

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 312, 314, and 601

[Docket No. 02N-0152]

Obtaining Timely Pediatric Studies of and Adequate Pediatric Labeling for Human Drugs and Biologics

AGENCY: Food and Drug Administration, HHS.

ACTION: Advanced notice of proposed rulemaking.

SUMMARY: Given the present authorities contained in the Best Pharmaceuticals for Children Act (BPCA), which was signed into law January 2002, the Food and Drug Administration (FDA) is issuing this advanced notice of proposed rulemaking (ANPRM) to solicit comments on the most appropriate ways to update the 1998 “pediatric rule” so that it can most effectively address FDA’s interest in timely pediatric studies of and adequate pediatric labeling for human drugs and biological products that are used or will be used in the treatment of children. FDA is interested in what mechanisms, if any, may be necessary to augment the programs described in the BPCA and what present authorities, if any, have not proven effective, are now redundant, or need to be updated because of the BPCA.

DATES: Submit written or electronic comments on the ANPRM by insert date 75 days after date of publication in the **Federal Register**].

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT: Terrie Crescenzi, Office of Pediatric Drug Development and Program Initiatives (HFD-960), Center for Drug Evaluation and Research, Food and Drug

Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-7337, e-mail: crescenzit@cdcr.fda.gov.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of December 2, 1998, FDA issued the final pediatric rule that requires manufacturers to assess the safety and effectiveness of certain human drugs and biological products in pediatric patients. This rule became effective in April 1999.

Under this rule, any application for approval of a human drug or biologic with a new active ingredient, new indication, new dosage form, new dosing regimen, or new route of administration is expected to contain data to assess the safety and effectiveness of the drug or biologic in pediatric patients. The pediatric rule also contains provisions for industry-FDA meetings and early consultation during the investigational study of a drug or biologic to facilitate the design and timely conduct of adequate pediatric studies of the drug or biologic, when appropriate to conduct such studies. In addition, this rule also provided FDA with the ability to require the development of a pediatric formulation, if necessary, to study a particular pediatric group; and to require manufacturers of already marketed human drugs and biologics to conduct certain pediatric studies when they seek approval for certain other changes to their drug or biologic. Manufacturers may obtain from FDA a waiver (e.g., the disease does not occur in the pediatric population) or deferral (e.g., pediatric studies to be conducted later in the development cycle) of some or all of these requirements. Under these provisions, many drugs have been studied in children and many companies have built an infrastructure that fosters pediatric studies of their products. In addition, under these provisions, as new drugs are developed, it has become more routine for companies to evaluate and plan appropriately for studying the new product in children.

For certain human drugs and biologics already on the market, under certain circumstances, the pediatric rule further authorizes FDA to require manufacturers to submit an application containing data adequate to assess whether the product is safe and effective in pediatric populations,

even when the company has not submitted an application for certain other changes to their drug or biologic. FDA has, to date, not invoked this latter aspect of the pediatric rule.

After FDA issued its proposed pediatric rule (62 FR 43900, August 15, 1997), but before it issued the final pediatric rule, Congress passed the Food and Drug Administration Modernization Act of 1997 (FDAMA). This act included a provision that authorized specific market exclusivity incentives to manufacturers who voluntarily conducted and submitted to FDA pediatric studies of their drugs as requested by FDA and who met certain statutory criteria. This provision has resulted in numerous pediatric studies of many of the drugs to which it applied. Nonetheless, when FDA issued the pediatric rule, the agency indicated that the FDAMA provisions left some significant gaps in obtaining pediatric studies to provide safety and effectiveness labeling information for certain products. Examples of these “gap” products include already marketed drugs no longer under patent or market exclusivity protection, certain antibiotics, biological products approved under section 351 of the Public Health Service Act (PHSA), and products for which the manufacturers simply choose not to perform pediatric studies requested by FDA, despite the exclusivity incentive to do so. The exclusivity incentive provision of FDAMA, as written, does not apply to biological products approved under section 351 of the PHSA, certain antibiotics, and products that did not have specific existing patent or exclusivity protection that could be prolonged under this authority. In addition, the exclusivity provision could only effectively be employed once with respect to an active ingredient. Thus, if further studies in certain groups of children (for example, neonates) were needed at a later date, the exclusivity provision was restricted and thus did not provide an economic incentive for the additional needed studies. Also, the exclusivity incentive provisions of FDAMA expired on January 1, 2002.

