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BIO Statement for the Institute of Medicine Committee on Pediatric Studies Conducted under BPCA and PREA

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The Biotechnology Industry Organization (BIO) thanks the Institute of Medicine (IOM) 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 for 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 current incentives for ongoing pediatric research.

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 the IOM 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. The following BIO comments discuss 1) the results of a BIO membership survey of internal company organization of pediatric research programs and 2) responses to the four IOM workshop questions.

PART I: BIO Survey on Internal Company Organization of Pediatric Research Programs

Prior to responding to the IOM's request, BIO's Pediatrics Committee sought to determine whether an increase in pediatric structure development is occurring in biotechnology companies as a result of BPCA/PREA. To obtain this data, the Committee sent a questionnaire to the members of BIO's Pediatrics and Regulatory Affairs Committees and received 14 responses. Only a subset of BIO's membership received and completed the survey - mostly companies interested in pediatrics policy issues - and, therefore, we recognize the survey's statistical limitations. While the results do not fully represent BIO's membership as a whole, we believe the findings will be instructive.

Most of the respondents (57%) reported having more than 5,000 employees and have incorporated pediatric drug development into their standard drug development process. In addition, 7% reported parallel pediatric development with adults, and 36% state that the pediatric process is team dependent. Almost half of the responding companies (42.9%) report that they have a pediatric committee that guides their company's pediatric drug development. Leaders of these committees are at a director level or above (with three Vice Presidents), and two-thirds of the leaders are pediatricians. The committees are composed of representatives from all therapeutic areas in 75% of companies, and most of the functional areas, including representation in over 75% of the committees from clinical, medical, regulatory departments and at least 20% of committees include pharmaceutics, pharmacology, safety, pharmacometrics, epidemiology, and toxicology representatives.

Pediatric committees meet at least monthly in 60% of companies, and the leaders of the committees spend up to 30% of their time on pediatric administrative work. Fifty percent of the committees were formed in the last three years since the passage of European Union (EU) legislation and FDA Amendments Act of 2007. Nearly 90% of the committees feel they provide the necessary leadership to guide pediatric drug development within their companies.

Most pediatric teams serve in an advisory capacity and provide education for the company, and are involved in the development of pediatric structure, external pediatric policy discussions, and operations for pediatric studies.

For those companies responding who did not have a pediatric committee, the most common reason was an uncertain regulatory environment (21%), a lack of pediatric expertise (21%), a lack of management support (14.3%) and insufficient pediatric work (14.3%).

The majority of companies responding (61.6%) employ more than ten pediatricians. If specific pediatric expertise is lacking for a specific team, a combination of internal and external expertise is used in over 80% of companies.

Due to regulatory requirements, companies need to address pediatric plans much earlier in development than in the past. 25% of respondents reported that they begin consideration of pediatric programs pre-clinically, 58.3% at the end-of-phase 1, and 25% at the end-of-phase 2.

Pediatric regulatory documents are prepared by most companies at the end-of-phase 1 (61.5%), end-of-phase 2a (46.2%) and end-of-phase 2b (15.4%), most likely reflecting the influence of EU regulatory requirements. This early goal is also reflected in new compound regulatory submissions (100% before phase 3 and 50% at the end of phase 1). The goal of simultaneous regulatory submission to EU and FDA has not yet been achieved for most companies. The most often mentioned reason for this lack of achievement appears to be related to variable response to filing requests by FDA divisions.

Most companies keep their pediatric work within the company (100% regulatory tasks). Pharmacokinetic studies were outsourced by 2 of 12 companies; clinical/safety studies and long term safety studies by 3 of 12 companies; toxicology and formulation outsourced by 2 of 13 companies.

PART II: IOM Public Meeting Questions

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?

Together BPCA and PREA 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 an incentive for such additional research. Second, by permitting Sponsors to submit a Proposed Pediatric Study Request and obtain the incentive 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 provide the necessary resources to fund the development of products that serve either small populations or populations for which the reward is unavailable; build the needed infrastructure to sustain pediatric drug development; and, ultimately, encourage important pediatric research as an integral component of all drug development. Included in building an infrastructure to develop medications for children are internal pediatric committees, pediatric pharmacometric, pharmacology and formulation expertise. Also included are developing relationships with pediatric academic experts, pediatric trials networks including NIH funded groups and the new European Network for Pediatric Research - European Medicines Agency (enpr-EMA), and Contract Research Organizations with

[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

new pediatric capacity. The amount of funding available in this private-public partnership far exceeds the amount of money and clinical research capacity that would be available with public or foundation funding alone.

BPCA and PREA work together to provide these critical tools for fostering pediatric drug development, and have some common strengths and weaknesses. They also have some that are unique, as summarized below:

Strengths:

- Under BPCA, the incentive for conducting pediatric studies. History shows that market forces 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 BPCA are met.

