

Alan Goldhammer, PhD
Associate Vice President,
US Regulatory Affairs



169 02 JUL -8 P2 34
July 8, 2002

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Docket No. 02N-0152: Obtaining Timely Pediatric Studies of and Adequate Pediatric Labeling for Human Drugs and Biologics; Advance Notice of Proposed Rulemaking; 67 *Federal Register* 20070; April 24, 2002

Dear Sir/Madam:

The following comments on the above Advanced Notice of Proposed Rulemaking (ANPR) are submitted on behalf of the Pharmaceutical Research and Manufacturers of America (PhRMA). PhRMA represents the country's leading research-based pharmaceutical and biotechnology companies. Our member companies are devoted to inventing medicines that allow patients to lead longer, happier, healthier, and more productive lives. In 2001, our members invested over \$30 billion in the discovery and development of new medicines.

PhRMA appreciates the opportunity to comment on how the Best Pharmaceuticals for Children Act (BPCA) should interface with the Pediatric Rule that was promulgated in 1998. Section 111 of the Food and Drug Administration Modernization Act of 1997 (FDAMA), has been a major success because it addresses the fundamental impediments that have hampered pediatric studies of medicines in the past, principally the limited number of pediatric patients. Given the success of the original statutory exclusivity provisions, the BPCA, which includes more comprehensive provisions designed specifically to address gaps in the original law, is likely to diminish the Pediatric Rule's importance as a blanket, default requirement for all new drug applications. The broad reach of the Pediatric Rule coupled with its more limited scope may misdirect the focus of pediatric studies. The BPCA allows for a broader, yet more focused examination of pediatric needs. Consequently, PhRMA contends that the Pediatric Rule should serve as a fall back for those products either not covered by the BPCA incentives or to BPCA-covered products whose sponsors decline to conduct needed studies.

PhRMA submits the following in response to the 4 questions posed in the ANPR:

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

02N-0152

C61

Pharmaceutical Research and Manufacturers of America

The following recommendations would assure that needed studies are conducted without presuming that nearly every drug development program is required to have a pediatric component.

The pediatric rule should be amended to specifically pertain to products that are not covered by the BPCA incentives and to BPCA covered products whose sponsors decline to conduct requested studies. Further, the Rule should only apply where there is a clear lack of adequate information in pediatric patients AND this information is necessary for the safe use of the drug in these patients. Thus, products covered by the Rule would include:

- Off-patent drugs for which the incentive is non-existent but are included in the NIH/FDA "lists" of drugs to be studied yet, no contract is awarded after a request for proposals is issued under the contract provisions of the BPCA;
- Older antibiotics that are included in the NIH/FDA "lists" of drugs to be studied yet, no contract is awarded after a request for proposals is issued under the contract provisions of the BPCA;
- Biologicals approved under the PHS Act; and
- Products for which all applicable alternative BPCA study mechanisms have been exhausted, including those for which an incentive may be available but for which the sponsor has declined to conduct the requested studies.

The pediatric rule should not constitute a blanket, default requirement for most new drug applications and supplements (for new uses, new dosage forms, new dosing regimens, or new routes of administration). For any product development program, the sponsor (and the FDA) should first consider whether pediatric studies are warranted. In making such determinations, FDA should bear in mind the unique ethical concerns pertaining to the conduct of pediatric drug research and minimize unnecessary exposures to experimental drugs when alternative approaches are possible. FDA and the sponsor should also consider, in addition to whether a "meaningful therapeutic benefit" would be gained, some of the 'adjuster' factors raised at the June 11, 2002 Pediatric Advisory Subcommittee meeting. Some relevant factors would be the severity and extent of the disease in children and infants, including the degree of pain and debilitation involved, any adult or animal data suggesting drug safety concerns, and the degree of anticipated use given expected benefits and risks.

Only if it is determined that pediatric studies are needed and inadequate incentives exist for the product should the FDA issue a Written Request to the sponsor of the new development program for the conduct of such studies. PhRMA recommends that the Written Request concept should be revised so that FDA can issue the "Initial Written Request" for studies without stipulating, in detail, the nature of the studies themselves. This would facilitate issuance of WRs on identified products and would, in general, be followed by a pediatric study proposal submitted by the sponsor. The "Final Written

Request" from FDA would be the document defining the needed studies. PhRMA wishes to clarify that either the sponsor's acquiescence to conduct a pediatric program and/or a pediatric study proposal submitted in response to the Initial Written Request should serve to satisfy the 180 day response time period set forth in Section 4 on the BPCA.

A copy of the Written Request should be sent to first to the innovator company who is the holder of the officially approved NDA for a particular product. PhRMA wishes to clarify that in such a case, for purposes of the BPCA, the original application holder will then be deemed to be the entity given a first right of refusal as described in Section 3 of the BPCA. If that company declines to conduct the requested studies, then a WR should be sent to all other sponsors holding approved applications for the drug. If none of the manufacturers of the drug respond to the request, the drug should be added to "the list" to be developed under the BPCA. Any protocol that is developed under the provisions of the BPCA for multi-source products should be published for review by all sponsors. The data from the studies should also be made available prior to any sponsor acceptance of a proposed change in the label. PhRMA envisions that there will be cases where the necessary data are not robust enough to support a label change. In such cases, the sponsor should not be forced into making a change in the label as this might expose the sponsor to potential product liability issues.