On January 4, 2002, the President signed into law the BPCA. This legislation both reauthorizes the exclusivity incentive program enacted originally in FDAMA (essentially without any change relevant here) and establishes an additional mechanism for obtaining information on the safe and effective use of drugs in pediatric patients. The new BPCA mechanism consists primarily of

authorizing several National Institutes of Health (NIH) funding mechanisms, including the NIH Foundation, as vehicles for funding, using both public and private funds, studies of certain drugs under certain circumstances if the manufacturers of those drugs decline to conduct the requested pediatric studies. BPCA also provides a mechanism for including information from such studies in the label of pediatric products. Because it involves paying others to do the studies rather than having to litigate with a company to force it to conduct needed studies, some have argued that this new BPCA mechanism is a more cost- and time-efficient way of achieving the goal of adequate pediatric safety and efficacy labeling of these “gap” products than are some of the provisions of the pediatric rule. Others point out that while these NIH funding mechanisms may be used to contract for pediatric studies of certain human drugs, the provision of BPCA for awarding study contracts does not extend to awarding contracts to study human biologics and certain antibiotics. In addition, the public funding of these mechanisms is dependent on yearly congressional appropriations and the private donations are purely voluntary. Whether funds appropriated for such studies will be adequate to ensure that studies are performed and data submitted for all needed drug products remains uncertain. By statute, the BPCA is to sunset in 2007. Because of these uncertainties in funding, limitations on the products covered, and the lack of required early planning regarding pediatrics in a drug’s development process, some have argued that without the “requirement” provisions of the pediatric rule, FDA will not have the authority it needs to ensure that all medicines used in children of all ages are indeed safe and effective for that use.

Given the present authorities contained in the BPCA and the pediatric rule, this ANPRM is intended to solicit comments on the most appropriate ways to balance FDA’s interest in timely pediatric studies of and adequate pediatric labeling for human drugs and biological products that are used or will be used in the treatment of children and FDA’s interest in not imposing unnecessary human drug and biologic study requirements. FDA is particularly interested in what mechanisms, if any, may be necessary to augment the programs described in the BPCA and what present authorities, if any, are perhaps now redundant because of the BPCA.

Therefore, FDA is soliciting comments on these issues. The agency is particularly interested in the relationship between the approach to acquiring pediatric labeling information promulgated in the pediatric rule, and the approaches authorized in the BPCA. While FDA is interested in hearing any comments the public would like to submit on this issue, questions of specific interest to FDA include:

1. What changes to the pediatric rule, if any, would be necessary to integrate the BPCA and the pediatric rule more effectively?

2. How would the criteria used by NIH and FDA under section 3 of the BPCA to request studies of already approved drugs relate to the standards promulgated in the pediatric rule and described in 21 CFR 201.23, 314.55, and 601.27 for requiring pediatric labeling for certain drugs and biological products? Which criteria are more appropriate for determining when studies are conducted?

3. What provisions, if any, of the BPCA could apply to biological products regulated under section 351 of the PHSA?

4. How does the provision in section 3 of the BPCA providing for a recommendation for a formulation change relate to the pediatric rule provision stating that in certain cases a sponsor may be required to develop a pediatric formulation? Should pediatric formulations be required in certain cases?

Resolution of these and other questions will be required before FDA can determine the optimum approach to ensuring that human drugs and biologics used in children have adequate information regarding the safe and effective use of these products in pediatric patients.

II. Requests for Comments

Interested persons may submit to the Dockets Management Branch (see **ADDRESSES**) written or electronic comments regarding this document by [*insert date 75 days after date of publication in the Federal Register*]. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets

in the heading of this document. Received comments may be seen in the Docket Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

This document was reviewed by the Office of Management and Budget under Executive Order 12866.

Dated: _____

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