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ASSOCIATE VICE PRESIDENT
US REGULATORY AFFAIRS



June 5, 2000

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

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Re: Docket No. 00N-1266; Report to Congress on Pediatric
Exclusivity; Request for Comments;
(65 Federal Register 26217) May 5, 2000

Dear Sir/Madam:

The comments on the above docket 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 that are devoted to inventing medicines allowing patients to lead longer, happier, healthier and more productive lives. Investing \$26 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for new cures.

Section 111 of FDAMA has been a success.

Section 111 of the Food and Drug Modernization Act of 1997 (FDAMA) provides an incentive to encourage the pharmaceutical industry to develop specific information about pediatric uses and doses of prescription medicines. It is fair to state that the legislation has markedly improved pediatric drug development, and that in the two years since its implementation, tremendous progress has been made towards providing meaningful new information on the pediatric use of drugs.

Stimulated by FDAMA, companies have proposed studies on 177 medicines to the FDA as of May 2000. This represents a remarkable increase in interest in pursuing pediatric studies. With input from professional organizations, such as the American Academy of Pediatrics, industry and the public, FDA has issued 145 written requests for pediatric studies. A total of 21 medicines have received extended exclusivity under the Act, and labeling has been changed with pediatric data for 7 medicines. It is important at this juncture to emphasize several points. The 145 written requests included 298 studies. 113 requested studies were classified as "efficacy and safety," 86 as pharmacokinetic (PK) and safety, 26 as "PK/PD," and 22 as safety. The nature of the requests in general have been

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based on evaluation of data required for the safe and effective use of the medication in pediatric patients of various ages.

Many of the studies required new formulation development to cover younger age ranges of patients, as well as the development of novel clinical trial designs and tools to evaluate safety and/or efficacy. Requests have covered drugs in a wide range of therapeutic areas from common problems such as treatment of fever and simple skin infections, to cardiac disease, endocrine problems, gastrointestinal disorders, serious infections including HIV, seizure and other neurologic disorders, and management of pain. Studies have included pediatric patients across all ages. The range of conditions addressed, the variety of drugs being studied, and the nature of the scientific data requested all suggest that FDAMA is successfully addressing unmet therapeutic needs in children. No other approach, legislative or regulatory, has had such a profound impact on the evaluation of medicines in children.

Why has this legislation worked so well when other approaches have failed?

The legislation has been such a success because it addresses the fundamental impediments that have hampered pediatric studies of medicines in the past, principally the small number of pediatric patients. Fortunately, most children are healthy. In the adult population, there are large numbers of patients with diseases such as heart disease and cancer, resulting in large numbers of patients to study in clinical trials, and a large market for medicines to treat these diseases. By contrast, among pediatric patients, serious and chronic illness is caused by a wide range of diseases, and relatively few children are affected by any specific disease. For example, fewer than 0.5% of patients with arthritis are children, and juvenile rheumatoid arthritis is a different disease than adult rheumatoid arthritis or osteoarthritis.

The limited patient population has several consequences. First, doing clinical trials with children is inherently more difficult than doing them 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 of medicines for accurate and compliant administration. For example, an oral liquid may be needed for young children (sometimes different concentrations for newborns), perhaps chewable tablets for somewhat older children, still unable to swallow pills or capsules. The pharmacokinetics of drugs varies widely across the age spectrum. 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 sickest populations of children. Added to this are the unique regulatory requirements imposed by the FDA. These regulatory requirements in most cases require the duplication of an entire clinical development program for each of the pediatric age categories for which an indication is sought. If the adult clinical development program included adults 16 and older, and the sponsor wishes to investigate safety and efficacy in children ages 12 to 16, tolerance studies are sometimes required.

these can be followed by bioavailability and finally safety and efficacy in children with the disease. If the sponsor then chooses to seek the indication in children ages 6 to 12, again the initial studies would be tolerance studies, followed by bioavailability before the safety and efficacy studies could begin. This process would continue for the age groups below 6, i.e., 3 to 6, 1 to 3, 6 months to 1 year, and less than 6 months. It is evident that the clinical development program necessary to address all of the age groups of children can be much more extensive than that needed to address the age group 16 to 65. Third, once formulations are produced and validated, studies 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. By establishing a financial incentive, Section 111 of FDAMA raises the priority for pediatric studies. By focusing on the needs of children, and recognizing fundamental impediments to pediatric drug development, the legislation is accomplishing the goals set forth by Congress.

