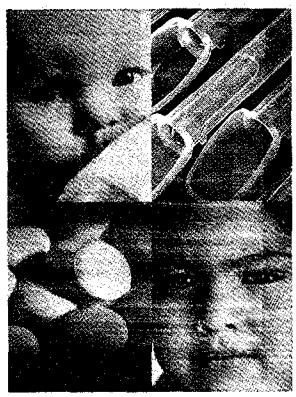
PEDIATRIC
PHARMACOLOGY
RESEARCH
UNIT
NETWORK

For the Safe Use of
Drugs in Children



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This is in response to the FDA request for comments on the pediatric exclusivity program established by Section 111 of the Food and Drug Administration Modernization Act of 1997. Specifically, these comments address the impact FDAMA has had on pediatric drug development during the past two years and the role the NICHD Pediatric Pharmacology Research Network has played in implementation of the pediatric provisions of FDAMA. In short, FDAMA has had an immediate and profound positive impact on drug development for children to an extent not seen during the preceding 30 years. We are pleased to provide documentation for this in the following comments.

The PPRU network was established in 1994 through funding by NICHD of seven pediatric centers to conduct pediatric clinical pharmacology studies. In 1999 the network was expanded to 13 sites. During the past five years the PPRU network has become a major resource to the pharmaceutical industry for the conduct of pediatric clinical trials. The impact of FDAMA on pediatric drug development is reflected in the increased number of studies conducted within the network since 1998.

From 1994-1997, pre-FDAMA, there were 17 Industry-sponsored protocols active in the PPRU. During 1998, the first year after FDAMA was promulgated, 21 protocols were active in the network. In 1999, 54 industry-sponsored protocols were active, a 300% increase over pre-FDAMA activity. During the first quarter of 2000, 43 protocols are active. This remarkable growth in pediatric clinical trials within the network reflects the overall increase in pediatric drug development during the first two years of FDAMA.

Not only has the number of pediatric studies increased, but the range of therapeutic categories studied has markedly expanded, early phase studies are being conducted in children, and studies are including the entire pediatric age range in contrast to pre-FDAMA pediatric studies.

Drugs in the following therapeutic categories have been studied by the PPRU 1998: antihistamines, anti-infectives, anti-hypertensives, analgesics, anti-pyretics, anti-diabetic drugs, GI drugs, psychiatric/behavioral drugs, sedatives, endocrine products, vasodilators, respiratory/asthma, and a poison antidote. This distribution of therapeutic categories reflects the major therapeutic categories on the FDAMA list of

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drugs designated as having therapeutic benefit for children.PPRU studies have included pediatric subjects well distributed across the entire pediatric age range to provide pediatric information across the entire developmental spectrum. Seventeen protocols have included patients 0-1 months; 37 have included infants 1 month - two years; 38 have included children .2 - 6 years; 56 have included children >6 - 12 years; and 47 have included adolescent subjects >12 years.

In contrast to pre-FDAMA, many more of the protocols today are targeted to early phase studies in children with an emphasis on pharmacokinetic/pharmacodynamic studies, so important to understanding the developmental differences in drug response. Ten protocols from 1994-97 involved PK/PD studies whereas 19 PK studies and 34 PK/PD studies were conducted or are in progress between 1998 and first quarter 2000. Since 1998 43 PPRU protocols have been phase I/II, 3 are phaseII/III, and 13 are phase III/IV.

The PPRU has played a major role in implementation of FDAMA. Since FDAMA, the FDA has issued 145 requests for pediatric studies and the company sponsors have responded to the majority of requests by designing and conducting pediatric studies. Twenty-two marketed drug products have been granted exclusivity by successfully completing pediatric studies. The PPRU performed all or part of the clinical trials supporting the exclusivity determination for eight of these drugs. During 1998-99 pediatric labeling was added to six marketed products based on studies conducted under FDAMA provisions. The PPRU conducted the studies to support the labeling changes of four of these six products. Because of the lag time from completing studies to effecting labeling changes, more pediatric labeling changes are anticipated from completed studies and studies now underway.

By all measures of success, FDAMA clearly has been successful and has accomplished a degree of drug development for children that has never been accomplished by any other regulatory or legislative initiative. It is stimulating the type of clinical research essential to assure that children have the same protections under the FD&C Act that adult citizens enjoy. The pediatric provision of FDAMA must be renewed in order to sustain the momentum that now exists and continue to rectify the lack of pediatric studies that has characterized drug development in the U.S. during the past three decades.

In spite of its success, there are weaknesses or deficiencies in the current law that should be addressed when the legislation is considered for renewal: 1) There currently is no provision to reward or fund pediatric studies of drugs that have no remaining exclusivity. This group of "orphaned" drugs needs to be studied in addition to drugs with remaining exclusivity; 2) the law needs to be revised to include currently excluded biologicals that are of therapeutic importance to children; and 3) provision must be made through user fees or otherwise to fund additional FDA personnel sufficient to expeditiously carry out the mandates of Section 111 of FDAMA. The FDA has done a commendable job of implementing FDAMA considering no additional resources were allocated to deal with the additional work load. However, inadequate FDA resources to implement FDAMA and conduct timely responses to requests and reviews of amendments has and continues to be a major threat to accomplishing pediatric labeling of drugs, which is the ultimate goal.

In summary, by all measures of success FDAMA has been successful beyond expectations and has stimulated a level of drug development for infants and children that heretofore has not existed. Sustaining this initiative beyond the first five years undoubtedly will provide benefits to children that have never before been provided and will have a measurable major benefit to the health of children in the future.

Sincerely,

Cheston Berlin

Chairman

PPRU Network Steering Committee

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