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PEDIATRIC RESEARCH
NETWORK**

July 3, 2002

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Dockets Management Branch
(HFA-305)

Food and Drug Administration
5630 Fishers Lane - Room 1061
Rockville, MD 20652

<http://www.fda.gov/dockets/ecomments>

Docket Number: 02N-0152

To Whom It May Concern:

The Elizabeth Glaser Pediatric AIDS Foundation is a leading non-profit organization that funds pediatric research, trains pediatric researchers and advocates for the best public policy for children with HIV/AIDS and other serious and life-threatening illnesses. The Foundation has been intimately involved in the issue of ensuring better information about pediatric therapeutics since our founding approximately 14 years ago, and we appreciate the opportunity to comment on the importance of the Pediatric Rule.

The Pediatric Rule continues to be needed for the same reason that the Food and Drug Administration (FDA) stated in 1998 in publishing the Rule. As the Agency noted at that time, "[m]ost drugs and biologics have not been adequately tested in the pediatric subpopulation." The Agency also stated that:

As a result, product labeling frequently fails to provide directions for safe and effective use in pediatric patients. This rule will partially address the lack of pediatric use information by requiring that manufacturers of certain products provide sufficient data and information to support directions for pediatric use for the claimed indications.

02N-0152

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The Foundation fully supported the Pediatric Rule for the reasons stated by the FDA, and the Foundation continues to believe that the Pediatric Rule is of urgent importance to our nation's children. We therefore strongly urge the FDA to preserve the Rule intact and to refrain from making any new rulemaking that will compromise any of the Rule's major provisions or reduce its effectiveness in assuring

important safety and dosing information about drugs used by children.

In March 2002 the FDA represented to the U.S. District Court in the District of Columbia that it intended to suspend the Pediatric Rule. While this position statement was withdrawn, the Agency subsequently issued an advance notice of proposed rulemaking, seeking comments on the Rule. These comments are a response to that request.

The Elizabeth Glaser Pediatric Aids Foundation believes that there is no justification for initiating a rulemaking concerning the Pediatric Rule. The Agency is still in the early phases of implementation of the rule and some of its authorities have not been used on even a single occasion. There is no inconsistency between the rule and the recently enacted Best Pharmaceuticals for Children Act. Given the uncertainty that the Agency has created about the status of the rule, it is imperative that it declare that there is neither a basis or intent to amend the rule at the present time and that it fully supports the rule's requirements pertaining to the pediatric testing of drugs and biologics.

The recent burst of new information about therapeutics for children is the result of a dual approach designed in the late 1990s. This approach includes the carrot of incentives, initially included in the Food and Drug Administration Modernization Act (FDAMA) of 1997 and renewed in the Best Pharmaceuticals for Children Act (BPCA) in 2002. It also includes the stick of the regulation known as the Pediatric Rule. These two mechanisms, working together, have each produced important information for children. In fact, during consideration of both FDAMA and the BPCA, Congress has indicated that it intends these two provisions to coexist, thereby providing children with maximum protection.

As the FDA itself has recognized, both the Rule and the BPCA are essential because neither mechanism, on its own, captures the full range of pediatric information that is essential to the nation's children. According to the FDA, the incentives have "resulted in numerous pediatric studies of many of the drugs to which it applied," although the exclusivity provisions in FDAMA "left some significant gaps in obtaining pediatric studies to provide safety and effectiveness labeling information for certain products."

These gaps are real and of enormous importance to children. Some of the crucial differences follow:

- **The Pediatric Rule includes biological products.** The BPCA provides incentives to the pharmaceutical industry to study drugs but does not address biological products, or therapies that include a live agent. For example, many new cancer drugs include a live agent. A significant portion of therapeutics used in children is biological products, and the number of biological products is expected to increase

over time. Without the Pediatric Rule there is no mechanism to ensure that pediatric studies are conducted on these important medications.

- **The Pediatric Rule captures drugs and age populations that the Best Pharmaceuticals for Children Act cannot.** The BPCA can only be applied once during the life cycle of a drug. When FDA issues a Written Request under BPCA, all potential pediatric uses must be anticipated in the request. This request cannot be expanded later if additional studies are needed in very young children or newborns or if a new use is discovered for a drug. Once studies have been completed and the incentive has been granted, there is no additional incentive or obligation on the part of participating companies to generate additional pediatric data.

For example, in many cases, studies of young children or newborns are not considered scientifically or ethically appropriate until studies in older children are already completed. Thus, FDA may issue a written request for drug studies in older children, and then grant exclusivity once those studies are completed. Once exclusivity has been granted, there is no longer a financial incentive for studies of newborns, and the Pediatric Rule is the only mechanism to ensure that such studies are completed.

In other instances, an entirely new use of a drug may be discovered that is also applicable to children. If exclusivity has already been granted for the drug, then the Pediatric Rule would be the only mechanism available for studying the proper dosage of this new use.

- **The Pediatric Rule is ongoing - the Best Pharmaceuticals for Children Act is time-limited.** The BPCA sunsets in 2007. When the law sunsets, there is no guarantee that industry will continue pediatric drug studies. The Pediatric Rule will allow pediatric studies to continue.
- **The Pediatric Rule is mandatory - the Best Pharmaceuticals for Children Act is voluntary.** Because BPCA is voluntary, not all sponsors are interested in complying with the terms. The Pediatric Rule applies to all drugs and biological products whose intended use in pediatrics is the same as their intended use in adults, thus ensuring appropriate pediatric information.

In other words, without the Pediatric Rule, there would be no way to obtain crucial safety and dosing information for children in many circumstances. Both mechanisms are needed if we hope to obtain the same level of safety and effectiveness for children that we expect for ourselves as adults.

