represent a significant therapeutic benefit over existing treatments for paediatric patients

The reason for the waiver must be justified for each age group and each indication by scientific data presented in the PIP. A waiver can be product-specific or a class waiver if it applies to a group of products.

EU Rewards and Incentives for Paediatric Development

Applications for new products will benefit from a six-month extension of the patent or supplementary protection certificate even if the agreed PIP and conducted studies fail to result in

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authorisation of a paediatric indication. Applications for modifications of products still under patent (paediatric indications, or formulations, or new routes of administration) also benefit from a six-month extension of the patent or supplementary protection certificate or a one-year extension if the new paediatric indication has significant clinical benefit. The product must be approved in all 27 member states, and the study results will be included in the product information.

For products with orphan drug designation, the incentives are increased. If the results of clinical studies collected in compliance with an agreed PIP are included in an application for an orphan medicinal product, two years of market exclusivity will be added to the existing 10 years, even if it fails to lead to the authorisation of a paediatric indication.

In contrast to the US, it is also possible to obtain market exclusivity for products where the patent has expired provided that there is a new paediatric indication for a suitable formulation and studies have been conducted in compliance with an agreed PIP. If a PUMA is granted, this product benefits from eight years of data protection and 10 years market exclusivity.

Best Practice for Fulfilling Paediatric Requirements in the US and EU

Both the PREA and PIP requirements mean that the initiation of paediatric studies must be included in the clinical development plan in parallel to the development of the product for adults.

It is essential that all relevant departments are aware of the requirement for an approved and validated PIP to be available prior to submission of the first application for marketing authorisation in Europe and that the studies included in the PIP reflect both PDCO and FDA requirements if at all possible.

The strategy for waivers and deferrals should be designed to keep paediatric studies off the critical submission path for first product approval in both Europe and the US. Compliance with both PREA commitments and the

approved PIP should be monitored regularly in order to ensure that amendments to a clinical protocol, which may occur during the course of a paediatric study, are incorporated into a PIP modification and are not 'discovered' in the last few weeks prior to a submission.

Since scientific advice for paediatric development is free of charge in both Europe and the US, the possibility of discussing the product development strategy at an early stage directly with the relevant authorities can help to clarify requirements well in advance of starting any clinical programme.

About the authors



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