It is important to comment on some of the "metrics" of success at this point. There is a time lag from when a company proposes studies to when FDA issues a written request. The agency must review the proposal and decide on the content of the written request to assure that the data generated will meet the therapeutic needs of children and the information needs of their physicians. The time required for this review process would be shortened with expanded pediatric resources at FDA. The actual studies performed by companies take substantial time; patient numbers and research centers are limited, and some of the necessary safety studies required, by definition, require substantial observation time. Once data are submitted to FDA, the review for exclusivity occurs within 90 days, but subsequent review of data for labeling changes may take 10-12 months (this too could be shortened with increased FDA resources). Thus, while only 7 labels have been changed as of May 2000 (actually, a remarkable accomplishment to date), the process to change a large number of labels and make information available to pediatricians has been initiated. It is expected that the vast majority of requests will result in label changes (except in certain circumstances where studies do not result in data warranting specific label changes).

The provisions of Section 111 should be renewed and made permanent.

PhRMA strongly believes that the provisions of Section 111 should be made permanent as it is not an exaggeration to state that this is vital to the future of pediatric therapeutics. The task has just begun of studying and labeling currently marketed medications for children. A significant number of the medications on the original FDA "list" are now being studied. The rate of increase in industry proposals and FDA written requests suggests ongoing progress, which will be adversely affected by the sunset of the legislation. In addition to marketed drugs, section 111 of FDAMA will be vital to assure the timely pediatric evaluation of new therapeutic advances. Some studies, particularly

in the neonate, require new study designs and understanding of pediatric diseases; FDAMA provides a means of pursuing these unique pediatric indications.

Several points are critical in understanding the need for making the provision permanent.

1. Regardless of other aspects of health economics and health care financing, the problems of the small number of pediatric patients with a given disease available for study, the complexity of the studies, and the ultimate small market will remain. If resources are constrained at any time, for any reason, research into the therapeutic needs of children is most likely to suffer. We must keep the needs of sick children competitive with medical needs of adults, and Section 111 of FDAMA does exactly that.
2. Section 111 of FDAMA remains the critical driver to study unique pediatric diseases and indications. Many pediatric diseases differ significantly from those in adults and the Pediatric Rule thus does not apply. This is particularly the case for diseases in the premature neonate. FDAMA thus is the best mechanism available to assure that children's unique therapeutic needs are met.
3. The FDAMA incentive encourages companies to initiate studies in a timely manner. With the incentive in place, rather than seeking deferrals, companies are more likely to initiate studies earlier in the drug development process. Pediatric studies, furthermore, should not delay the development of important new therapies for adults; access of a majority of patients to a new medication should not be delayed by studies for a small minority. A financial incentive to assure resources and timely study in pediatrics thus makes sense. As we move into a new era of advanced therapeutics with more and more novel therapies being developed, FDAMA can assure that children maximally benefit from these developments.

Adequacy of the incentive and economic impact

It would be difficult to estimate the positive economic impact of increased or better clinical information for the prescribing of medication for children. Potentially, appropriate use should almost always result in improved quality of care and improve child health.

The success of the program to date suggests that the incentives are reasonable. But the success and the value of the program in adding clinically meaningful pediatric information to package inserts has not been fully exploited. The sunset clause in the original initiative coupled with a lack of guidance from the FDA in the critical early days of implementation, caused many drug sponsors to focus only on the drugs that could be studied during the relatively short implementation period. Eliminating the sunset provision is critical so that sponsors, the FDA and patient groups can get on with addressing the remainder of the still unmet needs

Suggested Modifications

Several issues have arisen with implementation of Section 111.

