DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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STATEMENT OF

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FOOD AND DRUG ADMINISTRATION

BEFORE THE

SUBCOMMITTEE ON HEALTH

COMMITTEE ON ENERGY AND COMMERCE

UNITED STATES HOUSE OF REPRESENTATIVES

"Programs Affecting Safety and Innovation in Pediatric Therapies"

MAY 22, 2007

Release Only Upon Delivery

INTRODUCTION

Mr. Chairman and Members of the Committee, I am Rear Admiral Sandra Kweder, M.D., Deputy Director of the Office of New Drugs in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA or the Agency). I appreciate the opportunity to discuss FDA's role with respect to implementation of the Best Pharmaceuticals for Children Act (BPCA) and the Pediatric Research Equity Act (PREA). Congress enacted these initiatives to promote drug development for children because of the inadequacy of pediatric use information for the majority of drug products approved in the U.S. These two pieces of legislation are real success stories. As discussed below, there is no question that they have expanded access to important therapeutics for children, and promoted safety and innovation in drug development.

Although these statutes have resulted in significant improvements in the development of information on the use of therapeutics in children, there is still great need for additional studies. Because children may present with different symptoms and have different reactions to treatments, it is important to study products which have been used to address carefully diagnosed pediatric conditions. Pediatric patients are subject to many of the same diseases as adults, and are, by necessity, often treated with the same drugs and biological products as adults. Even with the advancements of the past 10 years, the majority of drugs still lack pediatric labeling information, and this absence of information can pose significant health risks for children. Inadequate dosing information may expose pediatric patients to overdosing or underdosing. Overdosing could increase the risk of adverse reactions that could be avoided with an appropriate pediatric dose; underdosing may lead to ineffective

treatment. The lack of pediatric specific safety information in product labeling also means caretakers and physicians are unable to monitor for and manage pediatric-specific adverse events. In situations where younger pediatric populations cannot take the adult formulation of a product, the failure to develop a pediatric formulation that can be used by young children (e.g., a liquid or chewable tablet) also can deny children access to important medications.

BACKGROUND: BPCA and PREA

Before enactment of the exclusivity incentive program in the Food and Drug Administration Modernization Act (FDAMA) in 1997, approximately 80 percent of medication labels in the Physician's Desk Reference did not have pediatric use information. Similarly, only 20-30 percent of drugs approved by FDA were labeled for pediatric use as evidenced by surveys from 1984-1989 and 1991-2001. In a survey covering 1991-1997, only 38 percent of new drugs potentially useful in pediatrics were labeled for children when initially approved. Many drugs were used "off-label" to treat pediatric patients without any data to establish the correct dose for pediatric patients or to confirm safety or efficacy in the pediatric population.

In 1997, as part of FDAMA, Congress provided marketing incentives to manufacturers who voluntarily conduct studies of drugs in children. This law provides six months of additional market exclusivity for a drug (active moiety) in return for conducting pediatric studies in response to a written request (WR) issued by FDA. To qualify for pediatric exclusivity, the pediatric studies must "fairly respond" to a WR issued by FDA that describes the needed pediatric studies (including, for example, indications to be studied, number of patients, etc).

The incentive, which applies only to those drugs regulated under section 505 of the Federal Food, Drug, and Cosmetic (FD&C) Act, has become the most successful pediatric initiative that the Agency has participated in to date.

In 2002, the pediatric exclusivity incentive was re-authorized in the Best Pharmaceuticals for Children Act (BPCA), a statute that added provisions for safety evaluation of products that received exclusivity, public dissemination of study information, and additional mechanisms for the study of drugs in children that drug sponsors decline to study, including active moieties with no remaining patent or market exclusivity.

In 2003, Congress passed another important law that works in concert with BPCA – the Pediatric Research Equity Act (PREA). PREA provides FDA the authority to require pediatric studies under certain conditions. PREA requires pediatric assessments of drugs and biological products for the same indications previously approved or pending approval when the sponsor submits an application or supplemental application to FDA for a new indication, new dosing regimen, new active ingredient, new dosage form, or new route of administration. PREA codified many provisions of the "Pediatric Rule," a regulation that FDA issued in 1998 that required certain pediatric studies but was struck down by the U.S. District Court for the District of Columbia for exceeding FDA's statutory authority. Both the Pediatric Rule and PREA were designed to work in conjunction with the pediatric exclusivity provisions of FDAMA and the successor provision, BPCA. As with BPCA, PREA has been extremely successful in generating pediatric studies on many drugs and helping to provide important new information in product labeling.

