BIOTECHNOLOGY INDUSTRY ORGANIZATION
1201 Maryland Avenue SW, Suite 900, Washington, DC 20024
202-962-9200, www.bio.org

August 13, 2010

Rachel E. Munn
Analyst - Health Care
U.S. Government Accountability Office
441 G Street NW, 5A62B
Washington, DC 20548

Re: GAO Request for Feedback regarding the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act (290831)

Dear Ms. Munn:

The Biotechnology Industry Organization (BIO) thanks the Government Accountability Office (GAO) for the opportunity to comment on the successes and ongoing challenges related to the *Best Pharmaceuticals for Children Act* (BPCA) and the *Pediatric Research Equity Act* (PREA). These dual statutes governing pediatric research have been remarkably successful in ensuring that the medications used in children are tested and labeled appropriately for their use. Together BPCA and PREA have generated a wealth of pediatric drug information for physicians and parents. However, despite a proven track record in encouraging pediatric medical research, both programs are scheduled to expire in 2012. BIO urges Congress to recognize the success of these programs, eliminate the sunset provision, and make permanent the incentives for ongoing pediatric research. The comments below also highlight areas where important improvements can be made to the programs.

1. Can you tell us about your organization and your role within the organization?

BIO represents more than 1,200 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding

the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

Feedback on these questions was developed by members of BIO's Pediatrics Committee. The BIO Pediatrics Committee seeks to minimize barriers to, maintain incentives for, and communicate the value of robust drug and biologic research in pediatric populations. The Committee provides a venue for biologics companies to discuss best practices and lessons learned with respect to the conduct and regulation of pediatric clinical research and development programs. Additionally, the group coordinates BIO's activities surrounding the implementation and reauthorization of BCPA and PREA. The group also works with FDA and international regulators to promote appropriate harmonization of pediatric regulatory requirements.

2. What are the strengths and weaknesses of BPCA and PREA?

BPCA and PREA work together to provide the tools necessary to foster pediatric drug development. They have some common strengths and weaknesses, but also some that are unique. These are summarized below:

Strengths:

- Under BPCA, the incentive for conducting pediatric studies. History shows that market forces, absent the incentive contained within the BPCA, are inadequate to stimulate pediatric research. Pediatric product development is a societal good, the cost of which cannot be borne by a single sector. The incentive helps to defray the cost of pediatric product development across the entire portfolio for a company. An additional strength is the provision under BPCA (Section 505A(h)) that allows Sponsors to earn the exclusivity incentive for pediatric studies required by another provision of law provided the terms of the BPCA are met.

- The appropriate pairing of a requirement (under PREA) with a voluntary approach (under BPCA). Under PREA there is a requirement to conduct pediatric studies in the same indication being sought for the adult population, while under BPCA there is a voluntary mechanism for conducting studies of other potential uses.

- Under BPCA, the opportunity for the Agency to request studies in conditions and ages for pediatric indications that are not directly linked to the adult indication. These studies are voluntary, but if completed in compliance with FDA's written request, result in the 6-month marketing exclusivity incentive provided in the statute. Sponsors can prompt FDA's written request by submitting a proposal. Most of these written requests are in fact proposed by industry and the requests are typically linked to medical need.

- Under BPCA, the clear requirement that FDA must issue a written request outlining the studies to be conducted. This leads FDA and Sponsors to consider pediatric needs and

develop a shared understanding of a comprehensive program. (Please also see "weaknesses" below regarding PREA).

- Under BPCA, the requirement for review of pediatric supplements under the 6 month Priority Review timeline. This helps to ensure that the label is updated in a timely manner, and patients and providers have access to the most up-to-date information.

- Transparency. No matter whether the study findings are positive, neutral, or negative, this information is shared with the public through the BPCA and PREA requirements that the results be reflected in product labeling.