- Under PREA, the requirement to conduct pediatric studies in the same indication being sought for the adult population, while providing a voluntary mechanism to conduct studies of other potential uses under the provisions of BPCA. The incentive allows pediatricians working within industry to plan and execute pediatric drug development programs with senior management support knowing that costs will be recovered with the incentive even though it may be over a decade before the incentive is realized.

- Under BPCA, the opportunity for FDA 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 (see "weaknesses" below regarding PREA). Pediatric studies under these acts are among the only drug development programs where FDA and industry agree to a research program in advance, and where completion of the programs regardless of the results can be considered a successful outcome. Certainly, there have been a number of studies with a less than definitive outcome, but performing research in this heterogeneous, growing and maturing population is very challenging, especially in light of the very short history of large pediatric clinical trials establishing normative data and evidenced based standards of care. Studies currently reflected in the literature were often less than optimal in study design, as the result of concerns about acceptance of studies by Independent Review Boards, parents, children and

investigators. As noted in the early antihypertensive trials in children, the wrong dose was often chosen due to concerns that the dose seemed too large relative to adult doses without acceptable determination of the proper dose performed prior to the clinical trial. Nonetheless, the partnership of regulators, industry and academia has made impressive progress since the FDA Modernization Act of 1997, and the current quality of studies being designed now are equal in rigor to those of adult programs. Due to the length of time required for enrollment of pediatric trials, it will take another 5-10 years before the literature will reflect these new evidence based programs.

- Under BPCA, the requirement for review of pediatric supplements under the 6 month Priority Review timeline 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 is a significant strength. 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 an updated guidance providing a clear description of appropriate information for a pediatric plan in the statute, including absence of information on timing of submission or need for FDA concurrence. This is in contrast to content guidance for both the BPCA Proposed Pediatric Study Request 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 proposed or planned 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 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 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. 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 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).

- Absence of delineation of decision rights or clear lines of authority between the Review Divisions and the Pediatric Review Committee, leading 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.

- Extrapolation to the pediatric population based on adult data appears to be handled differently by different divisions and pediatric committees.

- Inconsistencies in the guidance and timing for BPCA/PREA vs. EU pediatric requirements. The avowed goal of both FDA and EMA is to provide the necessary pediatric data while exposing as few children as possible to research medications. Closer timing and coordination of programs can only lead to better and more efficient research studies. Having permanent laws with FDA guidance for industry would be the first major step in harmonizing studies with the permanent EU legislation.

- 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 New Drug Application/Biologic License Application 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.

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 majority of BIO members are small companies that do not yet have a product on the market, but are at the forefront of biomedical innovation. BIO members welcome advances that enable more efficient drug development that is appropriate for pediatric drug development and reduce unnecessary testing.

(a) New technologies and the use of biomarkers may impact the understanding regarding potential safety and efficacy and allow extrapolation. However, currently the requirements to meet extrapolation criteria may not be feasible for many pediatric conditions, and it will take some scientific advances to get there. Extrapolation should be performed for pediatric drug development whenever possible when the phenotype, disease course, and concentration-response of the medication are sufficiently similar in adults and children or older to younger pediatric patients. Generally, long-term safety studies and dose determination (pharmacometrics) will still be required.

(b) As to the use of alternative endpoints in pediatric studies, the need is for endpoints that span the entire pediatric age range. This would allow for a smaller number of children to be enrolled and have adequate statistical power, versus having to conduct multiple pediatric trials based on older and younger cohorts. In some instances, it may be impossible to conduct an adequate and well-controlled trial using a clinical endpoint based on an outcome system that may seem reasonable based on adult trials or experience. In such situations, a surrogate endpoint in pediatric patients may be easier to assess or more responsive to change, which may make a scientifically valid trial feasible in this population. However, validation of these endpoints must be achieved before their widespread use. A partnership of multiple companies and research groups such as the NIH may be required to identify and refine these very necessary and validated endpoints.

In addition to the use of alternative endpoints in pediatric studies, other innovations in clinical trial methodology should be both allowed and encouraged. The use of adaptive design, for example, may allow trials with fewer patients. Other examples of innovative yet robust study designs that may be particularly suitable to pediatric settings include randomized placebo phase, randomized withdrawal, and concentration-controlled designs.

(c) There are several unique challenges that impact the number of drug studies that include neonates. For example, the need for specialized equipment; challenges in achieving study

consent; formulation issues and route of administration; difficulty in adverse event assessment; identification of appropriate clinical endpoints; and restricted blood volumes for chemistry, hematology, endocrinology, and pharmacokinetic sampling. Other challenges are related to the ongoing, rapid, normal development occurring in the neonatal period. Also, parents and guardians may be very reluctant to enroll their neonates in placebo controlled studies if a standard therapy is available, regardless of whether the standard therapy is approved for the pediatric indication being studied. Some of the challenges of conducting studies with neonates may be addressed via methods such as the use of adaptive designs and of dried blood spots for pharmacokinetic assessments. In addition, the appropriate use of topical anesthetics is valuable, although best practices in this regard are still being defined.

