

**PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA
TESTIMONY BEFORE THE
INSTITUTE OF MEDICINE COMMITTEE ON PEDIATRIC STUDIES
CONDUCTED UNDER BPCA AND PREA
APRIL 28, 2011 PUBLIC SESSION**

The Pharmaceutical Research and Manufacturers of America (PhRMA) appreciates the opportunity to provide comments on the questions posed by the Institute of Medicine (IOM) on the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). PhRMA is the nation's leading trade association representing research-based pharmaceutical and biotechnology companies that are devoted to inventing new, life-saving medicines. PhRMA members alone invested an estimated \$49.4 billion in research and development in 2010. Industry-wide research and investment reached an estimated \$67.4 billion.¹

Prior to passage of pediatric exclusivity provisions in the Food and Drug Modernization Act (FDAMA) of 1997, there were significant disincentives for biopharmaceutical companies to conduct clinical trials for pediatric use (generally speaking, under the age of 18) of a medicine developed primarily for adult use. At the same time, there were concerns that many FDA-approved drugs had not yet been clinically tested in children. For example, about 70 percent of medicines used in children had been dispensed without adequate pediatric dosing information.² Growing recognition of the need for pediatric-specific information prompted action by Congress and the FDA. Congress responded by providing incentives to encourage manufacturers to conduct pediatric studies of medicines with potential uses for children as part of FDAMA. The legislation included a provision that granted pharmaceutical firms an additional six-month period of exclusivity, known as pediatric exclusivity, upon the completion and submission to FDA of studies on the effects of a drug upon children that meet the terms of a written request from FDA.

Although FDAMA included a sunset provision effective January 1, 2002, Congress subsequently reauthorized these provisions in the Best Pharmaceuticals for Children Act (BPCA) in 2002 and again in 2007 as part of the Food and Drug Administration Amendments Act (FDAAA). Further, there are provisions in the Biologics Price Competition and Innovation Act of 2009 (BPCIA) to provide pediatric exclusivity for biologics if the sponsor submits pediatric studies in accordance with a written request from FDA. The pediatric exclusivity extends by six months the period after licensing a reference product before which a biosimilar application can be submitted to FDA (4 years) or licensed by FDA (12 years), and also applies to extend by six months orphan exclusivity applicable to biologics.

¹ Pharmaceutical Research and Manufacturers of America, Pharmaceutical Industry Profile 2011 (Washington, DC: PhRMA, April 2011).

² U.S. Pediatric Studies Incentive Led to New Labeling for Nearly 100 Drugs, Impact Report, Tufts Center for the Study of Drug Development, Vol. 7, No. 4, July/August 2005.

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Conducted Under BPCA and PREA. April 28, 2011

In addition to BPCA, PREA gives FDA the authority to require studies of drugs for the approved indication only, i.e., when the use being studied in children is the same as the approved adult indication. PREA gave FDA the authority to require manufacturers to conduct pediatric testing for certain new drugs and biologics and produce formulations appropriate for children, e.g., liquids or chewable form tablets. PREA applies to products that are already on the market if FDA determines that adequate pediatric labeling could confer a benefit on pediatric patients and after it exhausts the possibility of funding the pediatric studies through other public and private sources³.

BPCA and PREA have been a tremendous success for patients. According to the American Academy of Pediatrics, “Pediatricians are now armed with more information about which medicines are safe and effective for pediatric patients and at what doses.”⁴ Senator Christopher Dodd, then-Chairman of the Senate Health, Education, Labor and Pensions Committee, noted during debate over the reauthorization of BPCA and PREA in 2007, “The story of the Best Pharmaceuticals for Children Act is one of huge success for children and their families.” Statistics regarding the number of studies that have been conducted across a wide segment of diseases is overwhelming. For example, as of March 2011, 181 drugs have received pediatric exclusivity under BPCA.⁵ Since passage of FDAAA in 2007, 324 pediatric studies have been completed involving 125,125 patients.⁶ The medicines studied under BPCA cover 16 broad categories of diseases.⁷ Although we celebrate the major successes in pediatric research, more work remains.

