

File Pediatric  
Labeling

## PROPOSAL TO ADDRESS THE LACK OF PEDIATRIC LABELING FOR DRUGS

### BACKGROUND

Children suffer from most of the same diseases as adults, and, by necessity, are treated with most of the same drugs as adults. The majority of new drugs and biological products, however, have not been tested in pediatric populations. As a result, product labeling frequently fails to provide directions for safe and effective use in children, despite widespread use. An FDA survey of drugs prescribed during 1994 identified the 10 drugs prescribed most frequently to children without adequate labeling. Together, these 10 drugs were prescribed more than 5,000,000 times. Because of differences in size and ability to metabolize drugs, children require different doses than adults and may be subject to different adverse reactions. The absence of pediatric labeling information thus poses a serious risk of inappropriate dosing and unexpected adverse effects in children. It may also result in failure to provide children with optimal treatment in cases where physicians are reluctant to prescribe potentially toxic drugs to children before they have undergone pediatric testing. For example, a survey by the Pediatric AIDS Foundation found that fewer than 10% of children with AIDS were receiving protease inhibitors, the newest and most promising AIDS drugs.

In recent years, FDA has undertaken several initiatives to encourage the voluntary addition of pediatric use information to drug labels. FDA has implemented a "Pediatric Plan" designed to focus attention on and encourage voluntary development of pediatric data during drug development. FDA has also identified the top 10 drugs used in children without adequate labeling instructions, and has written the manufacturers of these drugs requesting that they submit supplemental applications to add pediatric use information to their drug labels. In 1994, FDA issued a new rule that allowed pediatric use information to appear on label on the basis of substantially less data than before, and that required manufacturers to survey existing data to determine whether there was sufficient information to support pediatric use information in the drug's label.

These voluntary efforts to increase the amount of pediatric use information in labeling have not resulted in significant gains, particularly with respect to new drugs entering the marketplace. A comparison of drugs approved in 1991 and 1996 showed that approximately 47% of the drugs approved in 1991 with potential use in children had pediatric labeling, while 37% of those approved in 1996 with potential use in children had pediatric labeling.

Year	total NMEs approved	potential use in children	pediatric labeling at approval	post-approval study promised	pediatric labeling later submitted
1991	26	15	7	7	1
1996	53	40	15	17	?

### PROPOSAL

FDA is considering proposing new regulations to address the lack of pediatric use information by requiring, for the first time, that applications for certain new drug and biological products contain pediatric data. The purpose of the proposed rule would be to ensure that important new drugs and biological products carry adequate pediatric labeling at the time of, or soon after, approval. The pediatric study requirement would be limited to a small group of new drugs and biologics: new molecular entities (the most innovative drugs) and biological products that (1) would provide a significant therapeutic advantage to children suffering from the disease or (2) would be expected to be used in a substantial proportion of children. Pediatric studies could be deferred until after approval if FDA found that it was appropriate to delay pediatric studies until sufficient data were collected in adults. The requirement could also be waived altogether under certain circumstances.

The proposed rule might also codify FDA's authority to require in compelling circumstances that manufacturers of already marketed drugs and biological products conduct studies to support pediatric use labeling. The circumstances in which FDA might require pediatric studies of a marketed drug would be: (1) where the drug is widely used in children and the lack of adequate labeling poses significant risks to children, or (2) where the drug offers a significant therapeutic advantage to children but additional information is needed to permit safe and effective use.

The absence of workable penalties has historically hampered FDA's ability to require pediatric studies. It is inappropriate from a public health standpoint to prevent the marketing of a drug that offers a clinical benefit to adults simply because the manufacturer has failed to study the drug in another subgroup of the population. FDA is therefore considering a different type of penalty for failure to conduct a pediatric study. FDA would take the manufacturer to court and obtain an injunction requiring the

study to be completed. Violation of the injunction would be punishable by contempt or fines.

# American Academy of Pediatrics



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December 1, 1997

The Honorable William Jefferson Clinton  
The White House  
1600 Pennsylvania Avenue, NW  
Washington, DC 20500

Dear President Clinton:

The American Academy of Pediatrics (AAP) reaffirms our support for your Administration's efforts and commitment to advancing the health of our nation's infants, children and adolescents through the proposed regulations to require manufacturers to assess the safety and effectiveness of new and already marketed drugs and biological products for pediatric patients. These regulations are necessary to ensure informed use of drugs for children because, under current regulations, most drugs enter pediatrics without study in children and only after use in adults. Pediatric drug testing and labeling is a step that should be taken without hesitation.

The AAP does not underestimate the opposition that might be mounted against the recommendation that all drugs be studied in children if the disease occurs in children. However, arguments against this position can not pass the "ethics" test. Within the proposed rule, the FDA seeks comments on ethical issues that may be raised by this proposal. Clearly, the most basic of ethical issues is the implication of administering drugs and biological products to pediatric populations without adequate information. This is no greater a medical ethical dilemma than that posed for those who treat children: to give a drug with sufficient information on safety and efficacy, or to withhold treatment and let the disease progress unabated.

Proper studies must be done to ensure that children receive optimal treatment. Currently, only 20 percent of all drugs marketed in the United States have been labeled for use by infants, children or adolescents. For example, asthma is the leading cause of hospitalization of children in the United States, and commonly affects children younger than age 5. Despite that, there is only one asthma drug labeled for use in children under the age of 6.

The impact of these proposed regulations, properly implemented, cannot be understated. Pediatricians and other health care professionals will have available more precise information that takes into account various stages of child development so that the best drug, at the right dose, can be prescribed.

Sincerely,

*Joseph R. Zanga, MD*  
Joseph R. Zanga, MD, FAAP  
President

JRZ:kbf



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December 1, 1997

The President  
The White House  
Washington, DC, 20500

Dear Mr. President:

Having recently submitted our detailed comments on the proposed Food and Drug (FDA) rules on testing of pharmaceutical products for pediatric use, I want to reiterate our association's strong commitment to your administration's efforts to ensure the safety and efficacy of pharmaceuticals for children.

Children's health care does not command the attention of the health care market place, because children represent less than 30 percent of the population, less than 15 percent of personal health care spending, and the poorest segment of society. It is not surprising that only about 20 percent of all drugs marketed in the United States have been tested and labeled for use by children. This lack of focus on children would not be a problem, if children's health care needs were the same as adults' needs. But, that is not the case.

The FDA's proposed rules, along with provisions in the new FDA reform legislation, seek to ensure the market's focus on children's needs by leveling the playing field for manufacturers through federal regulation. As we proposed in our written comments on the proposed regulations, all drugs should be presumed to be subject to testing. A panel of pediatric experts, recommended by the American Academy of Pediatrics and others, would be responsible for advising FDA on those instances in which testing of a particular product would not be necessary. And certainly it is our expectation that pediatric testing requirements should not impede the marketing of products for adult use.

The goal of the FDA proposal reflects not only prevailing judgment among pediatric providers but also the personal commitment of the First Lady and yourself to policy that helps every family meet its children's needs for health, education, safety, and security. Such a family-centered commitment is at the heart of every children's hospital's mission of service to its community.

Sincerely,

*Lawrence A. McAndrews*

Lawrence A. McAndrews

For immediate release  
December 11, 1997

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The Elizabeth Glaser Pediatric AIDS Foundation  
Response to the Pharmaceutical Manufacturers Association (PhRMA)  
On Testing Drugs for Safety for Children

In a story in the New York Times yesterday, representatives of pharmaceutical manufacturers argue against the FDA's proposed regulations to require that drugs be tested for safety and dosing for children's use. In that story, these representatives make a number of serious errors, omissions, and misleading statements.

The attached is an effort to correct the record. Today, World AIDS Day, is dedicated to "Giving Children Hope in a World with AIDS." On this day, the drug industry's arguments should not go unchallenged.

The current practice among pharmaceutical manufacturers is not to test drugs on children except in special circumstances. The Pediatric AIDS Foundation believes that presumption should be reversed: Drugs should be tested on children unless there is a reason not to. The proposed FDA regulation would accomplish that goal. The drug industry's arguments are without merit.

MORE

Response to the Pharmaceutical Manufacturers Association (PhRMA)  
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### Drug Industry Argument in Story

Developing drugs for children is too expensive.