In its notice of proposed rulemaking, the FDA suggests that additional rulemaking may be needed at this time because of the passage of the Best Pharmaceuticals for Children

Act (BPCA). Not only did the BPCA renew the pre-existing financial incentives for pediatric studies of drugs, but it also created two new mechanisms for the study of certain medicines that are currently in the "gap" categories noted above. Specifically, the Act authorizes the spending of public and private funds to conduct pediatric studies of medicines that are currently off patent or that companies have simply declined to study as a result of the incentives provisions. Public funds are authorized for a new Research Fund to conduct these studies, and the non-profit Foundation affiliated with the National Institutes of Health (NIH) is also authorized to receive designated contributions for these types of studies.

While the Foundation supported both provisions as part of the BPCA, it would be inappropriate (and we believe contrary to the Congressional intent) to engage in rulemaking based on new provisions that are completely untested and have very uncertain funding streams. The new Research Fund contained in the BPCA received no funding in FY 2002, the first year it was authorized, and FY 2003 appropriations are not yet approved. Thus, no funding has been approved for this provision, no studies have been initiated, no studies are in progress, and no pediatric information has been obtained.

The NIH Foundation has received pledges of just over \$1 million designated for pediatric studies in the first 6 months that designated contributions for this purpose could be made. Most of this funding will be provided over a period of three years. Since the average pediatric study costs approximately \$5 million, the Foundation is currently unable to fund even a single pediatric study. This is the case despite advance, written assurances supplied to Congress by the Pharmaceutical Research and Manufacturers of America (PhRMA) and individual pharmaceutical manufacturers that they would likely provide useful contributions.

While the Elizabeth Glaser Pediatric AIDS Foundation remains hopeful that both of these provisions will succeed and is engaged in advocacy efforts to obtain appropriations for the Research Fund, the Foundation strongly believes that it would be inappropriate for the FDA to base a rulemaking on the authorization of two provisions that have not yet produced any demonstrable results.

In fact, the Pediatric Rule itself is still relatively new. The Rule first took effect in April 1999, just over three years ago. There has been very little time to assess the impact of the Rule thus far. However, several facts about the administration of the Rule in the past three years are of crucial importance to the proposed rulemaking.

First, not only is the Rule new, but one crucial provision – the authority of the FDA to obtain pediatric information about already-marketed drugs --- has not yet even been invoked by the FDA. The FDA should not in any way act to compromise this untested authority in its rulemaking. Not only could it be the only way to obtain crucial

pediatric data (due to some of the gaps in the incentives noted above), but there is absolutely nothing in the BPCA that has removed the need for this provision.

Second, there has been no specific problem cited by the FDA, industry, or any other party in terms of the interaction of the Pediatric Rule and the incentives contained in FDAMA and the BPCA. The two co-exist, according to all public reports, without any noticeable conflict or concern. Thus, there is no inconsistency between the two initiatives and no need to remove any of the protections of the Rule.

Third, although there has been no formal reporting to Congress or the public on the impact of the Pediatric Rule, preliminary information supplied in public settings by the FDA suggests that the Rule has played an absolutely crucial role in obtaining new pediatric data. A top FDA official recently reported that, of 94 drugs studied for pediatric use since the Rule took effect, over 30 could be attributed to the exclusivity provisions of the BPCA. The remainder of the studies, according to the official, cannot be linked to the exclusivity law. While FDA cannot state that these studies are directly attributable to the Rule, "we can say that we can't come up with any other reason," said Diane Murphy, Director of the Office of Drug Evaluation IV, in a report in FDA Week dated June 21, 2002.

These facts -- that the Rule is still in its infancy, that a key part of the Rule has not even been invoked, that Congress intended the Rule and the exclusivity provisions to work together, that there are no problems in the interplay of the Rule and the incentives of the BPCA, and that preliminary data suggests that the Rule has produced dramatic, positive results -- all strongly demonstrate that any FDA action to limit the Rule's scope would be premature, unwise, and likely to compromise the health care of children throughout the nation.

The Pediatric Rule ensures that children are no longer a therapeutic afterthought by the pharmaceutical industry. It is an essential and successful tool in ensuring that children have the quality and quantity of drugs they need. All new drugs must be studied for pediatric use at the time a drug comes to market unless the FDA grants a waiver. This makes medications for children a certainty, not an option, and puts children on a level playing field with adults for the first time.

Children's and health advocates have been working for decades to ensure that drugs are studied for use by children. For too long, these efforts produced few demonstrable results. That record changed, however, in the wake of the dual approach put in place several years ago of incentives and the Pediatric Rule. Now, for the first time, we are seeing a tremendous burst of new studies that are clearly producing important new health information for our children. Significant changes in the Pediatric Rule could produce a real setback for children's health in America. It is essential that the FDA refrain from tampering with a process that is succeeding.

Again, we appreciate the opportunity to provide comments on this issue of crucial importance to our nation's children. If you have any questions or wish to contact us about this issue, please contact me or Mark Isaac, the Director of Public Policy, at (202) 296-9165.

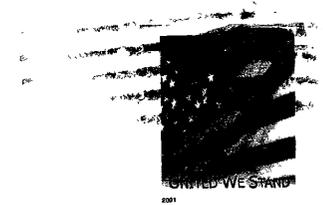
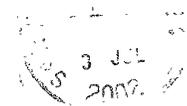
Sincerely,

A handwritten signature in black ink, appearing to read 'C. Prober', with a long horizontal line extending to the right.

Charles Prober, MD
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