Weaknesses:

- Under PREA, the absence of a clear description of requirements for a pediatric plan in the statute, including the absence of information on timing of submission or need for FDA concurrence. This is in contrast to both the BPCA Written Request requirement and EU's "pediatric investigational plan" for pediatric studies. FDA's report on the recently completed retrospective review of PREA 2003-2007 cites the absence of a detailed written description of required studies under PREA as the likely cause of perceived poorer quality programs under PREA compared with BPCA.

- Inadequate requirements for timeliness of FDA actions. While existing guidance on BPCA estimates a 120 day review period for response to a Proposed Pediatric Study Request, industry experience has been variable across review Divisions. Further, there are no specific requirements for timeliness of FDA actions on a proposal or plan amendment to a Written Request. Time delays in agreeing on a pediatric program can be particularly important under BPCA as the reward is tied to existing market protection. If patents and exclusivity expire before a pediatric program can be completed, the incentive cannot be applied even if the program meets all conditions. This can nullify the incentive because pediatric studies, especially in rare diseases, are often slow to enroll increasing the likelihood that the agreed-upon program cannot successfully be completed within the remaining period of market protection.

- Under BPCA, the need to submit final reports 15 months before expiration of exclusivity. The 15 month timeframe results from the combination of two current BPCA requirements for (1) determination of the exclusivity award by FDA at least nine months prior to expiration of marketing exclusivity, and (2) the 180-day period provided to FDA to make that determination combine. If this lengthy 15 month timeframe is not met, the incentive could be placed in jeopardy. This weakens the incentive for some products where the necessary studies take a long time to complete or products for which the remaining market exclusivity period is short.

- The 5-Year Sunset Provisions. The 5-year sunset results in an ever changing regulatory environment for pediatric drug development. This makes it difficult for industry to invest in

infrastructure to support development for pediatrics and impossible for FDA to issue regulations or guidance to promote understanding of the current regulatory framework.

- Absence of delineation of decision rights or clear lines of authority between the Review Divisions and the Pediatric Review Committee. This leads to frequent stalemating, for example in non-timely waiver/deferral decisions under PREA and delays in finalization of Written Requests and their amendments.

- Non-uniform interpretation and implementation of the complex pediatric statutes by the different review divisions. The repeated 5-year sunset provisions have contributed to this lack of uniformity because of statutory changes imposed with each reauthorization. FDA Guidelines would help make the interpretation uniform.

- Lack of clarity for both FDA and Stakeholders concerning what parts of pediatric programs are required under PREA versus those covered by BPCA.

- Lack of clarity and consistency regarding extrapolation. Extrapolation appears to be handled differently by different divisions and pediatric committees.

- Lack of international regulatory harmonization. Inconsistencies exist between the guidance and timing for BPCA/PREA vs. European Union (EU) pediatric requirements.

- The timing of pediatric studies often necessitates an additional user fee. The requirement that labeling changes must be made as a result of PREA studies, combined with the fact that FDA will often not engage in dialogue about such programs until NDA/BLA review, means that PREA studies are typically required post-approval commitments. The results of such studies must be submitted in an efficacy supplement that requires a user fee. Sponsors are left with no option but to pay the additional user fee in order to meet the requirement for conduct of pediatric studies.

3. Can you discuss the interaction between BPCA and PREA?

BPCA and PREA together provide an effective set of tools that have proven beneficial in promoting pediatric development. PREA assures that, regardless of the level of use of a product (revenue potential) or market protection status, pediatric studies must be considered and conducted if the core indication developed is relevant to pediatrics. BPCA provides two additional values: first, it encourages industry to consider additional potential pediatric uses that may be unique to pediatrics by providing a reward for such additional research. Second, by permitting Sponsors to submit a Written Request and obtain the reward even for products where the only studies needed are those required under PREA, it helps to fund those programs for which no reward is possible. It is the minority of products for which the six month exclusivity incentive provides rewards greater than costs associated with pediatric research, including

formulation development and maintaining pediatric formulations in the marketplace.[1] The current interplay between the two provisions helps to provide resources to fund development of products that serve small populations or for which the reward is unavailable, build the infrastructure necessarily to sustain pediatric drug development, and ultimately encourage important pediatric research as an integral component of all drug development.