Over the last 15 years, biopharmaceutical companies have learned a great deal about developing new medicines for children. We have applied the learnings from our clinical research in many ways – including publishing the results of many studies in peer-reviewed literature, as well as labeling changes to medicines to reflect new clinical knowledge. As we have increased our focus on pediatric research, we have continuously improved the quality of pediatric research. While the vast majority of our research endeavors have been successful, unfortunately that is not always the case. However, even when studies fail to prove safety or efficacy of a medicine in children, they can offer important lessons, the information is captured in the labeling of approved indications, and pediatricians can gain important knowledge in how they treat their

³ The statute authorizes FDA to require assessments for marketed drugs and biologics if certain conditions are met, i.e., the drug or biological product is used for a substantial number of pediatric patients for the labeled indications; and (ii) adequate pediatric labeling could confer a benefit on pediatric patients; (B) there is reason to believe that the drug or biological product would represent a meaningful therapeutic benefit over existing therapies for pediatric patients for 1 or more of the claimed indications; or (C) the absence of adequate pediatric labeling could pose a risk to pediatric patients.

⁴ “FDA Joins Children’s Health Groups to Mark Historic Milestone for Pediatric Drugs,” FDA Press Release, December 19, 2005.

⁵ FDA. Pediatric Exclusivity Granted. March 2011.

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/DevelopmentResources/UCM223058.pdf> (Accessed April 15, 2011)

⁶ FDA. Breakdown of FDAAA Completed Pediatric Studies.

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm190622.htm> (Accessed April 15, 2011)

⁷ FDA. Spectrum of Diseases by Therapeutic Area found in written Requests as of December 31, 2010.

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm050007.htm> (Accessed April 15, 2011)

patients. At times, our initial assumptions about research at the onset are later disproved. This type of learning is important since it allows us to conduct more effective studies in future research. In order for our research to continue at the pace it has over the last 14 years, it is imperative that Congress provide greater certainty to companies and allow a more predictable regulatory path, which would help to spur increased research. In the past two reauthorizations in 2002 and 2007, FDA had to reinterpret the law without issuing new regulations. This has led to uncertainty and has impacted the scope of some pediatric studies. It is our hope that Congress will permanently reauthorize BPCA and PREA to allow pediatric research to thrive and create more options for our most vulnerable population, children.

Below are answers to the four questions posed by IOM with regards to improvements to the regulatory process.

1. Do you have comments or suggestions about the use of written requests issued under BPCA or the application of requirements under PREA and about the assessment of studies and labeling changes associated with such requests or requirements?

While the current regulatory process works generally well under BPCA and PREA, there are several issues that could benefit from continued focus and improvement, which in turn will help biopharmaceutical companies to develop medicines for children.

First, pediatric product development would benefit from updated regulatory guidance to assist both industry and FDA review staff in achieving a common understanding of the requirements under the Federal Food, Drug and Cosmetic Act (FDCA). However, because of the 5-year BPCA/PREA sunset and reauthorization cycle, no such current guidance exists, because every authorization has brought new changes to the law. For example, the most recent guidance for PREA was issued in draft form in September 2005,⁸ and the draft guidance has never been finalized. The only guidance on compliance with the pediatric exclusivity provisions of section 505A was issued in September 1999 and is based on the 1997 FDAMA⁹ legislation, despite the fact that there have been two iterations of section 505A since then. Adding further complication is the fact that a compound during its pediatric development may be subject to two or three reauthorizations of the legislation given the typical length of product development. This creates additional challenges for sponsors involved in pediatric product development to incorporate any differences into its plans due to changes in statutory requirements. If Congress were to permanently reauthorize BPCA and PREA it would enable the FDA to publish and maintain up-to-date guidance.

Second, specific timelines and proactive, regular communications are critical to the success of both BPCA and PREA and would provide increased predictability and

⁸FDA. Guidance for Industry: How to Comply with the Pediatric Research Equity Act. September 2005. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079756.pdf>

⁹FDA. Guidance for Industry: Qualifying for Pediatric Exclusivity Under Section 505A of the Federal Food, Drug, and Cosmetic Act. Revised September 1999. <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM080558.pdf>

certainty to the research process – and thus benefit pediatric drug development. While existing guidance on BPCA estimates a 120 day review period for response to a Proposed Pediatric Study Request, the experience of companies has been variable across FDA review divisions. Further, there are currently no specific timeframes for FDA action on a proposal for an amendment to a Written Request. Having predictable timelines is greatly important. In extreme cases, time delays can result in a sponsor's decision not to proceed with a pediatric program. The reauthorization of BPCA in 2007 included a provision which requires that written requests are fulfilled 15 months prior to expiration of product market protection. This time limitation highlights the need for timely and clear communication between the sponsors and FDA.