1. Prior to the passage of FDAMA, antibiotics were approved under Section 507 of the Federal Food, Drug, and Cosmetic Act. Such drugs are ineligible for the exclusivity provisions of Section 111. Since many of these drugs are likely to have significant clinical benefits for pediatric patients, Congress should ensure that they are covered when the pediatric exclusivity provision is made permanent.
2. There has been significant variability in interpretation of the legislation, and in implementation of written requests among FDA review divisions. Much of this is understandable for a major new initiative. Often, disease definitions, extrapolation of disease similarity, and thus the nature of the requests have been inconsistent. Sometimes, this has been based on lack of fundamental understanding of pediatric diseases, sometimes due to lack of pediatric expertise in FDA review divisions. Where such issues have arisen, FDA and PhRMA have developed consensus approaches through the Pediatric Advisory Subcommittee, and have worked together with the American Academy of Pediatrics, NICHD (and its Pediatric Pharmacology Research Units, the PPRUs), other NIH institutes including NCI, parent/patient groups. All the parties have learned to stay focused on the therapeutic needs of children, and to work towards consensus in these areas. This has been a major unanticipated benefit. This has helped with several issues raised in the area of pediatric cancer. FDA has formed a new Pediatric Oncology Advisory Subcommittee, and prepared guidelines in the area of pediatric oncology. PhRMA has created a Pediatric oncology task force. These groups are all working together with the Children's Oncology Group and NCI. Recognizing the medical and scientific complexity of many of the areas which are now being addressed, for the legislation to work optimally, FDA needs to establish consistency among review divisions, based on the best of pediatric and pharmaceutical science. FDA needs increased pediatric resources to deal with these issues. Such resources must include personnel with detailed knowledge and expertise in pediatric investigation. Finally, there will be classes of pediatric information that may bear on unapproved indications. These should be allowed as a labeling supplement as opposed to a traditional supplement for a new indication.
3. The limitations in clinical investigative resources for pediatrics have become increasingly apparent. The creation of the NICHD-sponsored PPRUs has been a major advance. It is critical that pediatric studies be carried out at centers with in-depth pediatric expertise. The safety and welfare of research participants and the validity of the data generated are dependent on the expertise of the centers at which studies are conducted. PhRMA strongly supports new legislation to encourage the training of the next generation of pediatric clinical pharmacologists, by providing training funds to the PPRUs, and debt forgiveness for trainees who enter careers in pediatric drug development. This program will result in a pool of talent available to

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academic medical centers, industry, and FDA to assure that the advances in therapeutics which are occurring can be translated into medicines for children.

4. While FDAMA is working well to meet the needs of children, the incentives may not be able to overcome the barriers of very early initiation of pediatric studies for truly life-threatening, but very rare condition, such as certain pediatric cancers. There is substantial risk and difficulty to doing such studies on NCEs under development for large adult populations, and given the rarity of some of these conditions, truly no market. As we approach the renewal date for Section 111, consideration should be given to improving the climate for early initiation pediatric studies.

Summary

Section 111 of FDAMA is working for the benefit of sick children. Renewal of the legislation, extending it to antibiotics, and eliminating the sunset provision are crucial for the continued success of pediatric drug development. All other aspects of pediatric medicine will benefit from FDAMA as well. Providing training funds for pediatric pharmacology and other NIH funding for pediatric research and training will only be successful for children if there are career opportunities for trainees. FDAMA, the PPRU initiative and pediatric research in general are bound together as a way of assuring career opportunities for some of our brightest young physicians and scientists, and thus assuring that children will benefit from therapeutic advances. At a time of major scientific productivity, and of hope for cures for diseases which we could not have imagined 10 or even 5 years ago, society must continue to be mindful of keep the needs of children in the forefront. Section 111 of FDAMA is the mechanism that sick children need.

Sincerely,