If it is determined that pediatric studies are needed for a product that is eligible for an exclusivity award, including unapproved drug products, FDA should issue an Initial Written Request to the sponsor. As above, if the sponsor declines to do the studies, the drug should be added to the List, if there is an approved NDA, and all applicable alternative mechanisms for conducting studies as described in the BPCA should be exhausted before resorting to the mandatory pediatric rule.

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?

The BPCA requires FDA/NIH to determine:

- The availability of information concerning safety and efficacy in pediatric patients;
- Whether more information is needed (alternatively, FDA/NIH could find that there is sufficient information to support pediatric labeling);
- Whether new studies may produce health benefits in a pediatric population;
- Whether reformulation is necessary.

Under the Pediatric Rule, FDA can require studies in a marketed product for the labeled indication if:

- The drug may produce a meaningful therapeutic benefit in the pediatric population over existing treatments and lack of adequate labeling could pose significant risks; or
- The drug product is used in a substantial number of pediatric patients and the lack of adequate labeling could pose significant risks.

The criteria for the pediatric rule are not meaningfully different than those for determining pediatric studies under the BPCA, with the rule criteria somewhat more clearly articulated and easily implemented. PhRMA thus recommends that the final rule criteria should remain unchanged, and proposes that these final rule criteria would be a good basis for implementing the BPCA criteria in the future FDA BPCA guidance.

3) What provisions, if any, of the BPCA could apply to biological products regulated under section 351 of the Public Health Service Act (PHS Act)?

Currently, none of the provisions could apply to biologicals approved under the PHS Act. The BPCA exclusivity provisions only apply to those drugs approved under Section 505(b) of the Federal Food, Drug and Cosmetic Act.

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?

The BPCA "Recommendation for Formulation Changes" is a non-binding recommendation. Hence, like the written request, it is a voluntary program. Under the pediatric rule, a formulation change can be required only when the product has the potential to produce a meaningful therapeutic benefit over existing therapies. Thus, if invoked, it would be mandatory.

The Pediatric Rule should be amended to either remove references to this requirement in 21 CFR 201.23 or make this provision voluntary. In cases of meaningful therapeutic benefit over existing treatments for pediatric patients, it is reasonable to expect that the patient receive an accurate dose in a convenient formulation for the intended age group. However, this may not always require a new formulation. Sponsors must maintain the ability to determine development programs for new formulations, including feasibility, timing, appropriateness, and testing.

Additional Comments

Finally, in considering the pediatric rule in relation to the BPCA, the FDA should be aware of the central issues facing pharmaceutical companies as decisions on drug development are made. In the adult population, there are large numbers of patients

with diseases such as heart disease and cancer, not only making it more feasible to conduct clinical trials, but also resulting in adequate markets for new medicines to treat these diseases. By contrast, among pediatric patients, a wide range of diseases causes serious and chronic illness, but any specific disease affects relatively few children. For example, fewer than 0.5% of patients with arthritis are children, and juvenile rheumatoid arthritis is widely believed to be a different disease than adult rheumatoid arthritis or osteoarthritis.

The limited patient population has several consequences. First, conducting clinical trials with children is inherently more difficult than with adults. With relatively few children with a given condition, clinical trials are correspondingly smaller. The children are distributed over varying ages. They may need different, age-appropriate formulations for appropriate treatment and compliant administration. The pharmacokinetics of drugs varies widely across the age spectrum, impacting the dose. Second, age-specific study designs to assess effectiveness and safety may need to be developed. Studies are particularly complex in tiny premature infants who may weigh less than a pound, and yet who represent one of the most seriously ill populations of children. Third, once studies are performed, regulatory hurdles met, and labeling ultimately changed, the market for most medications in children is very small.

Research resources are finite. Pediatric studies are always in competition with studies of important new medicines for large numbers of adult patients. Mandatory pediatric studies in the absence of incentives will likely divert limited resources away from important investments in other areas of drug research, thus having ramifications for overall public health. By establishing a financial incentive, the BPCA raises the priority for pediatric studies and helps to provide the financial resources necessary to accomplish the desired goals of the program. By focusing on the needs of children, and recognizing fundamental impediments to pediatric drug development, including ethical considerations, the BPCA legislation is accomplishing the goals set forth by Congress. As a result, the BPCA approach to pediatric drug testing should be the primary method for generating the needed information.

PhRMA hopes that these comments are useful as the FDA moves ahead in consideration of this issue.

Sincerely,

A handwritten signature in black ink, appearing to read "Alan Goldhammer". The signature is written in a cursive style with a long, sweeping underline.