Response This is factually mistaken and morally wrong.

The comments of the head of the drug industry lobby are particularly disturbing. He is quoted as saying that the requirement to test important drugs for safety in children would divert money and resources from drug research that is more beneficial to the general public.

These comments are a clear example of the problem. The drug industry does not see children as part of the "general public." Sick children and their families would find this research to be extremely beneficial, even if the drug industry does not.

The FDA estimates that the cost of testing drugs for safety in children would be \$13 to \$21 million per year.

By any estimate—the number of sick children who stay sick, the number who have adverse reactions, the number of needless hospitalizations, or the eight ten thousandths of one percent of the revenues of the top ten pharmaceutical companies—this is a modest amount.

The drug industry itself estimates that the current cost of development of *each* new drug is \$500 million. The cost of pediatric trials is almost vanishingly small in this context.

### Drug Industry Argument in Story

The drug industry is primarily concerned about protecting the safety of children and avoiding exposing children to the risks of research.

Response Children are now placed at significant risk through the industry practice of failure to test drugs. As the American Academy of Pediatrics has noted, the use of untested drugs "may place more children at risk than if drugs were administered as part of well-designed, controlled clinical trials."

Response to the Pharmaceutical Manufacturers Association (PhRMA)

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Drugs that are untested in children are widely used already. Five million prescriptions a year are written for the top ten unstudied drugs alone. These drugs are administered without adequate testing for safety in children.

Guidelines have been established by both HHS and the American Academy of Pediatrics about the protection of children in research.

The proposed regulation contains a specific waiver if there are grounds to believe that the drug is unsafe in children.

#### Drug Industry Argument in Story

The drug industry is primarily concerned about the ethics of testing drugs for safety in children.

Response: No one is more concerned about the ethical treatment of children than children's advocates, such as the Foundation, the American Academy of Pediatrics, the National Association of Children's Hospitals, and the AIDS Policy Center for Children, Youth, and Families. All of these groups support the proposed FDA regulation that the manufacturers are opposing.

The true ethical issue is the drug industry's continued practice of routinely refusing to study drugs for safety in children, even though the industry knows that these drugs are given to children. More children are placed at risk through this practice than would be through well designed and monitored clinical trials.

The HHS and American Academy of Pediatrics' guidelines about the protection of children in research have fully addressed the ethical concerns about how to design safety trials.

Drug Industry Argument in Story: There are practical difficulties in testing drugs for children and in developing formulations appropriate for them.

Response: All drug research has some practical difficulties, not just children's research.

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The proposed regulation offers a specific waiver of the children's research requirement if the study is highly impractical and another specific waiver if reasonable efforts to develop a pediatric formulation (when needed) fail.

Drug Industry Argument in Story: Developing special formulations for young children is impractical

Response: Although industry argues that special formulations are often a problem, this Drug Industry Argument is applicable only to very young children who cannot swallow pills. If problems in formulation were the reason that industry fails to do research on children, one would expect that research on older children would be routinely done. It is not. Manufacturers have largely failed to do research on children under the age of 12, and some have done no research on children under 16.

The proposed regulation offers a specific waiver of the children's research requirement if reasonable efforts to develop a pediatric formulation (when needed) fail.

Drug Industry Argument in Story:  
Adult drugs should not be delayed

Response: Agreed. There should be no delay in drugs for adults. The only action proposed in the regulation if a manufacturer fails to do pediatric research is a court order requiring them to do it, but no delay in approving the drug for adults.

# HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

P98-37  
FOR IMMEDIATE RELEASE  
November 27, 1998

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## FDA ACTS TO MAKE DRUGS SAFER FOR CHILDREN

The Food and Drug Administration announced today final regulations to provide health care practitioners with specific information on the safe and appropriate use of new drugs and biologics in children. The regulations require that new drugs and biologics that are therapeutically important for children, or will be commonly used in children, have labeling information on safe pediatric use.

Today's announcement marks an important milestone in the administration's effort to make drugs safer and more effective for children.

"Our children are the nation's most precious resource and we must do everything possible to ensure they get the best medical treatment," said President Clinton. "Today's action represents our continuing commitment toward this goal."

Every year more than half of newly approved drugs and biologics that are likely to be used in children lack information to permit safe and effective use. Without adequate information, physicians may be reluctant to prescribe certain drugs for their pediatric patients, or they may prescribe them inappropriately. The new rule makes it more likely that children will receive improved treatment because doctors will have more complete

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FDA ON THE INTERNET: <http://www.fda.gov/>

information on how drugs affect children and what age-appropriate doses are needed.

"Pediatricians and other health care providers will now have more specific dosing information based on scientific evidence," said First Lady Hillary Rodham Clinton. "This will make prescribing medication for children safer and may also lessen the number of side effects."

The rule also allows FDA to require pediatric testing of already-marketed products in certain compelling circumstances such as when a drug is commonly prescribed for use in children, but the absence of adequate labeling could pose significant risks.

FDA issued a regulation in 1994 simplifying the type of information needed to demonstrate the safety and effectiveness of drugs in children to encourage drug manufacturers to submit pediatric data voluntarily for review. While these voluntary efforts were helpful, there are still a large number of drugs and products without adequate pediatric labeling.

"We are committed to ensuring that health care providers get the best information they need to treat children," said Michael A. Friedman, M.D., Acting FDA Commissioner. "By simplifying the information requirements, providing financial incentives in the FDA Modernization Act and enacting these new regulations, we have taken great strides forward."

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The final rule allows pediatric data to be submitted after a drug has already been approved if FDA has safety concerns about testing the drug on children prior to testing it on adults. FDA, however, will not delay the approval of a drug for adults if the pediatric studies are not yet completed.

Even if the drug is one that is commonly used in children or will be therapeutically important for children, the pediatric study requirement can be waived entirely if:

- FDA finds that the product is likely to be unsafe or ineffective in pediatric patients,
- pediatric studies are impossible or highly impractical, or
- reasonable efforts to develop a pediatric formulation have failed.

**###**

Pediatric Labeling File

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**TODAY'S DATE: Nov. 25, 1998**

**THIS FAX IS FOR: Chris Jennings/Devorah**

**FROM: Bill Schultz/Lisa Barclay**

**FAX NUMBER: (202) 456-5557**

**NUMBER OF PAGES W/O FAX COVER: 1**

**COMMENTS: Background materials for the  
pediatric labeling final rule.**

## PEDIATRIC LABELING RULE

**BACKGROUND.** Most drugs and biologics entering the marketplace have not been adequately tested in children. As a result, product labeling frequently fails to provide directions for safe and effective use in children. Nevertheless, because children suffer from most of the same diseases as adults, they are by necessity treated with drugs and biologics lacking adequate directions for their use. The absence of pediatric labeling information poses a number of dangers to children, including the risk of under- or over-dosing leading to ineffective treatment or excessive or unanticipated adverse effects. There are many reported examples of serious adverse reactions in children exposed to inadequately tested drugs, including seizures and cardiac arrest caused by bupivacaine, an anesthetic, and withdrawal syndrome in infants and small children following prolonged administration of fentanyl, a pain killer used as an adjunct to anesthesia. The absence of adequate pediatric labeling may also result in failure to provide optimal treatment to children because of the lack of appropriate scientific data. For example, a survey on the use of protease inhibitors, newest and most promising AIDS drugs, found that, before these drugs were studied in children, fewer than 10% of children with AIDS were receiving protease inhibitors.

In recent years, FDA has undertaken several initiatives to encourage the voluntary addition of pediatric use information to drug labels. FDA has implemented a "Pediatric Plan" designed to focus attention on and encourage voluntary development of pediatric data during drug development. FDA has also identified the top 10 drugs used in children without adequate labeling instructions, and has written the manufacturers of these drugs requesting that they submit supplemental applications to add pediatric use information to their drug labels. In 1994, FDA issued a new rule that allowed pediatric use information to appear on label on the basis of substantially less data than before, and that required manufacturers to survey existing data to determine whether there was sufficient information to support pediatric use information in the drug's label.