SUCCESS OF BPCA AND PREA

Together, BPCA and PREA have generated pediatric studies on many drugs and helped to provide new information in product labeling. Both statutes continue to foster an environment that promotes pediatric studies and to build an infrastructure for pediatric trials that was previously non-existent. These programs have encouraged the development of important new safety, effectiveness, and dosing information for drugs used in children. They have enabled FDA to obtain important pediatric information and numerous labeling changes.

Since 1997, the exclusivity incentive program has generated labeling changes for 128 products. The labeling changes have significantly increased the information available to health care professionals to use in the treatment of pediatric patients. The labeling for 83 products has been updated to include new information expanding use of the product to a broader pediatric population; the labeling of 25 products had specific dosing adjustments; the labeling of 28 products were changed to show that the products were found **not** to be safe and effective for children; and 37 products had new or enhanced pediatric safety information added to the labeling (these numbers add up to a number greater than 128 because some products had more than one change to the labeling).

Moreover, sponsors have submitted 504 proposed pediatric study requests to FDA, and 341 WRs have been issued by FDA to drug sponsors requesting over 703 pediatric studies (a WR may request more than one study). FDA has made 150 exclusivity determinations and granted exclusivity in 136 of those determinations. The studies conducted under BPCA have

made a significant contribution to the public health as demonstrated by the labeling changes that have resulted from these studies. Also, safety (adverse event) reviews have been presented to the Pediatric Advisory Committee (PAC) for 65 products. In addition, FDA has placed 56 products on the BPCA off-patent priority list and issued 16 WRs for off-patent products to obtain needed pediatric information.

Since PREA was enacted, FDA has approved 496 new drug applications (NDAs) and supplemental NDAs that fell within the scope of PREA (i.e., applications for new active ingredients, new dosage forms, new indications, new routes of administration, or new dosing regimens). These approvals have resulted in approximately 40 labeling changes involving pediatric studies linked to PREA assessments since the enactment of the legislation in 2003. In addition, FDA has approved 58 biologics license applications (BLA) and supplemental BLAs that fell within the scope of PREA.

BPCA & PREA PROCESSES: HOW DO THE PROGRAMS WORK?

BPCA – "On-Patent"

The goal of the BPCA process is to obtain pediatric studies that will enable a sponsor to fully label the drug (active moiety) for pediatric use. The BPCA process applicable to drugs with remaining patent or market exclusivity can be initiated in two ways. FDA, after background research and an extensive literature review, can determine if there is a public health need for additional pediatric studies for a particular drug and issue a WR for such studies. Alternatively, a drug sponsor can initiate the process by submitting a proposed pediatric study

request (PPSR) to FDA suggesting the studies that the sponsor believes are appropriate. FDA will review the PPSR and, as appropriate, can use it as a starting point for drafting the WR. It is important to note that FDA does not issue a WR if we determine there is not a public health need.

CDER has a pediatric team (the Pediatric and Maternal Health Staff) that coordinates CDER's pediatric activities. The review divisions have primary responsibility for drafting WRs. During the drafting process, the review division may consult with the pediatric team. Once drafted, the WR is reviewed by the Pediatric Implementation Team (PdIT). PdIT is composed of individuals from various disciplines within the Agency and members of the pediatric team.

More specifically, after the division develops a WR, the process then continues through the following steps:

- Review by PdIT (with potential additional changes by review division).
- WR Issued – the sponsor has 180 days to respond, accepting or declining.
- If accepted, the sponsor completes the studies and submits them in a priority supplemental application or NDA (the review is subject to Prescription Drug User Fee Act [PDUFA] timelines).
- The Pediatric Exclusivity Board (PEB), an FDA committee, separate from PdIT, also comprised of individuals from various disciplines within the Agency, makes an exclusivity determination within 90 days after submission.

- The reviewing division's scientific reviews of studies submitted to FDA in response to a WR are to be completed within 6 months for priority NDA supplements, and within 10 months for full NDA applications.

- For supplements, summaries of medical and clinical pharmacology reviews are posted on the Web.

While the BPCA process is integrated within the standard process of drug review for pediatric studies submitted in applications or supplements, the implementation of BPCA does have aspects that distinguish it from the standard drug review process, such as:

- all supplemental applications are reviewed as priority under PDUFA goals;

- the exclusivity determination must be made in 90 days; and

- summaries of medical and clinical pharmacology reviews are publicly posted regardless of approval status.

It is important to note that for pediatric studies submitted under BPCA, there are two review processes that occur in parallel: a review to determine if the studies "fairly respond" to the WR, thus qualifying the product for exclusivity; and a review of the supplement or NDA to determine whether the supplement or NDA should be approved under FDA's ordinary review process. Both are carried out by CDER with input from the Office of Pediatric Therapeutics.