Included here are additional challenges to conducting neonatal studies:

- 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, in some respects, as different from full-term neonates as children are to adults, and a two-day old neonate has vastly different physiology from a four-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. Furthermore, 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 in a uniform manner.

- It is often difficult to obtain clear diagnoses in the neonatal population.

- The relevance of pre-clinical safety information (even that obtained in neonatal animals) to human neonates with respect to predicting safety is often unclear.

- Vascular access for parenteral drugs is difficult in neonates.

- Blood laboratory sampling also presents challenges. 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.

(d) Sharing blinded data may support consent for new patients, but increases the risk of bias, particularly that related to safety.

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

An inherent tension exists between the need for pediatric drug development to address the unique unmet health needs of children and the ethical duty to protect children from undue risk of harm. BIO members seek ways of protecting children *through* research rather than *from* research. Specific issues are delineated below that make pediatric research challenging and difficult to accomplish; however, industry does not feel that these laws require research that is unethical in children:

- Appropriately balancing the benefits/risks to pediatric patients of experimental drugs in early phase research vs. the benefits/risks to pediatric patients of off-label use of approved drugs in clinical practice. Industry recognizes and shares the ongoing societal concerns about the risks posed to pediatric patients when a drug that is approved and marketed for an adult indication is used off-label and without adequate data in the pediatric population. This use is a form of experimentation without realistic expectation of gaining acceptable knowledge of the drug's safety and efficacy.

- There is a lack of public awareness of the scope of 21CFR50 on the protection of human subjects in clinical trials and its application to studies in and outside the U.S.

- Terminology and categories of pediatric research used in 21CFR50 and their application by Independent Review Boards. There is considerable variability in the interpretation of regulatory terms, yet how these terms are interpreted is critical to the assessment of appropriate benefit and risk. Explicit guidance is needed for consistent application of these terms.

- There are ethical challenges to investigating drugs for prophylaxis of diseases in normal children or in children expressing a biomarker for a disease.

- The rarity of many childhood disorders, multiple clinical trials and the need for adequate sample sizes.

- Lack of precedents that can inform thoughtful clinical development plans, study designs, and sample sizes such that the least amount of children are asked to serve as research subjects.

- There are possibilities for multiple vulnerabilities. It is well accepted in bioethics that pediatrics patients fall into a category of "vulnerable subjects or patients" because of their immaturity and lack of ability to provide individual informed consent. However, there may be additional circumstances that apply multiple vulnerabilities onto a pediatric patient.

- Access to the study drug at the end of a trial and assent of the child.

- Transition from adolescence to adulthood and how to handle adolescents who become adults during the course of a clinical trial.

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?

Biologic drugs are dramatically improving the odds and providing tailored therapies for millions of patients with serious and life threatening diseases. For biologic drugs with the same molecular target for both adults and children, there is opportunity for coordination of adult/pediatric drug development. Knowledge of the expression of these molecular targets in infants, children and adolescents will be required to understand the potential safety and efficacy impact of these drugs before their use.

Ensuring connection of legislation and incentive between large molecule biologics and small molecule medicines will be essential. Under current legislation, approval of a biologic drug for an adult indication will trigger a requirement for pediatric studies under PREA unless the requirement for pediatric studies has been waived. The Biologics Price Competition & Innovation Act of 2009 (BPCIA) creates an approval pathway for biosimilar drug products and permits data exclusivity to be extended by 6 months for the biologic innovator if pediatric studies are performed under Written Request. As described in the response to question 1, the exclusivity incentive has been an important stimulus for pediatric research for small molecule drugs. It is important that the pediatric legislation and incentive apply to both large and small molecules.

There are likely areas associated with biologics in which FDA could provide additional direction and guidance and set priorities. One example may be in formulation development issues. Recently, the Office of Oncology Drug Products engaged the pediatric subcommittee of the Oncology Drug Advisory Committee (ODAC) to discuss pediatric development plans for several drugs. The Oncology Office Director stated the intent to leverage the pediatric subcommittee of ODAC to help select appropriate drugs for pediatric development. Other review divisions could consider leveraging the pediatric subcommittees of their therapeutic area advisory committees for similar purposes. In the situation of oncology drugs, there are more drugs to test than there are children with which to perform the research, and thus this kind of prescreening process may be of benefit, but may also be of risk to pre-judge a medication without proper research.

Finally, it is important to recognize that biologics are a relatively new and complex area in drug development, and that the expansion of BPCA/PREA to include the investigation of biologics in pediatric patients is even newer. Given this, there is a need for continued development of the science to support such efforts, and, while the involvement of industry and FDA is clearly essential, NIH and academia also have important roles to play in advancing the science. Industry and the FDA cannot do this alone, nor should they, given the importance of children to society as a whole.

CONCLUSION:

BIO appreciates this opportunity to comment on the Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act. BIO fully supports the permanent reenactment of BPCA and PREA with the current incentive structure. We would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Kelly Lai
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Biotechnology Industry Organization (BIO)