Despite these efforts, the majority of new drugs and biological products still enter the marketplace insufficiently tested in the pediatric population and the labeling of drugs widely used in children carries little or no information on pediatric safety and effectiveness. For example, the 1994 rule requiring manufacturers to survey existing medical literature about the pediatric use of their products and to add pediatric use information to their labels produced only 65 supplements that contained adequate labeling information for all relevant pediatric age groups and another 35 with adequate labeling for some but not all age groups.

The medical and patient communities have strongly urged FDA to take effective steps to increase the quantity and quality of pediatric labeling.

The agency recognizes that a mixture of incentives and requirements is most likely to lead to improved pediatric labeling. The FDA Modernization Act of 1997 (FDAMA) included a provision providing financial incentives in the form of 6 months of market exclusivity to manufacturers who conduct pediatric studies on some drugs. Although FDA is hopeful that the FDAMA incentives to produce many additional pediatric studies, the agency believes that this final rule is still needed to significantly improve the current lack of adequate pediatric labeling. Because FDAMA exclusivity applies only to products that have exclusivity or patent protection under the Drug Price Competition and Patent Term Restoration Act and the Orphan Drug Act, it provides no incentive to conduct studies on certain categories of products, including most

antibiotics, biologics, and off-patent products. In addition, the voluntary nature of the incentive provided by FDAMA is likely to leave many drugs, age groups, and indications unstudied. For example, given limited resources to conduct pediatric studies, it is probable that manufacturers will elect to conduct pediatric studies on those drugs for which the incentives are most valuable, i.e., on drugs with the largest adult sales. This may leave unstudied drugs that are greatly needed to treat pediatric patients, but that have smaller markets. Manufacturers may also elect not to study drugs that require study in neonates, infants and young children, because studies of these age groups are particularly difficult and may require the development of new pediatric formulations. In addition, FDAMA provides exclusivity to a manufacturer who conducts a requested study, even if the results of the study are inconclusive and do not provide useful information on how to use the drug in children. Finally, FDAMA does not require manufacturers who conduct pediatric studies to put the information gained into their drug labels. FDA believes that the final rule will address many of the gaps left by the FDAMA incentives. Studies conducted under this rule are eligible for 6 months of exclusivity under FDAMA, if they otherwise comply with the statute.

**PROVISIONS OF THE REGULATION.** The final rule requires applications for new drugs and biological products to contain sufficient data and information to support directions for pediatric use for the claimed indications if they (1) provide a meaningful therapeutic benefit to children over existing treatments, or (2) are likely to be used in a substantial number of pediatric patients. The required study can be deferred until after approval if, for example, FDA finds that it is appropriate to delay pediatric studies until sufficient data are collected in adults, or if imposition of the requirement would delay the availability of a new drug for adults. The requirement can also be waived if FDA finds, among other things, that the product is likely to be unsafe or ineffective in pediatric patients, that pediatric studies are impossible or highly impractical, or that reasonable efforts to develop a pediatric formulation had failed. In response to comments, the scope of the final rule is broader than the proposed rule. The proposed rule would have applied only to "new chemical entities" and to never before approved biological products. Many comments argued that modifications of existing products, may be more clinically significant in the treatment of children than the original products. Therefore, the final rule applies to new active ingredients, new indications, new dosage forms, new dosing regimens, and new routes of administration.

The rule would also codify FDA's authority to require, in compelling circumstances described in the regulation, that manufacturers of already marketed drugs and biological products conduct studies to support pediatric use labeling for the already approved indications. FDA believes that, in exercising its discretion whether to require studies of already marketed drugs, it is appropriate to first learn whether manufacturers will undertake the needed studies voluntarily in response to FDAMA. Therefore, before exercising its authority to require studies of already marketed products, FDA intends to give the FDAMA incentives an opportunity to produce new pediatric studies. If manufacturers do not take advantage of the incentives, FDA will then require studies where there the compelling circumstances described in the regulation are met. FDA expects to require studies on about 2 drugs per year.

In the event that a manufacturer fails to carry out a required pediatric study, FDA would not seek to disapprove or withdraw approval of the product, because such an action could deprive adult patients of important therapies. Instead, FDA would anticipate seeking an injunction from a federal court requiring the manufacturer to conduct or fund the needed studies.

## PEDIATRIC LABELING Qs and As

### 1. What does this rule require?

It requires the manufacturers of drugs and biological products that are widely used in children or that provide a meaningful therapeutic benefit to children to provide information on the safe and effective use of the products in children, including adequate dosing and safety information. The information may be required at the time the product is first approved, or may be deferred until a short time after approval if pediatric studies cannot be completed before the drug is ready for approval in adults. The rule also authorizes FDA to require manufacturers of marketed drugs and biologics to study their products in children in compelling circumstances.

### 2. Why are you doing this now?

Despite efforts in recent years to address this issue, most drugs still lack adequate pediatric labeling. Every year more than half of all newly approved drug and biologic products that are likely to be used in children lack information to support their safe and effective use in children. Thus, when new drugs enter the market, pediatricians lack information on dosing and safety necessary to prescribe these products to children who may need them. For products already on the market, information is eventually made available to physicians by journal articles, handbooks and other references, but usually years after a drug is approved (and even then the information isn't available on the label and may not be adequate for some age groups). An FDA survey of drugs prescribed during 1994 identified the 10 drugs prescribed most frequently to children without adequate labeling. Together, these 10 drugs were prescribed more than 5,000,000 times. Over the years, this lack of information has led to under-treatment and to serious adverse events in children.

### 3. Can't you achieve the same effect through voluntary compliance?

FDA has taken a number of steps in recent years to address inadequate pediatric labeling, including issuing a rule in 1994 requiring drug manufactures to survey existing data and determine whether those data are sufficient to give information on how to use a drug in pediatric populations. These attempts at voluntarily compliance have not worked, as illustrated by the fact that the majority of drugs important to children still lack adequate pediatric labeling. In response to the 1994 rule, FDA received approximately 430 supplementary applications for label changes, a small fraction of the total number of products on the market. Over half of the supplements submitted simply requested the addition of the statement "Safety and effectiveness in pediatric patients have not been established." Many others requested minor wording changes or submitted unorganized, unanalyzed collections of possibly relevant data. Only 15% of the small number of supplements received (approximately 65) provided adequate pediatric information for all relevant pediatric age groups, and another 8% (approximately 35) provided adequate pediatric information for some but not all relevant age groups.

### 4. How many comments were received on the proposal and what did they say?

FDA received 55 comments on the proposed rule from pediatricians, parents, medical societies, organizations devoted to specific diseases, and the pharmaceutical industry. The comments from the pediatric and medical communities and from parents supported the rule, and sought to broaden its coverage. Many of the comments from the pharmaceutical industry opposed the rule as unnecessary and beyond FDA's legal authority, although a few supported it.

5. What changes have been made in the final rule?

In response to comments that the scope of the proposal did not cover those drugs that would be of most importance to children, the rule now covers new active ingredients, indications, dosage forms, dosing regimens, and routes of administration. FDA has also responded to many comments seeking creation of a panel of outside pediatric experts to oversee implementation of the rule by agreeing to create such a panel and to seek its advice on a range of issues related to the rule.

6. Will this requirement hold up drug approvals?

No. FDA will not delay the approval of drugs that are ready to be approved for adults even if studies in children have not been completed. The rule provides for other methods of ensuring that the pediatric studies are completed in a timely way.

7. Given the financial incentives for pediatric studies in the FDA Modernization Act of 1997 (FDAMA) to encourage voluntary compliance, why is this rule necessary?

FDA believes that a combination of incentives and requirements provides the best hope for improving pediatric labeling. Although FDA is hopeful that the FDAMA incentives will encourage many new pediatric studies, those incentives are likely to leave a number of important drugs and age groups unstudied. For example, given limited resources to conduct pediatric studies, it is probable that manufacturers will elect to conduct pediatric studies on those drugs for which the incentives are most valuable, i.e., on drugs with the largest adult sales. This may leave unstudied drugs that are greatly needed to treat pediatric patients, but that have smaller markets. Manufacturers may also elect not to study drugs that require study in neonates, infants and young children, because studies of these age groups are particularly difficult and may require the development of new pediatric formulations. In addition, FDAMA provides exclusivity to a manufacturer who conducts a requested study, even if the results of the study are inconclusive and do not provide useful information on how to use the drug in children. Finally, FDAMA does not require manufacturers who conduct pediatric studies to put the information gained into their drug labels. FDA believes that the final rule will address many of the gaps left by the FDAMA incentives. Studies conducted under the rule are entitled to 6 months of exclusivity under FDAMA if they otherwise satisfy the terms of the statute.