BPCA Exclusivity Determination

First, the exclusivity review is conducted after the submission of the studies performed in response to the WR. The scientific division responsible for reviewing the drug being studied initially reviews the submission to determine if the submitted studies "fairly respond" to the WR. Because the division also is charged with review of the scientific aspects of the submission, FDA has found it important that they present their findings to an independent body, the PEB. This board is composed of individuals from multiple components of the Agency including the review divisions, and the Office of General Counsel, among others. Based on the information provided by the division, the PEB either makes a recommendation to grant or deny pediatric exclusivity or requests additional information. Exclusivity is granted (or denied) solely on the basis of whether the studies submitted "fairly respond" to the WR. Under the terms of the statute, the pediatric exclusivity determination must be made within 90 days of the submission of the studies. If the sponsor's submission fairly responds to the WR, is timely submitted, and the studies are conducted in accordance with commonly accepted scientific principles and protocols, FDA will grant the six months pediatric exclusivity at that time.

Because the 90 day timetable for exclusivity determinations is shorter than the timeframe under which the related application or supplement is being reviewed, in most cases, the exclusivity determination for the active moiety will be made before the scientific and medical review of the submitted labeling changes has been completed. It should be noted that an award of pediatric exclusivity does not mean the supplement or the NDA is approved or that it is guaranteed approval. The grant of exclusivity does not depend on approval of the

application or supplement and does not depend on there being a labeling change that results from the studies because exclusivity attaches to the entire moiety and not simply to the particular drug product for which the application or supplement is submitted.

Scientific Review and BPCA

The scientific review of the application (supplement or original NDA) by CDER is subject to the same scientific rigor and administrative terms and conditions as other application reviews. Under BPCA, all supplements submitted in response to a WR are classified as priority reviews, with a six month Prescription Drug User Fee Act (PDUFA) goal date. Timelines are determined according to PDUFA- so the "clock" for review stops and starts depending on the action taken – such as a request for more information from the sponsor or an amendment to the application.

As part of the scientific review of the application, FDA decides whether labeling changes are warranted. FDA includes both positive and negative information from study reports submitted in response to a WR in the labeling because both types of information may be useful to physicians and pharmacists. BPCA includes a dispute resolution process where the FDA can refer labeling disputes to the PAC for decision to ensure timely labeling changes. FDA has been successful in obtaining labeling changes related to pediatric safety and efficacy and has not had to use the dispute resolution process.

BPCA also provides a mechanism for WRs for drugs currently protected by patent or exclusivity to be referred to the Foundation for National Institutes of Health (NIH), if the sponsor declines to conduct the studies included in the WR.

BPCA – "Off-Patent" Process

In 1997, the FDAMA provisions required FDA, after consultation with experts in pediatric research, to develop, prioritize, and publish an initial list of approved drugs for which additional pediatric information may produce health benefits in the pediatric population. FDA published the initial list on May 20, 1998. The list included a number of drugs for which there was no remaining patent or exclusivity. The additional exclusivity was not an incentive for those sponsors with "off-patent" drugs and few of those drugs were studied under that provision.

In response to the need for pediatric studies in many "off-patent" drugs, the reauthorization of the pediatric exclusivity incentive in BPCA included a mechanism to address such studies. Under its provisions, FDA and NIH jointly develop a prioritized list of off-patent drugs for which we believe pediatric studies are needed. This list is published annually in the *Federal Register*. FDA can issue WRs for these drugs under the usual process. If the sponsor declines the WR, FDA can refer the WR to the National Institute for Child Health and Human Development (NICHD) at NIH.

BPCA -- Pediatric Advisory Committee and the Office of Pediatric Therapeutics

The BPCA expanded and enhanced the initial pediatric exclusivity process in two important ways. First, it authorized FDA to establish the Pediatric Advisory Committee (PAC), and provided for post-marketing safety review by PAC of all pediatric products granted exclusivity by FDA. FDA provides PAC with all adverse events received within a one-year period after the product is granted exclusivity so that PAC can do a safety review and provide input to FDA. If appropriate, PAC can make recommendations after its review about things that should be modified in labeling, additional areas for investigation, and even requests for FDA to work with sponsors to obtain additional clinical trial data. The other novel aspect of BPCA is that it promotes transparency by requiring that summaries of the studies conducted under the BPCA be posted regardless of the regulatory action (e.g., approval, non approval).

Second, BPCA created the Office of Pediatric Therapeutics (OPT) which, as part of FDA's Office of the Commissioner, provides scientific expertise and ethics advice, and coordinates and facilitates activities that may have any affect on the pediatric population or the practice of pediatric medicine, or may involve pediatric issues. The office includes an ethicist specializing in pediatric ethics to assist in its responsibilities. OPT manages PAC and coordinates the review by PAC of adverse event reports for drugs granted pediatric exclusivity. OPT also coordinates and provides liaison activities both with internal FDA/Department of Health and Human Services offices and groups, and with external groups, including international organizations.

