

Pediatric Exclusivity and Drug Development Requirements in the Overall Pediatric Population

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1 INTRODUCTION AND OVERVIEW

Although children suffer from many of the same diseases as adults and are often treated with the same drugs, only a small fraction of the drugs marketed and used as therapies in the United States have been studied in pediatric patients 0–16 years of age. Recent data demonstrates that only about 25% of approved drugs marketed in the United States have adequate pediatric data to support approval of product labeling by FDA for dosing, safety, or efficacy in children.¹ This lack of appropriate pediatric testing and labeling increases the chances of incorrect dosing, thereby exposing pediatric patients to either an increased risk of adverse reactions or less than optimal therapeutic benefits.² In addition, the failure of pharmaceutical companies to manufacture drugs in dosage forms that can be easily and properly used in all pediatric age groups denies pediatric patients access to necessary medications.

Most drugs prescribed for children lack sufficient pharmacokinetic, pharmacodynamic, efficacy, or safety data to support use in the pediatric population. The pharmaceutical industry traditionally has had little incentive to undertake pediatric clinical trials, which has resulted in off-label use in the pediatric population, ranging from 60 to 90% in children and newborns.³ Reasons cited for the lack of studies in the pediatric population include smaller target populations, increased recruitment challenges, consent and ethical issues, and lower potential for market return on corporate investment compared with that seen in adult populations.³

Legislation has been enacted in the United States over the past 10 years to provide incentives for pharmaceutical industry sponsors to conduct drug studies in the pediatric population. To encourage pharmaceutical sponsors to undertake clinical studies in the development of pediatric indications for drugs and biologics, Congress and FDA have granted marketing exclusivity if certain provisions and requirements are met. Sponsors must be aware of the provisions of these enactments to allow for appropriate pediatric programs that fulfill FDA requirements and provide necessary and meaningful information regarding the safe and effective use of drugs in children. The central goal of such legislation is to change the labeling of existing drugs to reflect pediatric use. In an initial September 1999 guidance document, FDA determined that pediatric exclusivity will attach to exclusivity and patent protection on a drug as listed in the Orange Book for any drug product containing the same active moiety as the drug studied and for which the party submitting the studies holds the approved New Drug Application (NDA) (505A(a) and (c)).⁴ For studies conducted with a previously unapproved drug, pediatric exclusivity will also attach to any exclusivity or patent protection that will be listed in the Orange Book upon approval of the drug.

2. LEGISLATIVE HISTORY OF PEDIATRIC EXCLUSIVITY

In an attempt to encourage drug sponsors to obtain more pediatric drug data, FDA implemented a number of measures in the early 1990s to encourage the submission of pediatric labeling

information. However, because these efforts were largely voluntary and new studies were not required, the measures failed to produce significant increases in pediatric labeling.⁵ In 1997, Congress enacted the Food and Drug Administration Modernization Act (FDAMA), which established economic incentives for conducting pediatric studies.⁶ Section 505A of the FDAMA, known as the Pediatric Exclusivity Provision, provided an additional 6 months of patent protection, or marketing exclusivity, to be attached to any existing exclusivity or patent protection on a drug in return for the sponsor performing pediatric studies as requested by FDA. This 6 month period of exclusivity included all active moieties of a drug studied in the pediatric population.

In 2002, Congress enacted the Best Pharmaceuticals for Children Act (BPCA), which reauthorized the financial marketing incentives as established by the pediatric exclusivity provision of the FDAMA.⁷ The 6 month marketing exclusivity was extended to the first company that conducted the clinical studies and obtained FDA approval for the pediatric indication. The 6 months of market exclusivity is in addition to other patent term extensions or market exclusivity provisions. In return, drug sponsors are required to publicly post study results and report adverse events for 1 year after exclusivity is granted. This process includes the issuance of a Written Request (WR), a legal document sent by FDA to sponsors requesting studies in the pediatric population, which identifies the indication, types of studies to be performed, number of patients per study/arm, safety and efficacy parameters, and the patient age groups to be studied. Pediatric exclusivity under BPCA attaches whether the study, as specified in the WR, produces positive or negative results.

Prior to issuing a WR to a sponsor, FDA requires that certain criteria be met regarding the proposed pediatric studies: there must be an expectation of a public health benefit and of a substantial use in the pediatric age group, there must be a threshold of 50,000 pediatric patients in the United States with the disease or condition, there must be the expectation of a meaningful therapeutic benefit in the treatment and diagnosis or prevention of the disease compared with already approved drugs or biologics, and adequate animal and/or human safety data must exist to permit studies in the target pediatric population(s).⁸

The BPCA incorporates a rather involved process by which FDA formally requests that a company conduct specific pediatric studies.⁷ Upon FDA's formal WR to the sponsor to conduct specific pediatric studies, the sponsor has 180 days to accept or reject the request or to identify to FDA any aspects that need to be discussed. If the sponsor agrees to conduct the study, the sponsor must follow the designated protocol and comply with applicable regulatory requirements, submit adverse events, and submit a final report to FDA. Upon submission to FDA, the study data is reviewed by the Office of Pediatric Therapeutics. This internal FDA committee is mandated to publish the results, thus making data available to the public on both on-label and off-label uses.