8. Have children been at risk in the past?

The lack of adequate pediatric labeling has resulted in the use of many products that have only been tested for adults, causing an increased risk of inappropriate and unexpected adverse effects. (For example, there were deaths that resulted in neonates from chloramphenicol, an antibiotic. Other cases in which inadequately studied drugs have resulted in serious adverse effects in pediatric patients include 1) seizures and cardiac arrest caused by bupivacaine toxicity, a local anaesthetic; 2) development of colonic strictures in pediatric cystic fibrosis patients after exposure to high-dose pancreatic enzymes; 3) hazardous interactions between erythromycin, an antibiotic, and midazolam, a short term anaesthetic; 4) teeth staining from the antibiotic tetracycline; 5) nuclear jaundice, a skin condition caused by sulfa drugs; and 6) withdrawal symptoms following prolonged administration of fentanyl, a pain killer used as an adjunct to anesthesia in infants and small children. These cases occurred from the 1950's through the 1990's.) Also, sometimes useful drugs not have been used in children because their effects in children were uncertain.

9. How many drugs that are commonly used in children lack this data?

FDA estimates that over one-half of the drugs approved in the past six years that had potential usefulness in kids had no pediatric labeling at the time of approval.

10. What kinds of drugs are commonly missing pediatric data?

Drugs such as anti-asthmatics, steroids, drugs to treat gastrointestinal problems, strong pain medications, antidepressants, anti-epilepsy drugs, and antihypertensives commonly lack appropriate pediatric labeling.

11. What drugs now have the best pediatric data?

Vaccines and antibiotics are the most adequately labeled drugs for children.

12. How many products will be affected by the rule?

FDA estimates that about 80 drugs and biological products will be studied in children under this regulation per year. (FDA estimates that a large proportion of these would probably have been studied voluntarily under the FDAMA incentives, although perhaps not as early.) The rule also gives the agency authority to review drugs already on the market to determine which ones should have pediatric studies. FDA intends to see whether manufacturers respond to the FDAMA incentives for conducting pediatric studies on marketed drugs before imposing any requirements on this category of products.

13. Does this regulation cover all drugs?

It covers all drugs and biological products that are used in a substantial number of pediatric patients or that will provide a meaningful therapeutic benefit to children. If a manufacturer shows

that a drug will not be used in a substantial number of pediatric patients and will not provide a meaningful therapeutic benefit to children, the pediatric testing requirement will be waived.

FDA will also waive the requirement if (1) the drug is likely to be unsafe or ineffective in children; (2) it is impossible or highly impractical to study the drug in children, because, e.g., the pediatric population is too small or geographically dispersed, or (3) reasonable efforts to develop a pediatric formulation (if one is needed) have failed.

14. How will these waivers work and won't they make the regulation meaningless?

The waivers are only intended to be used in those cases in which the drug would not be widely used and would not represent a meaningful benefit over existing treatment or where the studies are impossible or highly impractical or pose undue risks to pediatric patients.

15. What do doctors do when they don't have adequate pediatric safety and effectiveness information?

Many physicians rely on referenced pediatric handbooks for dosing and use information. (This information may or may not be based on adequate testing.) Others are reluctant to prescribe certain products to children without adequate pediatric labeling on the product.

16. Why haven't companies provided this information in the past?

Some companies do provide this information. However, pediatric labeling has not been required until now. Lack of familiarity with pediatric studies, need for a pediatric formulation, and cost may account for the lack of adequate pediatric information.

17. Would pediatric study participants' lives be at risk if they are entered in studies before all the data on adults are collected?

Pediatric patients will not be enrolled in studies until enough data on the drug have been obtained in adults and in animals so that the risk to the pediatric patients does not outweigh the potential benefits. Children are currently entered into studies of some drugs, for example of antibiotics, before the drugs are approved in adults. The considerations that will determine when enough data have been collected in adults to begin pediatric studies under the rule are the same as those currently used in deciding when to begin studies in children. The timing of pediatric studies will depend, among other things, on the type of drug being studied, the severity of the disease for which it will be used, the availability of other adequate treatments, and what is known about the safety of the drug.

18. How much will this cost drug manufacturers?

The costs of pediatric studies will be less than 1% of the total costs of developing a drug.

Although some drugs may require more than one study, e.g., for different pediatric age groups, FDA estimates that an individual pediatric study costs between \$100,000 to \$150,000. FDA also estimates that if a company must produce a pediatric formulation, the new formulation an average of \$1,000,000. FDA estimates that the total annual industry costs will be approximately \$47 million per year (for an industry with domestic U.S. sales in excess of \$66 billion per year). FDA also estimates that the benefits of the rule will exceed \$100,000,000 in reduced health care costs for children.

FDA has also developed a rough estimate that the FDAMA incentives will be worth approximately \$350-\$400 million/year to the pharmaceutical industry.

19. Will drug prices increase as a result of this regulation?

Because the cost of pediatric studies to manufacturers is expected to be small, it is anticipated that there will be no significant price increases to patients.

20. What kind of "legal action" can FDA take to force companies to provide this data on approved drugs?

FDA can go to court and ask the court to order the company to comply with the regulations. If the company does not comply, the court can impose penalties.

21. Why doesn't it cover medical devices? Do we not have this kind of problem with medical device pediatric data?

Once the agency gains experience in requiring pediatric studies for drugs and biologics, it will assess the need for such labeling for devices.

22. What kind of improvement can we expect in our children's health as a result of this regulation?

We expect safer and more effective medicines for children. The primary benefits expected are the reductions in avoidable adverse drug reactions and under or over treatments that would result from better informing health care practitioners about whether, and in what dosages, a given drug was safe and effective for use in children.

23. When will this regulation go into effect?

The rule becomes effective 120 days after publication in the Federal Register. Manufacturers of new drug and biologic products who are required to conduct studies under the rule will have 2 years from the date of publication to comply with the pediatric study requirement. FDA will not delay the approval of any applications otherwise ready to be approved for adults while awaiting the submission of pediatric studies required under the rule.

24. When can parents expect that information to support safe and effective use of products in children will become available?

We believe that, in some cases, the information already exists and the drug companies merely need to analyze and compile it. In these cases, the information can be made available on the labeling of the products fairly quickly. In other cases, studies need to be conducted. Under the requirements of our 1994 regulation, where the effects of the product and the disease for which it is indicated are sufficiently similar in both adults and children, the studies needed can be done within one year.

**PRMA**

To: Chris Jennings

Chris, as promised.

Alan

12/2



Alan F. Holmer  
PRESIDENT

November 13, 1997

Dockets Management Branch  
Food and Drug Administration  
HFA-305, Room 1-23  
12420 Parklawn Drive  
Rockville, MD 20857

**Re: Docket No. 97N-0165 Pediatric Patients; Regulations Requiring  
Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biologic  
Products; Proposed Rule**

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, happier, healthier and more productive lives. Investing nearly \$19 billion a year in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures for children and adults.

As discoverers and developers of innovative pharmaceuticals, but also as parents and as responsible citizens, we want to see more and better medicines developed to help and heal children. The pharmaceutical industry has a fundamental commitment to this goal.

PhRMA commends the Agency for initiating the 1994 rule, then extending the application of some of the concepts in the 1994 rule, and for recognizing the importance of periodic FDA/sponsor discussions about potential pediatric use at each stage of drug development.

Pharmaceutical manufacturers are responding to the FDA's current, flexible system, which is built mainly on the Agency's December 1994 pediatric rule. Indeed, 75 companies are now developing 146 new drugs that have been or will be studied in children. Nineteen of the 20 new drugs that were approved last year and that may have potential for pediatric use, have been or will be studied in children. In addition, manufacturers have responded to the December 1994 rule by submitting more than 200 supplements for changes in labeling to include more pediatric use information.