4. What are some of the reasons that drugs are not studied?

The primary reason is that a product has gone off-patent and has no existing market protection and no further developmental programs that would trigger PREA requirements. Various legislative efforts to fix this issue have not been successful. For example, even the EU's Pediatric Use Marketing Authorization (PUMA) provision has not resulted in pediatric programs for these products.

One potential fix is to devise appropriate mechanisms to encourage sponsors to perform the pediatric drug development trials for the off-patent drugs.

Small populations and sub-populations can also create barriers to pediatric research. Different age groups and stages of development can challenge the ability to enroll sufficient numbers of children and make studies impractical. Small populations and sub-populations can also create barriers to pediatric research. Current legislation, appropriately, exempts sponsors from the requirement for the study of children if the adult indication is an Orphan indication (<200,000 in US). Sponsors may still do pediatric studies, if relevant, for this indication, other indications or as part of a BPCA/Written Request.

There is also "competition" for enrollment between companies. The requirement to do studies applies to all companies and to all new products and line extensions of existing products, but the available pool of pediatric research participants is limited in some therapeutic areas. This affects the ability to complete studies in a timely way. Pediatric programs may have to be global, and as a result, may take a long time to complete, and be more expensive per patient than similar adult development programs

Pediatric studies lag in time behind adult studies and in some circumstances once a product is approved for adults, off-label pediatric use impacts ability to enroll patients in trials. Indeed, FDA is aware of this issue and their written requests always require a detailed review of off-label drug use, both published and unpublished (review of inpatient and outpatient hospital databases).

Formulation challenges may affect the age-groups studied. For example, some drugs in oral tablet or capsule form cannot be re-formulated into either a solution or suspension for the younger aged children. This would then prohibit a product's use in research, *e.g.,* when tablet or

[1] Jennifer S. Li, MD, MHS; Eric L. Eisenstein, DBA; Henry G. Grabowski, PhD; Elizabeth D. Reid; Barry Mangum, PharmD; Kevin A. Schulman, MD; John V. Goldsmith, PhD; M. Dianne Murphy, MD; Robert M. Califf, MD; Daniel K. Benjamin, Jr, MD, PhD, *Economic Return of Clinical Trials Performed Under the Pediatric Exclusivity Program*, JAMA. 2007 February 7; 297(5): 480–488, http://www.ncbi.nlm.nih.gov/entrez/eutils/elink.fcgi?dbfrom=pubmed&retmode=ref&cmd=prlinks&id=17284698

capsule size is an issue, or if the drug needs to be dosed on a mg/kg basis. Other issues can include the need for clean water to reconstitute the drug or the need for refrigeration in developing countries. Solid dosage forms may not be possible to develop, or may not be useful if they make accurate dosing a challenge. The PREA appropriately allows a waiver if a Sponsor can provide evidence that attempts at producing an appropriate formulation have been unsuccessful. The Sponsor's justification for the waiver is a public document under the law.

5. Are there any estimates of how private and government funded pediatric research has changed as a result of BPCA and PREA?

Certainly, the requirements imposed on the NIH for the study of off-patent products has created a mandate for increased government work in pediatric drug development. Unfortunately, resources have not kept up with the need. For this and potentially other reasons, the NIH has not been successful in obtaining approval on any off-patent drug in children. Conversely, the partnership of industry and NIH for development of pediatric compounds, *e.g.*, in the Pediatric Oncology Group or the Pediatric Heart Network, has been extremely successful and important.

As discussed above, it may be worthy of consideration to develop incentives for another type of partnership in which companies perform the pediatric studies for off-patent compounds at the company's expense thereby saving the government money.

6. How important is the BPCA exclusivity incentive? What has been the impact of the BPCA exclusivity incentive on pharmaceutical companies?