With regard to PREA, sponsors are required to commit to timelines for completion of PREA requirements prior to approval of the product. Although many FDA review divisions will respond to PREA proposals early in the development of a medicine, the formal commitment is for the plan to be submitted at the time of the submission of a new drug application (NDA) or biologics license application (BLA). Once PREA commitments are agreed upon, usually at the time of product approval, there are no timing goals for FDA review divisions to respond to companies on PREA related topics. Such review time goals are necessary to enhance pediatric drug development.

Third, since the European pediatric legislation (<http://www.emea.europa.eu/htms/human/paediatrics/regulation.htm>) came into effect in January 2007, the FDA and EMA have increased their cooperation on pediatric issues. For example, FDA and EMA have established monthly teleconferences to discuss and to better coordinate pediatric development plans in the European Union and the US to the extent feasible.

We believe that efforts to improve harmonization are beneficial and even greater attention and focus in this area would be helpful in order to help bring new medicines to children sooner. Some examples of potential benefits of increased collaboration and harmonization include:

- **Agreement on pediatric plans:** Agreement on pediatric plans between the EU and US can help drive greater research efficiencies in resource allocation and can speed the completion of pediatric trials so that patients around the globe can benefit in a more timely fashion.
- **Timing of pediatric plans:** In the US, PREA has requirements for the generation of pediatric data in clinical drug development that is based on a pediatric development plan. Often, such a plan is requested after “Clinical Proof of Concept” has been established and in some cases pediatric trials may not begin until efficacy and safety have been established (post-NDA approval) in the adult population. The European Pediatric Regulation states that a pediatric investigation plan (PIP) should be submitted to the PDCO when relevant pharmacokinetic data in adults are available; i.e., about finalization of phase 1. The different timing of PIPs and Pediatric Plans in the EU and US, respectively, presents a challenge to the industry as the PIP, including specific pediatric clinical trials, agreed with the PDCO may not necessarily be accepted by the FDA Pediatric Review Committee. Due to different requirements in the regions, there is a risk of having to conduct separate trials in US and EU. Having

agreement and better harmonization of pediatric plans between the US and EU in a timely manner would greatly improve the industry's ability to conduct efficient clinical trials and result in speedier access to information derived from the trials.

2. Do you have comments or suggestions about (a) the use of extrapolation in pediatric studies, (b) the use of alternative endpoints in pediatric studies (defined as alternative to endpoints used in adult studies), (c) the conduct of neonatal studies, and (d) the reporting and evaluating of safety data during clinical trials?

The use of the best tools to optimize data collection while reducing unnecessary testing in children, dictates that extrapolation, modeling, and the use of alternative endpoints all have appropriate roles in pediatric drug development.

(a) *the use of extrapolation in pediatric studies*¹⁰

The concept of extrapolation is largely based on the tenets of the International Conference of Harmonization (ICH) - ICH E 11 which provides guidelines for pediatric studies, centering on the concept of similarity of disease between children and adults, or, between younger children and older children.

Extrapolation assumes that there is some understanding of drug distribution, metabolism and pharmacokinetics (DMPK) in children (requires dedicated pK and safety studies in each applicable age group, sometimes relying on modeling) and some confidence that the adult and pediatric indications are sufficiently similar such that there is a reasonable expectation of a similar response in children.

Currently, FDA allows appropriate data extrapolation from adult or other pediatric populations in order to reduce the need for additional pediatric trials or reduce the number of pediatric patients needed to produce interpretable data. Greater use of extrapolation would further minimize exposure of the pediatric population while still providing valuable data.

(b) *the use of alternative endpoints in pediatric studies (defined as alternative to endpoints used in adult studies)*

The use of alternative endpoints may be related to several different factors, including the similarity/dissimilarity of the adult and pediatric manifestations of the target indication (e.g., RA pain/inflammation vs. JRA pain/inflammation). It may also be necessary when a pediatric patient cannot reliably perform a procedure (i.e., pulmonary function test) that is central to describing the efficacy of a drug. The concept of specific biomarker responses (surrogates) for infant or neonatal patients where older children/juvenile patients can verbally provide feedback on their status (e.g., allergy, pain, etc.) should be promoted or developed.

¹⁰ There are 7 labels that reference extrapolation from adults to pediatric patients.

The choice of an alternative endpoint may also be heavily influenced by competing/conflicting standards applied to clinical trials in pediatric patients in different regions (globally).