Congress, in the just-passed "Food and Drug Administration Modernization and Accountability Act of 1997," has made clear that an incentive approach is the appropriate manner to address this issue. Accordingly, we urge the FDA to follow Congressional

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*Pharmaceutical Research and Manufacturers of America*

direction and to allow the effect of the December 1994 rule and the new statutory incentive to be fully realized.

In light of the recently passed pediatric labeling incentive provision, and the ongoing testing and development of medicines for use in children, we question whether a government mandate is justified. Moreover, we believe that such a mandate might, in fact, be counterproductive. Requiring that clinical studies be conducted concurrently in adults and children could delay drug development time and approvals for adult populations. Mandates also may increase development costs and discourage sponsors from pursuing higher risk projects.

In addition, PhRMA doubts whether FDA has the legal authority to require a sponsor to study and label a medicine for any age group, or for any indication, for which the sponsor does not choose to market the product. Despite the FDA's references to various sections of the Food, Drug, and Cosmetic Act (FDCA), PhRMA doubts that the FDCA authorizes the FDA to require that manufacturers conduct pediatric studies either for new compounds or for drugs already on the market. FDA staff members, including former Commissioner Kessler, have stated that the FDA does not have "the authority to require manufacturers to seek approval for indications which they have not studied."<sup>1</sup>

Nevertheless, despite the significant industry response to current FDA pediatric policies and the Agency's knowledge of the incentive provisions in the bills before Congress, in August the FDA issued this Proposed Rule. We believe the Proposed Rule, while well-intentioned, contains several provisions that are counter to its goal to help children. Instead, they may divert resources from needed scientific study of other medicines in children and may actually put children who participate in some clinical trials at increased risk for minimal benefit. We believe that the objectives addressed by the Proposed Rule could be better achieved by establishing a flexible, science-based approach to increasing the information about uses of drugs in children.

As currently drafted, the Proposed Rule would require testing of new medical compounds in children:

- before safety in adults has been studied adequately;
- before effectiveness in adults has been established; and
- in young children and neonates without adequate information about the effects of the drug in older pediatric patients.

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<sup>1</sup> Remarks by David A. Kessler, M.D., at the Annual Meeting of the American Academy of Pediatrics (October 14, 1992) at 1.

The best approach to efficient, safe pediatric clinical trial design should be based on scientific knowledge of a new drug's metabolism and clearance from the body in adults, as well as other adult pharmacokinetic, safety, and effectiveness information. Earlier studies in children might be appropriate for life-threatening diseases, unique pediatric indications (e.g., surfactant), or compounds in a class of drugs already well-studied in children (e.g., some antimicrobials). This approach, however, mandates a flexible, not a fixed, schedule for sponsors to develop pediatric formulations, dosing information, and testing.

Those who argue for testing in children concurrent with adult testing focus on the "benefits" to patients of new treatments without, we believe, an appropriate recognition that clinical trials of new medical compounds pose risks. By presuming that all, or even many, compounds should be tested in children before there is evidence of safety and effectiveness in adults, the Proposed Rule would needlessly place many children at risk. We expect that parents, even those anxious for a treatment and a chance for a cure for a child, will ask for scientifically- and medically-based reasons for clinical trials. The Agency acknowledges this in its discussion of the possibility that some compounds that would be tested in children under the Proposed Rule would not be approved for marketing for either children or adults. The FDA should work with sponsors on an ongoing basis to ensure that studies are begun only when the medical and scientific information justify the exposure to risk in this vulnerable population, based on the perceived or likely benefit.

The Proposed Rule also establishes rigid age divisions for required studies. Scientific issues, not mandates, should guide the decisions about appropriate age categories, depending on the nature of the compound being studied. Thus, the method by which the compound is cleared from the patient's body must be considered in light of what we know about physical development in neonates and infants. The ability to measure the study end-points in very young children must also be considered.

In addition, the Proposed Rule is inconsistent with requirements in Canada, Europe, and Japan. Under the regulatory systems in Canada, Europe, and Japan, pediatric studies are, in general, not conducted until considerable information about the compound's safety and effectiveness in adults is well-studied. When sponsors in these regions begin pediatric testing, the guidelines direct that studies begin with older children, moving later to younger children and infants. PhRMA recommends that the FDA harmonize its pediatric initiatives with the Canadian, European, and Japanese requirements, working with the International Conference on Harmonization (ICH) or other international body.

In spite of our serious reservations about the Proposed Rule, we are submitting extensive and detailed comments. We believe that efforts to improve information about

medicines for children are important, and we submit these detailed comments for this purpose. If the FDA feels compelled to issue this rule in final form, these comments are intended to make the rule more workable and more likely to help children and other patients.

While we have concerns with the details of the Proposed Rule and do not believe that the Agency needs to finalize it, the research-based pharmaceutical industry is deeply committed to improving the health of children by working with the Agency and other public and private entities and organizations to increase the information available to pediatricians about the safe and effective uses of prescription drugs for children.

We commend the FDA for its initiative in holding a public hearing on October 27, 1997, and scheduling the formulation workshop for next spring. We urge the FDA to accept the unanimous recommendation of the witnesses at the October 27 joint FDA-AAP public hearing on the Proposed Rule and appoint an advisory committee of parents, the American Academy of Pediatricians, the Pediatric Pharmacology Research Units funded by the National Institutes of Health, pediatric pharmacologists, representatives of the pharmaceutical industry, and the FDA to identify the specific diseases for which pediatric medicines are especially needed and those already-approved drugs for which pediatricians need labeling information. The FDA should then work with industry and other organizations to develop creative ways to obtain the needed labeling information for already-approved products.

The pediatric incentive provision in the "Food and Drug Administration Modernization and Accountability Act of 1997" directs the Secretary of Health and Human Services to consult with experts to establish and prioritize a list of drugs for which pediatric information is needed. We believe involvement of PhRMA, the representative of the research-based pharmaceutical industry, is essential to the success of this effort. We urge the Secretary to convene a group as quickly as possible.

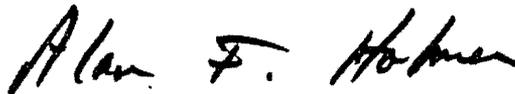
Finally, we want to raise an issue for which no easy answer is apparent and which is addressed only indirectly in the Proposed Rule – off-patent or unpatentable drugs. We share the concern that, where appropriate, pediatric labeling be developed. Many off-patent brand-name drugs face significant generic competition, limiting the range of incentives available to the FDA to encourage sponsors to conduct studies to develop information about uses of the drugs in children. We do want to collaborate with the Agency and others to find a solution to this challenging problem. The American Academy of Pediatrics can assist the Agency in developing a list of such drugs for which the pediatric community feels additional dosing information is important. The federally funded Pediatric Pharmacology Research Units (PPRUs) of the National Institutes of Child Health and Development (NICHD) would be a logical resource to address this list and find creative ways to develop, or assist others to develop, the information needed.

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page 5

We want to work with the FDA to accomplish the shared goal of expanded information about new and already-marketed drugs. But we reiterate our position that voluntary cooperative efforts will be, and have been, more successful than mandatory regulations.

We would be happy to meet with any FDA staff to work on any of these suggestions. PhRMA appreciates the opportunity to comment on this important Proposed Rule.

Sincerely,

A handwritten signature in black ink that reads "Alan F. Holmer". The signature is written in a cursive style with a large initial "A".

Alan F. Holmer

Attachment

November 13, 1997

COMMENTS OF THE PHARMACEUTICAL RESEARCH  
AND MANUFACTURERS OF AMERICA

SUBMITTED TO THE  
DOCKETS MANAGEMENT BRANCH  
OF THE FOOD AND DRUG ADMINISTRATION

ON DOCKET NO. 97N-0165

PEDIATRIC PATIENTS  
PROPOSED RULE  
REQUIRING MANUFACTURERS  
TO ASSESS THE SAFETY AND EFFECTIVENESS  
OF NEW DRUGS AND BIOLOGIC PRODUCTS

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, happier, healthier and more productive lives. Investing nearly \$19 billion a year in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures for children and adults. As pharmaceutical developers, but also as parents and as responsible citizens, we want to see more and better medicines developed to help and heal children. The pharmaceutical industry is committed to this goal.