BPCA incentives are critical for performance of high quality, evidence based studies for pediatric drug development. As a result of the incentives, companies are doing more pediatric research and are building up internal expertise to support all pediatric work, which ultimately should facilitate more effective and efficient research.

Currently, with the incentive in place, companies seek to complete high-quality studies within regulatory time frames. BPCA brings to the table scientists and clinicians who explore potential pediatric indications for a given compound even when the compound's indication in adults is not relevant to the pediatric population. In the presence of the incentive, clinicians designing the studies feel very comfortable that adequate resources will be available and approved to perform top of the line studies necessary for children. A mandate to perform studies alone in the absence of the incentive would lead to pediatric studies being performed, but the studies would likely be performed with very tight budgets and minimal resources.

7. To what extent do studies conducted under BPCA impact medical professionals? Do any of these drug's labeling changes also have an impact?

Labeled and published clinical trial results of BPCA studies have vastly increased the information available to practicing medical professionals for the safe and effective use of

medications originally labeled only for adults. BPCA has also provided tremendous opportunities for academicians to work with industry and regulators to design and perform studies that will truly provide a positive impact on their patients' care.

A number of high profile FDA Advisory Committee meetings have been held to discuss the safety of medications in pediatric patients (for example, medications for depression, ADHD, anti-psychotics). These meetings in conjunction with publications and labeling changes have increased awareness and monitoring of patients by health care providers and patient families.

8. To what extent do drug companies hire pediatric experts to facilitate pediatric research?

Pediatric experts are used extensively in various parts of the pediatric drug development process, and how they are involved varies tremendously among different companies. Enactment of BPCA and PREA has been a critical element in encouraging companies to build and develop the infrastructure needed to undertake important pediatric research. Many of the larger companies have incorporated internal pediatrics groups or networks to facilitate sharing knowledge and expertise within their companies and respond to the large number of pediatrics programs they must execute for their products. Most companies have a limited number of pediatricians on staff, but seek to use their expertise efficiently and to liaise with the pediatric community.

Generally external pediatric experts - leaders in their fields - are brought into the pediatric drug development process very early. Companies seek opinions on the appropriate need for the drug in pediatrics, ages to be studied, uses for the drugs, formulation issues, possible study designs given the number of available patients, etc. Some experts may be asked to help run the studies with the company, for example by becoming members on internal committees such as the Data Monitoring Committee. Finally, these experts assist with making the results available to the practicing community of pediatricians. New partnerships among regulatory agencies, industry and academia are providing a level of research for new therapies in children previously unseen in this country or worldwide.

9. Has the linkage formed by the National Institutes of Health and the Food and Drug Administration because of BPCA been beneficial to those conducting pediatric drug trials?

The benefits of this linkage on off-patent pediatric drug assessment have been uneven at best. BIO understands that the linkage between FDA and NIH is intended to prioritize needs for pediatric studies, and facilitate research particularly where industry is unable to do it. However, this has not greatly stimulated industry pediatric research on off-patent products. Nonetheless, the FDA/NIH interaction may help to identify unique needs for research that Sponsors can initiate under BPCA, and it is our understanding is that it does provide opportunity for non-industry study grants.

10. Can you discuss barriers that may impact the number of drug studies that include neonates?

- The neonatal period is short (the first four weeks of life) so in some instances administrative issues may make it difficult to process neonatal patients into studies and to complete the studies to a relevant endpoint while the patients are still "neonates."

- Premature neonates are as different from full-term neonates as children are to adults, and a two day old neonate has vastly different physiology from a 4 week old. Thus it is difficult to identify barriers that apply to all "neonates".

- During the neonatal phase physiology and drug metabolism systems change rapidly. Further there is variation in gestational maturity as well as chronologic age within the population of neonates. This may mean that dose and formulation needs are difficult to estimate and address.

- Difficulty of clear diagnoses in the neonatal population.

- Relevance of pre-clinical safety information (even that obtained in neonatal animals) to human neonates with respect to predicting safety.