(c) *the conduct of neonatal studies*¹¹

Neonatal studies are extraordinarily challenging to conduct, especially when some studies include sick premature babies on multiple drug regimens. Neonatal physiology is very different from other pediatric age groups (in many significant systems) and the difficulty in assessing subjective outcomes is compounded by the limited ability to gain direct feedback from the neonatal patient. In addition, there may be significant challenges in finding a suitable formulation for neonatal administration. Further, while successful blood draws are generally challenging in many pediatric populations, the ability to draw PK samples is particularly constrained by the size of the neonate patient.

There is also a very real temporal constraint placed on the conduct of neonatal studies. The defined period only extends out to 28 days post-natal, which can be further complicated by gestational age issues (premature infants). There should be a greater focus on the practical aspect of conducting such studies in the face of a patient population that may already be very sick. As noted above, given the limited availability of narrowly defined neonatal patients for inclusion in clinical trials, the patient population may have to include a broader definition to cover gestational and post-natal age.

(d) *the reporting and evaluating of safety data during clinical trials*

Separate benefit/risk assessments may be required for each pediatric sub-group and eliciting information from very young children, infants and neonates about any treatment-emergent adverse drug reactions/adverse effects, is severely limited. The safety of a drug product should always be evaluated in the context of the much larger safety information derived from adults and then the individual elements that are specific to the pediatric patients should be assessed. These include issues like route of administration and subsequent hyper-sensitivity (for injectibles, parenterals, etc.) which may be absent in the adult population.

As in drug development in adults, biopharmaceutical companies must rely on appropriate pharmacovigilance to learn the long-term effects and rare events that a drug product may cause in children. This goal cannot be achieved through clinical trials alone. Decades of experience in drug development for adults has taught us that the clinical trial process is not able to elucidate the complete benefit/risk profile of a medicine.

¹¹ Five references to information on newborn/neonates in labels. 4 with affirmative information, 1 with a contraindication (“has not been studied/not recommended for use...”).

3. Do you have specific concerns about any ethical issues in the conduct of pediatric clinical studies conducted under BPCA or PREA?

Society, through its medical ethicists, scientists, clinical research centers, legal experts, patient advocates, industry, and regulators, has sought to manage ethical issues raised by clinical trials in vulnerable populations. Stringent and often appropriately redundant safeguards governing the approval and conduct of studies in these populations have been established. These measures are designed to assure that subjects in clinical trials drawn from vulnerable populations are protected from exploitation and that their rights and safety are of paramount concern in any clinical investigation.

With regard to studies in pediatric populations, the safeguards involve multiple independent reviews to provide assurance that studies are ethical and are carried out with the utmost attention to the rights and safety of pediatric patients. 21 CFR Part 50 Subpart D (Additional Safeguards for Children in Clinical Investigations) specifically provides further protections to children enrolled in clinical investigations beyond even those protections for adult clinical trial participants.

In addition, the FDA has the authority to suspend or place on hold any clinical trial conducted under an investigational new drug application (IND) which, upon review of the protocol, it considers to pose unacceptable risk to subjects or for which the design is inadequate to meet its stated objectives. FDA's 2008 Final Rule (21 CFR 312.120) requires compliance with ICH Good Clinical Practice for all studies (including studies not conducted under an IND) if sponsors plan to submit such studies in support of marketing approval in the US.

Another protection is the requirement for studies to be reviewed and approved by Ethics Committees (ECs) or Institutional Review Boards (IRBs) employed by institutions where studies will be carried out. Under U.S. regulation 21 CFR 56.103, "any clinical investigation which must meet the requirements for prior submission to the Food and Drug Administration shall not be initiated unless that investigation has been reviewed and approved by, and remains subject to continuing review by, an IRB." As stated earlier, Subpart D of 21 CFR Part 50 provides additional safeguards for children in clinical investigations. Further, Article 4 of the EU Clinical Trials Directive includes the need for appropriate expertise in the EC when providing an opinion on a clinical trial to be performed in children of any age group.¹² An Ad Hoc Committee of experts provided additional recommendations on the implementation of this provision of the Clinical Trial Directive.¹³ EC/IRB rules require that refusal of a study by any EC/IRB must be conveyed to all other sites involved in the study.