PhRMA concurs with the Agency's goal to lay the groundwork for the ongoing and prospective development of pediatric labeling for drugs and biologics and commends the Agency for initiating the December 1994 rule and then extending the application of some of the concepts in the 1994 rule, particularly with respect to the extrapolation of efficacy for similar disease indications across ages (supported by pharmacokinetic and/or pharmacokinetic/pharmacodynamic studies). It is also to be commended for its recognition of the importance of FDA/sponsor discussion, at each stage of drug development, about potential pediatric use. The Proposed Rule contains many helpful suggestions and approaches to address the unique problems posed by pediatric drug development.

The FDA has, in cooperation with the American Academy of Pediatricians, scheduled a workshop for early in 1998 to address the multitude of issues involved in development of pediatric formulations for prescription drugs. In light of the difficulties

some manufacturers have encountered in attempting to develop pediatric formulations, this workshop will be an important step toward the Agency's goal of more pediatric information for prescription drugs.

These comments begin with several general comments of aspects of the Proposed Rule and other alternatives that PhRMA recommends that the FDA explore. Those are followed, beginning on page 15, with Specific Comments in response to questions posed by the FDA in the preamble to the Proposed Rule.

#### Pediatric Use of Prescription Drugs is Important to the Research-based Pharmaceutical Industry

One indication of the pharmaceutical industry's attention to pediatric labeling and new products for the treatment of diseases in pediatric populations is the number of new drugs in development. In a 1997 survey, published as *New Medicines in Development for Children*, PhRMA reports that 75 companies are developing 146 new medicines for children, including 36 for cancer, the leading disease killer of children; nine for AIDS, the prime cause of death among young children in some cities; and five for cystic fibrosis, the most common fatal genetic disease affecting children and young adults. All 146 medicines have been or are being tested in children. All of the 75 companies developing these medicines intend to seek the Food and Drug Administration's approval for pediatric use of these drugs.

A survey published by PhRMA in 1990 reported that 114 new drugs in development were aimed at pediatric populations. There has been a 28 percent increase from 1990 to 1997 in the number of new drugs in development for pediatric uses.

A review of the 53 new drugs that the FDA approved in 1996 reveals that 20 have easily recognized potential for pediatric use. Of these 20, four already have FDA approved pediatric labeling; fourteen have pediatric studies planned or in progress; one is switching to being sold over-the-counter. For only one of these 20 drugs, the sponsor has no immediate plans for pediatric labeling activities.

#### Significant Progress in the Past Five Years Belies the Need for New Requirements

In publishing this Proposed Rule, the FDA failed to take sufficient credit for the results of its recent initiatives. These initiatives already have had a major impact on companies and the Agency, although the direct effect on pediatricians and patients has not yet been fully realized because the development of new medicines and indications is a deliberate and time-consuming process. Nevertheless, the initiatives are stimulating the development of more labeling information for children – as even an updated version of the data cited by the FDA to justify the proposed rule shows – and should be given more time to work before the Agency changes direction and resorts to a mandatory system.

The FDA's initial steps were voluntary, reasonable, and flexible, encouraging the Agency and a drug sponsor to plan and work cooperatively on an individual drug for a specific disease during the development process. They included the December 1994 pediatric labeling regulation and implementation of a "Pediatric Plan" by CDER and CBER to spur voluntary development of pediatric data during development and after approval of a new drug.

There is still considerable work to be done to take full advantage of the December 1994 rule. For already-approved products, the 1994 rule directed manufacturers to review existing data and submit appropriate supplemental applications by April, 1997. The supplements were to indicate that either (1) existing data support additional labeling information for children, or (2) a labeling statement should be provided that safety and effectiveness have not been established in pediatric patients. Now the FDA needs to devote the resources necessary to complete the review of supplemental New Drug Applications submitted in response to the December 1994 rule.

According to the *Pink Sheet*,<sup>1</sup> the FDA has estimated that pharmaceutical manufacturers have submitted 200 supplemental NDAs in response to the 1994 rule. It is not clear how many of those would result in inclusion of pediatric use information in product labeling. In an informal survey, PhRMA members reported that they had reviewed the medical and scientific literature for, on average, 20 products. Based on the information obtained during the reviews, companies had submitted an average of 3 supplemental applications to add information about pediatric use of the product, excluding supplemental applications to add a statement that information on pediatric use was not available.

To date, the FDA has responded to some, but not all of those supplemental applications. The FDA and the drug's sponsor may sometimes have different interpretations of the evidence available from the medical literature, which would explain, in part, why the FDA did not receive as many supplemental applications to add pediatric use information to product labeling as the Agency anticipated.

PhRMA recommends that the FDA complete the task it has already undertaken in response to work it has imposed on manufacturers. Only when that task is substantially complete will the Agency be able to determine whether there is a need to impose new requirements on manufacturers and new risks on children who might be recruited for clinical trials as a result of this Proposed Rule.

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<sup>1</sup> *F-D-C Reports - The Pink Sheet*, September 1, 1997 at T&G-9.

In view of the attention to expanding the labeling information about pediatric uses of new and already-marketed drugs, PhRMA questions the need for a regulation that mandates testing of drugs and biologics in children and questions whether the Agency has done the requisite risk/benefit and cost/benefit analyses to justify so broad a proposal.

Unfortunately, the Proposed Rule takes no cognizance of the current industry effort in pediatric clinical trials. Instead, through use of 1994 IMS America, Ltd. prescription drug usage data, it incorrectly implies that physicians are bereft of information about how to accurately prescribe for their pediatric patients. To the contrary, extensive pediatric prescribing information, typically in the product labeling, is or soon will be available for most of the 10 drugs that the FDA reports "were most widely prescribed for pediatric patients," a crucial fact omitted in the *Federal Register* notice. Specifically:

- Albuterol – Albuterol is labeled as a pediatric inhalation solution at two strengths for use for age two and older and as an aerosol for children age four and older. All these formulations received approval from FDA before the publication of the Proposed Rule.
- Phenergan® – Labeling for this treatment for allergic reactions is being reviewed and revised based upon specific correspondence between the FDA and the sponsor. Current labeling includes information on children under the "Dosage and Administration" section, and provides information for use in children within comments under various subsections. The "Precautions" section also addresses children.
- Ampicillin – Although pediatric use information for this antibiotic is not included in the package insert, every pediatric and standard medical reference contains extensive dosing information for children on all Ampicillin dosage forms. This information is widely known within the pediatric and family medicine communities.
- Auralgan® – As a drug with an exemption under the grandfather clause, this topical anesthetic has no NDA on file to which labeling changes can be made. From a researcher's point of view, it is interesting to consider what type of clinical safety, efficacy, or pharmacokinetic studies FDA would desire for a topical anesthetic in a glycerine vehicle that has been safely marketed for more than forty years.
- Lotrisone® – The "Precautions" portion of the label for this treatment for topical infections contains a section on "Pediatric Use" and a clear statement that "Lotrisone® Cream use in diaper dermatitis is not recommended." The statement is there because potent concentrations of the active ingredient would be harmful to infants and young children.

- Prozac® – Initial studies of this product in depressed pediatric patients are nearing completion.
- Intal® – Labeling for this asthma treatment provides for use of the nebulizer solution in children age two and older and the metered dose inhaler (MDI) for children age five and older. The nebulizer solution is the preferred method of administration for Intal® in children younger than 5, as the MDI is not always easy for a young child to use correctly. Intal® Nebulizer was developed for use in the young pediatric population for this specific reason.
- Zoloft® – Labeling for this anti-depressant provides for pediatric use to treat obsessive compulsive disorder on October 10, 1997.
- Ritalin® – The labeling for this treatment for attention-deficit disorders and narcolepsy provides for use in children age six and above. Evaluation of available data for children under age six is in process.
- Alupent® – Revised labeling for this asthma treatment was approved by FDA in February, 1997; one dose of the syrup formulation is approved for children 6 and over while another syrup dose is approved for children 12 and over.

This impressive overall record, PhRMA believes, shows that substantial progress is being made in providing more pediatric labeling information and that the FDA's December 1994 rule has been on the right track.