In 2003, Congress enacted the Pediatric Research Equity Act (PREA), which is related to the BPCA.⁹ The PREA requires the conduct of pediatric studies for certain drugs and biologic products (unless waived or deferred by FDA) and establishes a Pediatric Advisory Committee. For all NDAs, Biologic License Application (BLAs), or supplements to these applications, the sponsor is required to conduct pediatric studies for a new active ingredient, new indication, new

dosage form, new dosing regimen, or new route of administration unless waived or deferred. The results of the pediatric studies must contain data adequate to both assess the safety and effectiveness and to support dosing and administration for each relevant pediatric subpopulation. The PREA applies to studies that are required and is limited to the indication under development. In contrast, pediatric studies conducted under the BPCA are voluntary.

3 RECENT LEGISLATION

With the enactment of the Food and Drug Amendments Act (FDAAA) of 2007, Congress incorporated updates of 2003 PREA and 2002 BPCA.¹⁰ As included in the 2003 PREA, the current 2007 PREA¹¹ affects NDA and BLA applications and supplements for new active ingredients, indications, dosage forms, regimens, or routes of administration. In addition, pediatric studies of currently marketed drugs and biologics may be required if the product is used by a “substantial” number of children, if adequate pediatric labeling would provide “meaningful” therapeutic benefit compared with existing treatments for children for the claimed indication, or if the lack of “adequate” labeling poses a risk for the pediatric population. FDA’s hope is that forcing such studies and assessments will increase sponsors’ awareness of pediatric uses and make it more likely that sponsors will seek approval for a pediatric indication. As previously noted, a sponsor may seek a waiver for the obligation to submit a pediatric assessment for reasons such as the lack of safety, efficacy, or impracticability for a pediatric population. In that event, FDA requires that the waiver be included in the product labeling so that physicians will be informed prior to using the drug for an off-label pediatric purpose.

The 2007 PREA explicitly permits the sponsor to extrapolate data from different subpopulations, which may reduce or eliminate the need for age-specific clinical studies.¹¹ The 2007 PREA also addresses the extensive off-label use of drugs in the pediatric population, in that FDA can require not only the assessments mandated for newly submitted NDAs but also such assessments for drugs that have been approved and for which there is no pending NDA.¹¹ The 2007 updated PREA also requires FDA to make the “medical, statistical, and clinical pharmacology” information contained in the pediatric assessments publicly available to provide information to physicians who are considering using the drug for off-label purposes.¹¹

The FDAAA also reauthorized the pediatric exclusivity incentive as put forth initially in the BPCA of 2002.¹⁰ In the updated legislation as found in the BPCA of 2007¹², a single WR for pediatric studies may include more than one indication, and these indications may be either “on-label” or “off-label”. In addition, the WR may include nonclinical studies. Other changes in the BPCA of 2007 include the submission of all adverse event reports with the final pediatric study report, the finalization of the exclusivity determination based on new WRs to be made within 180 days of response to the WR, the grant of exclusivity only if there are 9 months of exclusivity or patent protection remaining at the time of determination, and the priority review of any application or supplement submitted in response to the WR.¹² Of note, a sponsor must submit its application (or supplement) for pediatric exclusivity 15 months prior to expiration of adult exclusivity.

4 BENEFITS OF PEDIATRIC EXCLUSIVITY TO SPONSORS

FDA is required to treat any application submitted as a result of a pediatric study conducted under the BPCA as a “priority application”.¹³ By mandating a faster review, an economic incentive is provided to the sponsor. As noted above, in exchange for conducting the appropriate pediatric studies that meet the terms as specified in the WR issued by FDA, the sponsor’s drug may receive 6 months of additional market exclusivity during which the sponsor retains sole marketing rights to all forms of a drug product line containing the active moiety. This marketing control makes pediatric exclusivity an attractive financial consideration.

In a March 2007 report issued by the U.S. Government Accountability Office (GAO), it was found that sponsors initiated pediatric studies for most on-patent drugs, agreeing to study 173 of the 214 drugs that FDA had requested in a WR.¹⁴ The GAO also determined that approximately 87% of drugs granted pediatric exclusivity prompted labeling changes based on derogatory information uncovered in pediatric studies, such as ineffective dosing, overdosing, ineffective drug action, or previously unknown side effects. Drugs were studied in the pediatric population in 17 broad categories of disease from common to life-threatening.

5 REFERENCES

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