



Global Paediatric Studies – a CRO perspective

14th April 2011

FOCUS. EXPERTISE. QUALITY.

Overview



- PREA and PIP – similar, but different
- Keeping your paediatric commitments feasible
- Choosing your CRO partner
- Ensuring compliance with PIP and PREA
- Key points for successful paediatric studies

PREA and PIP – similar, but different



<u>Pediatric Research Equity Act (PREA)</u>	<u>Paediatric Investigation Plan (PIP)</u>
Applicable to all NDAs and BLAs with	Required for all marketing authorisation applications for
New active ingredient	New substances
New indication	New indications for patent protected authorised products
New dosage form	
New dosing regimen	
New route of administration	

PREA and PIP – similar, but different



Products developed for the US market may fall under PREA requirements although a PIP is not required for a marketing authorisation in the EU



Products developed for the EU market may require paediatric studies if they are to be marketed in USA

- Requirements for paediatric studies need to be assessed early in development and planned into the development strategy

PREA and PIP waivers



<u>PREA waiver conditions</u>	<u>PIP waiver conditions</u>
<p>Paediatric studies are impossible or highly impractical (e.g. number of patients too small or geographically dispersed)</p>	<p>Product is ineffective or unsafe in part or all of the paediatric population</p>
<p>Strong evidence that drug or biological product will be ineffective or unsafe in paediatric age groups</p>	<p>Disease or condition only occurs in adults</p>
<p>No meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of paediatric patients</p>	<p>Product does not represent a significant therapeutic benefit over existing treatments for paediatric patients</p>
<p>Partial waiver if reasonable attempts to produce a paediatric formulation necessary for a particular age group have failed</p>	

PREA and PIP waivers



A waivers may be granted for paediatric studies by the FDA...



but the conditions for granting a waiver may not be fulfilled in EU so that studies are required to obtain a marketing authorisation

PREA and PIP deferrals



<u>PREA grounds for deferral</u>	<u>PIP grounds for deferral</u>
<p>Drug or biological product is ready for approval for use in adults before paediatric studies are complete</p>	<p>If it is appropriate to perform studies in adults prior to initiating studies in children</p>
<p>Paediatric studies should be delayed until additional safety or effectiveness data have been collected</p>	<p>In order prevent a delay in the availability of new medicinal products to the adult population</p>
<p>There is another appropriate reason for deferral</p>	

PREA and PIP deferrals



Deferrals until after approval in adults may be granted for paediatric studies by the FDA...



but if the PDCO identifies an unmet need in the paediatric population, studies may have to be conducted earlier to obtain marketing authorisation in Europe

PREA and PIP – similar, but different



- PREA and PIP requirements are not identical
- Differences in definitions of “new” products, as well as conditions for waivers and deferrals can affect both the requirements for studies and their timelines
- A comparison of the US and EU paediatric requirements should be conducted early during development if the product is intended for both markets
- Strategic paediatric trial planning is essential!

Keeping your paediatric commitments feasible



Promises, promises...

“We have some commitments to perform paediatric studies, but we would like to go back to the FDA and try to renegotiate”



“We must not promise what we ought not, lest we be called on to perform what we cannot” *Abraham Lincoln*

Keeping your paediatric commitments feasible



- Make sure the data on the prevalence and incidence of the paediatric condition in the literature is reliable
- Check the feasibility of finding paediatric patients who will fit the protocol(s) and use the results of these feasibility studies to justify the paediatric development plan
- Consider whether the studies are ethically viable (e.g. blood sampling, placebo groups, pharmacokinetic studies, contraceptive requirements)
- Remember you are not alone...there will be (more and more) competitive studies
- Try to avoid agreeing to do something until you know you can!

Keeping your paediatric commitments feasible



Case study:

A large pharmaceutical company made the following commitment to FDA:

- Perform a paediatric study in a very rare indication in 31 patients
- Single treatment study
- Based on calculations of disease incidence over 24 months, only 1 patient expected to be recruited per country
- Study therefore required initiation of one site with one patient in 31 different countries

Keeping your paediatric commitments feasible



Implications of the commitment were:

- Difficult logistics
- High costs due to regulatory submission fees for numerous countries, multiple site initiation costs, far ranging project management, drug importation hurdles, etc.
- No guarantee of finding the patients within the 24 month timeframe

Choosing your CRO partner



Checklist for your choice of CRO

- ☑ Experience of conducting paediatric studies in both USA and Europe
- ☑ Experience in the relevant indication
- ☑ Understanding of the paediatric legislation as well as the health authority and ethical requirements in both USA and EU
- ☑ Understanding of the work and views of the FDA paediatric division and the PDCO

Choosing your CRO partner



Experience confirms:

“The difference between theory and practice tends to be very small in theory, but in practice it is very large indeed”

Anon

Ensuring compliance with PIP and PREA



A paediatric development plan must be submitted along with the NDA or BLA at the latest, and it is reviewed together with the rest of the application by the review division responsible for the relevant therapeutic area.



A PIP is reviewed and approved by the PDCO well in advance of any application for marketing authorisation for the product. An approved and **compliant** PIP is required for validation of the application.

Ensuring compliance with PIP and PREA



Modifications to the paediatric development plan can (and should) be discussed with the FDA during the approval process in order to avoid unworkable commitments.



Due to the 'theoretical' nature of the PIP originally approved, modifications will generally be required prior to MA submission to adapt to the 'real life' situation and these should be planned into the development strategy and timelines.

Ensuring compliance with PIP and PREA



Adapting to reality...



Sponsors should submit their proposed changes to a Written Request or Pediatric Proposal communications, along with scientific and clinical-based evidence to support their suggested modifications, to the FDA as amendments to the IND or NDA.

Amendments to paediatric research plans may be made by Sponsors until all aspects of the WR or the PP have been scrutinized and/or analyzed for feasibility and scientific merit; or until the FDA's threshold for issuing waivers/partial waivers have been met.

All changes and agreements with FDA must be made in sufficient time to meet the timetable outlined in the agreements.

Ensuring compliance with PIP and PREA



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA XX-XXX

WRITTEN REQUEST
Amendment #6

ABC Pharma
100 Main Street
Philadelphia, PA 19102

Attention: John Q. Doe
Director, Regulatory Affairs

Dear Mr. Doe:

Please refer to your correspondence dated March 10, 2009, requesting changes to FDA's June 2, 2005, Written Request (WR) for pediatrics studies for drug XXX.

We have reviewed your proposed changes and are amending **Number of Patients and Study Endpoints** sections of the Written Request. All other terms stated in our Written Request issued on June 2, 2005, as amended by this letter and by previous amendment(s) dates May 6, 2006, April 27, 2007, May 5, 2008, and October 15, 2008, remain the same.

Ensuring compliance with PIP and PREA



Adapting to reality...



- Modifications to a PIP are possible if there are difficulties with the PIP implementation i.e. the original plan is either unworkable or is no longer appropriate
- Modifications should preferably be prospective
- Multiple modifications are possible
- New waivers/deferrals can also be requested
- New opinion supersedes original
- All changes have to be justified

Key points for successful paediatric studies



- 👉 Plan your PREA and PIP strategy early in development
- 👉 Be aware of the differences between US and Europe in requirements and timelines for paediatric plans
- 👉 Conduct adequate feasibility on proposed studies to ensure these are practicable
- 👉 Chose a CRO partner experienced in paediatric trials
- 👉 Monitor amendments to protocols and check for impact on key binding elements of the PDCO opinion
- 👉 Justify all modifications and submit in a timely manner!



Any Questions?



Thank you for your attention!