The FDA's Pediatric Initiatives Should Not Mandate that Children be Exposed to Unnecessary Risks

Principle of Graduated Risk – The FDA has, in its estimate of the costs of the Proposed Rule, acknowledged that its mandate approach would expose children to clinical testing of compounds that do not eventually gain the FDA's approval for use in any population. The FDA estimates that 30 percent of the children who would be exposed to drug testing under the Proposed Rule would be needlessly put at risk. PhRMA urges the FDA to consider the implications of that statement and reconsider whether there are other ways to encourage the development of pediatric use information, ways that do not expose such a large number of children to unnecessary clinical trials.

Indeed, it would seem to be unethical, except when the drug is intended to treat a disease specific to young children, to begin pediatric studies before enough adult safety and efficacy data have been accumulated for the drug or biologic sponsor to make a decision that the compound is likely to be approved for use in adults and that the sponsor should, therefore, proceed with development of a New Drug Application. In the interest of protecting infants and small children, it would be appropriate for the FDA to

encourage studies in adolescents and older children prior to involvement of infants and small children. To do otherwise would expose thousands of children to test substances unnecessarily. An Institutional Review Board would be likely to raise questions about a proposed study that focused on young children without adequate information about the effects of the drug in older children, except for drugs to treat conditions unique to children.

The best approach to efficient, safe pediatric clinical trial design should be based on knowledge of a new drug's metabolism and clearance, adult pharmacokinetics, PK/PD relationships, and adult safety and efficacy (therapeutic index). Ascertainment of adult dose and PK relationships should, in general, form the basis of initial pediatric dose selection. In some instances, the available evidence may indicate that pre-clinical studies would be needed before the sponsor could consider whether the drug could be used in young children. Earlier studies in children might be appropriate for life-threatening diseases, unique pediatric indications (e.g., surfactant), or compounds in a class of drugs already well-studied in children (e.g., some antimicrobials). In other words, PhRMA urges the FDA to flexibly apply the knowledge generated by developmental pharmacological science to the study of compounds in young children.

Because of the potential for diagnostic, therapeutic, or ethical misadventure, special consideration must be given to the design of clinical trials in children. The decision about whether to structure the trial to compare the drug to placebo or to some other treatment option requires careful review; outside consultation may be appropriate. Many technical problems may be encountered, such as difficulties in giving injections, drawing frequent blood samples to collect trial data rather than for treatment purposes, fright, and separation from parents and family or familiar surroundings. It is likely that, for medications other than vaccines, only small numbers of children will be available to participate in a clinical trial. FDA may need to adjust its expectations in terms of size of the clinical trials or acceptable statistical evidence. For diseases for which several products are already approved, researchers conducting studies for different products may find themselves competing for the same patients; a rational process to identify the drugs for which pediatric studies are actually needed would avoid this potential problem.

PhRMA urges the FDA to retain the principle of graduated risk, which requires that manufacturers not expose pediatric patients to clinical trial risks, for drugs to be used in adults, until adequate information is available about the compound's safety and effectiveness in adults. Thus, the Proposed Rule should not mandate when pediatric studies should be started. Without a mandate for the start of pediatric studies, the FDA would have no need for a formal waiver system to excuse sponsors from the need to start pediatric studies early in the development process.

Children are not a Single or Simply-divided Subpopulation – nor can they be divided by rigid application of age categories. As physicians recognize, premature

infants present different pharmacologic and clinical trial issues than do full term infants. The same is true of a 13-year-old who is well into adolescence versus an immature 13-year-old whose puberty is delayed.

To support its Proposed Rule, the Agency identified examples of past problems, most from the 1950's. These dated examples provide little insight into current pediatric pharmacology issues. For example, the Proposed Rule at page 43904 implies that chloramphenicol cannot be used in neonates when, indeed, it can be used if the dose is correct. Similarly, quinolones are used safely and effectively in children with cystic fibrosis and children with chronic urinary tract infection.<sup>2</sup> Information concerning these unique uses, however, is more frequently obtained by physicians from case reports in the current literature than from the package insert label. Thus, practicing pediatricians have access to dosing and use information, although the information in the medical literature may not meet the FDA's criteria for data that a drug's sponsor can use to support a supplement to change the drug's labeling.

Clinical Studies in Small Populations May Be Unwise – PhRMA questions the wisdom of mandating trials in small population subsets. When the FDA suggests that 100,000 prescription uses might constitute a "significant use," without looking at that use in the context of the total disease population and /or the population of the age range cited, the FDA may be proposing to require studies in very small groups. In many disease states there is the possibility that a prescription may have one or more refills within a year's time. For example, a patient using an asthma drug may receive several prescriptions during the course of the year. Thus, 100,000 prescriptions may represent only 25, 000 patients. To require studies in such small subgroups sets an unwise precedent that could considerably harm the public health and the very groups the Agency is trying to serve. The FDA must recognize that no amount of labeling will ever cover all uses of all medicinal products in all population subgroups.

The decision whether pediatric studies are needed should turn on the question whether there is an unmet medical need for a drug to treat a specific disease or condition, not the number of "uses" identified by physicians in an IMS survey. To address this question for already-marketed drugs, PhRMA recommends that the FDA convene an Advisory Committee, as unanimously recommended at the October 27 public hearing.

Clinical studies in small populations, such as children in a specified age range, may also require extra time and expertise to complete. For young children, some researchers may need to define new endpoints, because of the difficulty of obtaining

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<sup>2</sup> See, e.g., Poole, M.D., "Quinolones in the pediatric patient," *Ear Nose and Throat Journal*, 72:162, 1993; Orenstein, D.M., Pattishall, E.N., Noyes, B.E., et al., "Safety of ciprofloxacin in children with cystic fibrosis," *Clinical Pediatrics*, 32:504-6, 1993.

some outcome measures, i.e., young children may not be able to describe their symptoms. With small populations, recruitment of study participants often requires more than the usual number of trial sites. Successful trials may require changes from the FDA's normal definitions of well-controlled clinical trials. PhRMA recommends that the FDA work with sponsors to identify the information needed for pediatric labeling, approve innovative clinical trial designs, and recognize the increased time that may be necessary to conduct pediatric studies.

The legal issues that accompany any clinical trial are compounded with pediatric trials. Parental informed consent may be found by future courts not to be binding, allowing adults to sue years later for injuries allegedly incurred from participation in pediatric trials. Manufacturers are understandably reluctant to assume the risk of litigation years in the future for trials involving compounds that the FDA has not yet approved for adult indications. Thus, the FDA should not mandate that pediatric studies be undertaken early in the drug development process.

Pediatric Formulations May be Difficult to Develop – As Dr. Clemente stated at the October 27 hearing, for some drugs the process of developing acceptable pediatric formulations may pose multiple problems. Improved compliance can be obtained if the pediatric formulation reduces the frequency of dosing, simplifies the method of administration, improves the side effect profile, and improves the taste. Indeed, the importance of taste was highlighted in an informal survey of PhRMA member companies. They reported that taste and palatability were the most difficult aspects of developing a pediatric formulation. The second most frequently-cited problem was achieving stability.

In the informal survey, responding companies reported that it took from 5 months to four years to develop a pediatric formulation for one or more products. The estimates of the cost of that work ranged from \$500,000 to \$3.5 million. While the longer time and higher cost figures are clearly for products that pose formulation difficulties, they do highlight the need to adjust requirements and time schedules to the realities of individual medical compounds.

#### The Proposed Rule is Inconsistent with International Requirements

Contrary to the approach of the Proposed Rule, which could potentially delay approval of important drugs in the adult population if a sponsor did not conduct a concurrent pediatric study program, or commit to a post-approval pediatric study program, the Agency should follow the lead of the regulatory agencies in other regions. For example, the European Committee for Proprietary Medicinal Products (CPMP), in their "Clinical Investigation of Medicinal Products in Children," makes several statements about the timing of pediatric studies but clearly states that, "Clinical trials in children will usually follow completion of adult Phase III trials." In addition, the CPMP

document establishes different age categories for testing from the categories FDA presents in the Proposed Rule. This difference could force sponsors engaged in global drug development to conduct duplicative studies, unnecessarily exposing additional children to test products.