PREA PROCESS

In contrast to BPCA, which provides a voluntary mechanism for obtaining needed studies on either approved or unapproved indications for a given drug, PREA requires pediatric assessments (based on studies in pediatric populations) of certain drugs and biological products, but only in the indications that are approved or for which the sponsor is seeking approval, and only under certain circumstances. PREA is triggered when an application or supplement is submitted for a new indication, new dosing regimen, new active ingredient, new dosage form, and/or a new route of administration. It also can be invoked by FDA for a product for which an application or supplement is not being submitted if a WR issued under BPCA has been declined by the sponsor and other BPCA-created mechanisms to obtain the studies have been exhausted. PREA includes provisions allowing FDA to defer or waive the required pediatric assessments under limited circumstances.

Also, in contrast to BPCA, PREA applies not just to NDAs but also to BLAs. Thus, CDER and CBER are both responsible for implementation of PREA, while CDER is the only Center in FDA that implements BPCA. Sponsors develop a *pediatric plan* - a statement of intent that outlines the pediatric studies (e.g., pharmacokinetics/pharmacodynamics, safety, efficacy) that the applicant plans to conduct and addresses the development of an age-appropriate formulation and whether, if so, what grounds, the applicant plans to request a waiver or deferral under PREA.

Applicants are encouraged to submit their pediatric plans, and information to support any planned request for waiver or deferral, as early as possible in the drug development process and to discuss these plans at critical points in the development process for a particular drug or biologic. In each Center, for products for life-threatening diseases, the appropriate review division will provide its best judgment at the end of Phase I (the first phase of clinical studies involving human subjects) meetings on whether pediatric studies will be required under PREA and whether the submission will be deferred. For products not intended for life-threatening or severely debilitating illnesses, applicants are encouraged to submit and discuss their pediatric plan no later than end of Phase II meeting. The review divisions that handle that particular drug or biologic provide their best judgment about (1) whether a pediatric assessment is required, (2) whether its submission can be deferred or waived, and (3) if deferred, the date studies should be due.

FDA can grant a deferral under PREA when the product is ready for approval in adults but the pediatric studies have not been completed; when additional safety and effectiveness information in adults is needed before beginning studies in children; or there is another appropriate reason for deferral. The PREA requirements also can be waived either in full or in part. Full waivers, covering the entire pediatric population, are granted when the necessary studies are impossible or highly impracticable (such as, for example, when a disease or condition does not ordinarily occur in children); evidence strongly suggests the product would be ineffective or unsafe in children; or the drug or biologic does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients. Partial waivers are granted when these same criteria

apply only to a subset of the pediatric population, or when the sponsor can demonstrate that it has made reasonable attempts to produce a pediatric formulation, but that its efforts have failed. PREA specifically requires that, if a full or partial waiver is granted because available evidence suggests a product would be unsafe or ineffective in children, this information must be included in the labeling for the product.

CONCLUSION

The number of pediatric clinical trials for FDA-regulated products has increased dramatically since 1997 and has resulted in the development of invaluable efficacy, safety, and dosing information regarding the use of these products in the pediatric population. BPCA and PREA work in tandem to encourage and require pediatric studies that are vital to the health and welfare of this important population. PREA helps to fill the need for those studies not addressed by BPCA, and we believe that it is important to keep these programs working side by side. We would like to see the programs continue to succeed in years to come.

The incentives provided by BPCA should continue to lead to significant advances in pediatric medicine. It is important to have that wide reaching but voluntary program balanced with the more limited but mandatory studies that can be obtained under PREA. The two statutes have acted in concert to provide important safety, efficacy, and dosing information for drugs used in children. FDA wants to build on these improvements with more studies to produce new labeling information that is of value in treating children.

Despite the successes of these two programs, there is more work to be done. There are still a large number of drug and biological products that are inadequately labeled for children. More broadly, long-term safety and effects on growth, learning, and behavior are critically important to safe use of certain medications and continue to be understudied. Due to technical challenges and the need for sequential studies, neonates also still remain mostly unstudied and little is known about the safety and efficacy of the therapies being used to treat them. These issues are still of concern, as it is this youngest population that is undergoing marked physiologic and developmental changes, which are affected by drug therapies. FDA intends to persist until these are all studied.

FDA welcomes the opportunity to work with Congress to ensure that the benefits of an incentive program can continue, in conjunction with FDA's authority to require mandatory studies, as Congress considers the reauthorization of the BPCA and PREA programs. Thank you for sharing our interest in pediatric medicine and the health of our children.