- Difficult vascular access for parenteral drugs.

- Difficult blood laboratory sampling. Heel sticks are painful and traumatic, but usually necessary to conduct studies. Ethical issues arise if the number of heel sticks must be increased beyond that necessary for the care of the child.

- Difficulty in gaining parental consent for research studies for their neonates.

11. Does your organization have a position regarding the sunset provisions of BPCA and PREA?

During the last 15 years since enactment, BPCA and PREA, working together, have been widely acknowledged as effective in promoting pediatric drug research. There is no logical reason to continue to allow such important legislation to sunset as the ambiguity associated with this situation causes resources to be expended for reenactment and also has the potential for limiting or endangering the pediatric research infrastructure that companies have been endeavoring to build and expand. It can be even more effective with a permanent law in place that would allow for appropriate FDA guidelines to be put in place for industry since the complexity of pediatric research is exacerbated by the often subtle differences between the new pediatric legislation introduced every five years (sometimes the same drug development program straddles multiple pediatric legislations.)

12. What is your organization's position regarding the lack of formal industry guidance for PREA and the lack of updated guidance for BPCA?

The lack of formal industry guidance is a concern for industry. We recognize that some level of flexibility allows for different, thoughtful approaches which may make sense when a product-specific approach is better than a "one size fits all" approach. However, lack of formal, updated industry guidance does leave many unanswered questions, and industry would welcome additional guidance and consistency. Pediatric drug development guidance should minimally cover the following:

- Timelines for reviews of pediatric program proposals;
- Clarification around the roles of the various FDA players and how and when industry should best interact with them;
- Expectations around labeling changes; and
- The process for products for review at the pediatric Advisory Committees.

As noted above, permanent laws would facilitate FDA's ability to issue updated, formal guidance.

Sponsors often interact with multiple organizational units with FDA and these units typically have a varied focus and are responsible for different aspects of the development program. We believe that the provision of formal guidance may also assist internal coordination at FDA among the Office of Pediatric Therapeutics, the Pediatric Review Committee (PeRC), the various review divisions within CBER and CDER. Our members report that mixed messages are common when they approach FDA about pediatric program requirements and time frames. Specifically, time frames for review for pediatric programs, Proposed Pediatric Study Requests (PPSR), issuance of Written Requests, *etc*, are often unclear and variable. Permanent PREA and BPCA laws are needed such that FDA can issue reasonable guidances for industry and all parties - FDA or industry or academia - can know and adhere to the same set and interpretation of the rules.

It is also worth noting that the Office of Pediatric Therapeutics has regular contact with their European Medicines Agency (EMA) counterparts to discuss issues relative to pediatric drug development and safety. This is very useful in terms of confidence building across the regions to develop common understandings and approaches to pediatric drug development. Because of the need to conserve scarce resources overall, and especially with respect to the number of patients available for enrollment in clinical trials, we would encourage health authorities to cooperate to minimize barriers to the development of global pediatric development plans. While we understand that there will always be differences in approaches to public health and safety as well as to the practice of medicine in the various regions, there still needs to be attention in this area to ensure that all of the barriers that can be eliminated are dealt with effectively. BIO is considering some initiatives in this area, and we would be interested in working with the FDA and with other stakeholders to develop consensus programs that would address this need for global pediatric development programs.

13. Can you recommend any other organizations or individuals we should be in contact with for our engagement regarding these issues?

- American Academy of Pediatrics
  www.aap.org

- Children's Oncology Group
  www.childrensoncologygroup.org

- Cedars-Sinai Steven Spielberg Pediatric Research Center
  www.cedars-sinai.edu/Patients/Programs-and-Services/Pediatrics/Treatment/Steven-Spielberg-Pediatric-Research-Center.aspx

CONCLUSION:

BIO appreciates this opportunity to comment on the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/s/

Andrew J. Emmett, MPH
Director for Science and Regulatory Affairs
Biotechnology Industry Organization (BIO)