BPCA and PREA were originally established to address the ethical dilemma of using

¹² European Parliament and the Council. Directive 2001/20/EC
<http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2001:121:0034:0044:en:PDF> (Accessed March 21, 2011)

¹³ Ethical Considerations for Clinical Trials on Medicinal Products with the Paediatric Population.
<http://www.child-medicines-research-info.com/images/public/Ethical%20Considerations%20for%20Clinical%20Trials%20on%20Paediatric%20Population%20-%20European%20Commission%20%20FINAL%202008.pdf> (Accessed March 21, 2011)

medicines in children in the absence of information on safety and efficacy established through rigorous clinical testing in the pediatric population. Although pediatric patients in trials conducted under BPCA and PREA are still largely enrolled in the US and the EU, at times clinical research extends into other parts of the world. While some have attempted to raise issues with pediatric trials conducted outside the US or EU, it is important to note that 21CFR 50.1(a) states, "This part applies to all clinical investigations regulated by the Food and Drug Administration under sections 505(i) and 520(g) that support applications for research or marketing permits for products regulated by the Food and Drug Administration ." Thus, the protections described in 21 CFR Part 50 apply to industry sponsored studies conducted anywhere in the world under an IND in support of FDA approval. In addition, PhRMA members conduct clinical trials globally under a code of principles¹⁴ that call for members to commit to sponsoring clinical research that fully complies with all legal and regulatory requirements. The PhRMA Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results also requires that members work with local governments, non-governmental organizations associated with the United Nations, and local institutions to ensure the appropriate selection of research participants, appropriate use of placebo comparators, and access to post-trial treatment for research participants.

Further, in the US (as is the case in the EU), the exclusivity reward is predicated on pediatric studies being conducted in accordance with sound scientific and ethical principles. Programs under US law are sanctioned by FDA in the form of (1) a Written Request for BPCA; (2) pediatric plans under PREA must also be submitted in advance for review; all pediatric plans and written requests are reviewed by the review division and a special Pediatric Review Committee (PeRC); (3) FDA review divisions further review protocols under both BPCA and PREA for safety and adequacy of design to meet their stated objectives. In short, there are multiple, overlapping protections even within the FDA review process for pediatric research to ensure studies are performed ethically.

Besides review by adequately constituted ECs/IRBs and other committees, most studies conducted under BPCA and PREA have an additional data oversight body to monitor the trial. These protective steps are consistent with the ethical guidelines of the American Academy of Pediatrics.¹⁵ Indeed, industry regularly consults and adopts such guidelines to ensure appropriate safeguards are enforced.

PhRMA strongly believes that the necessity of every study under BPCA or PREA should be carefully evaluated before allowing such study to be conducted. FDA should endeavor to make the best use of existing data (published or otherwise) as well as information the Agency may garner from other regulatory authorities.

In summary, PhRMA believes that the robust structure of legal and regulatory requirements and ethical protections for all populations of patients, but especially the most vulnerable helps assure that multiple stakeholders with varied interests and perspectives pay careful attention to the ethics of any proposed study involving pediatric

¹⁴ PhRMA. Principles on Conduct of Clinical Trials and Communication of Clinical Trial Results http://www.phrma.org/sites/default/files/105/042009_clinical_trial_principles_final.pdf (emphasis added).

¹⁵ American Academy of Pediatrics. Committee on Drugs. Guidelines for the ethical conduct of studies to evaluate drugs in pediatric populations. *Pediatrics* 1995; 95:286-294.

patients. We believe that the current structure has been extremely effective in allowing needed clinical research to go forward, thereby providing essential, well-studied, safe, and effective treatments for children.

4. Do you have comments or suggestions about encouraging research on biologics that have not been studied in children or about setting priorities for such research?

The same considerations PhRMA has noted above regarding the importance of generating data in the pediatric population apply to biologics. As with other agents, both FDA and EMA agree that it is beneficial to study biologic agents for effects in pediatric populations to treat pediatric-specific indications. To the extent possible we have encouraged both health authorities to support efforts to harmonize their acceptance criteria for such studies in order to reduce unnecessarily increasing the number of children participating in a pediatric clinical trial as well as exposure to increase the efficiencies of drug development. This is especially relevant to biologic agents, where long-term monitoring for safety effects is important in this developing population.

As you are aware, biologics were not included in BPCA legislation. There are provisions in the Biologics Price Competition and Innovation Act of 2009 (BPCIA) to provide pediatric exclusivity for biologics if the sponsor submits pediatric studies in accordance with a written request from FDA. The pediatric exclusivity extends by six months the periods after licensing a reference product before which a biosimilar application can be submitted to FDA (4 years) or licensed by FDA (12 years), and also applies to extend by six months orphan exclusivity applicable to biologics. We support full FDA implementation of these provisions in the BPCIA through guidance or regulation by mechanisms that are conducive to the realization of the incentives that Congress intended.

In conclusion, PhRMA appreciates the opportunity to provide comments to the IOM regarding how BPCA and PREA may be enhanced to further the development of medicines for children.