Likewise, in Canada, for drugs with an adult use, the presumption is that clinical testing will occur after the development of evidence of safety and effectiveness in adults. The 1997 draft guideline states that:

For therapeutic products under development where it is anticipated that children of various age categories may use the product, the enrollment of children may proceed in late Phase III clinical trials, following the documentation of substantial evidence of safety and efficacy in adult patients. By this stage it is expected that all preclinical toxicologic studies would be completed.<sup>3</sup>

In Japan, a guideline issued by the Ministry of Health and Welfare in 1992 directs that, in general, studies in children should be excluded from Phase I and Phase II trials. In addition, when clinical trials are to be conducted in children, the trials should begin with older children and then be extended to younger children and infants. The exception, of course, is for drugs intended to treat a disease occurring only in infants, when they would of necessity be the focus of the clinical trials.

PhRMA recommends that the FDA harmonize all of its pediatric initiatives with the Canadian, European, and the Japanese requirements and hold implementation of the Proposed Rule in abeyance until the International Conference on Harmonization (ICH), or other international body, can harmonize pediatric study guidelines globally.

#### Incentives Will Accomplish FDA's Goal

Congress, in the just-passed "Food and Drug Administration Modernization and Accountability Act of 1997," has made clear that an incentive approach is the appropriate manner to address this issue. The pediatric labeling provision in the "Food and Drug Administration Modernization and Accountability Act of 1997" provides an incentive – six months of additional market exclusivity – for sponsors that conduct pediatric studies requested by the FDA. It also directs the Secretary of Health and Human Services to consult with experts to establish and prioritize a list of drugs for which pediatric information is needed. We believe involvement of PhRMA, the representative of the

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<sup>3</sup> Canadian Department of Health, Therapeutic Products Directorate Guideline: Inclusion of Pediatric Subjects in Clinical Trials, "New Therapeutic Products under Development" (August 1997 Draft) at 6.

research-based pharmaceutical industry, is essential to the success of this effort. We urge the Secretary to convene a group as quickly as possible.

In addition, PhRMA has grave concern that the "stick" approach reflected in the Proposed Rule will in fact be counter-productive and not achieve the goal we mutually share. It is conceivable that the rigidity of the Proposed Rule will require another level of bureaucracy simply to deal with reasonable deviations from the requirements, such as waiver requests. PhRMA urges the Agency instead to adopt a flexible approach that adapts the Agency's pediatric information goals to the three general classes of products: new drugs, already-approved drugs with significant market protection, and off-patent drugs, as well as the unique characteristics of each product and each disease. The General Considerations for the Clinical Evaluation of Drugs in Infants and Children, published in 1977 by the U.S. Public Health Service, reinforces this posture and states, "Flexibility in approach is essential to permit the necessary modification according to the nature of the drug and its intended use, and the age of the patient."

For new drugs, a flexible approach would be characterized by early and frequent dialogue between the Agency and the sponsor on pediatric development plans for the specific product. The Agency should not withhold approval for adult uses as a mechanism to encourage or require sponsors to conduct pediatric studies. The current practice, where the reviewing officer tracks pediatric development plans with the sponsor, has been well-received in the pharmaceutical industry and has been an effective tool in stimulating pediatric drug development. In an informal survey of PhRMA member companies, they report that for the large majority of products, the decision to pursue one or more pediatric formulations was made during drug development, not after submission of the application for an adult indication. Thus, the Agency's success over the past three years in adding pediatric drug development for new compounds demonstrates the strength of a cooperative, not mandatory, approach.

For already-approved products, the FDA's current approach should be continued and strengthened, as authorized by the incentive in the "Food and Drug Administration Modernization and Accountability Act of 1997." Resorting to the development of a mandatory regulation and, presumably, to the courts to remove a product as misbranded if the manufacturer does not submit a supplemental application with pediatric data, or delay of approval of a new drug for adult use, is wasteful of resources for industry and the FDA and accomplishes little for the children we want to help and protect. The FDA's existing rule, however, may need some fine-tuning. In some circumstances, the FDA and the drug's sponsor may have different interpretations of the evidence available from the medical literature. These different interpretations may explain why the FDA did not receive as many supplemental applications to add pediatric use information to product labeling as the Agency anticipated. It is not clear what the FDA would do if its reviewers concluded that the medical literature did, and the sponsor concluded that the literature did not, support pediatric use labeling. Product liability concerns might lead the sponsor to

err on the side of caution in proposing to add pediatric use information. On the other hand, the results of an informal survey of PhRMA member companies may illustrate the other side of this complex situation. At least three companies have had one or more pediatric supplements rejected by the FDA.

Because of the differences in circumstances for already-approved products with and without significant remaining patent or market exclusivity protection, the FDA will need to apply different incentives and approaches to develop pediatric labeling. For off-patent products, the FDA will need to work with multiple groups to facilitate development of pediatric use information. Below, PhRMA proposes one alternative.

Appropriate incentives are more likely to achieve our common goal. We encourage FDA to be as creative in stimulating sponsors through appropriate incentives as the Agency has in times past been in relying on the threat of punishment. Incentives might include increased product exclusivity, the promise of shorter review times for pediatric supplements, or the granting of priority review status for the adult NDA application when the pediatric studies/plans meet the FDA's criteria. Exemption from User Fees for pediatric supplements, as noted in the Proposed Rule, is also an appropriate incentive.

The FDA notes at page 43903 of its Proposed Rule that it already has authority to provide incentives to manufacturers that seek approval for labeling for pediatric uses. These incentives include 3 years of market exclusivity under sections 505(c)(3)(D)(iii) and (j)(4)(D)(iv) of the Food, Drug, and Cosmetic Act (FDCA), 21 USC §§ 355(c)(3)(D)(iii) and (j)(4)(D)(iv), and 7 years of exclusivity under the Orphan Drug Amendments, FDCA § 527, 21 USC § 366cc. PhRMA recommends that the Agency consider creative ways to use its existing incentives to encourage manufacturers of approved products to submit supplemental applications for pediatric labeling, as appropriate for particular drugs, and to encourage manufacturers submitting New Drug Applications to work with the Agency to determine whether, when, and how to collect the information to support pediatric labeling.

#### An Alternative for Off-Patent Products

For new products under development, the FDA has a close working relationship and can provide incentives for sponsors to conduct pediatric studies to gain pediatric labeling. In contrast, for marketed products that are off patent, the original sponsor's financial resources and incentives for additional investment have been diminished by generic competition. As a result, the incentives available to the Agency are more limited. PhRMA suggests a multi-step process. The American Academy of Pediatrics can assist the Agency in developing a list of such drugs for which the pediatric community feels additional dosing information is important. The federally funded Pediatric Pharmacology Research Units (PPRUs) of the National Institutes of Child Health and Development

(NICHD) would be the logical resource to address this list and find creative ways to develop, or assist others to develop, the information needed. PhRMA stands ready to work with the FDA, the American Academy of Pediatrics and the PPRUs to develop the list of priority drugs and to find ways to ensure that the necessary information is collected to expand the drugs' labeling to include information about pediatric uses.

Such an alternative may be especially important because a mandate in a final rule that sponsors of already-approved products develop pediatric use information would impose an enormous start-up burden on researchers and clinical trial facilities. While the Proposed Rule at 43911, in the discussion of cost estimates, projects that only two already-approved drugs per year would require additional data, the Proposed Rule does not note how the Agency identified that number or how the Agency intends to identify the specific already-approved products each year that would require additional data.

#### An Appeal Mechanism Would Facilitate Agency-Sponsor Communication

The FDA's 1994 rule and the "Pediatric Plan" direct sponsors and the FDA to discuss the possibility of pediatric uses, and pediatric studies, at various steps in the drug development process. The 1994 rule and the "Food and Drug Administration Modernization and Accountability Act of 1997" provide incentives for sponsors to conduct pediatric studies and seek supplemental approval for labeling changes to include pediatric uses for already-approved products. In all of these situations, sponsors and the FDA are working to develop pediatric use information. However, sponsors may encounter problems on the way to that goal, such as difficulties in developing pediatric formulations. We can also anticipate that sponsors and FDA staff will sometimes disagree about the nature or importance of those problems. When such disagreements occur, they can most readily be resolved if the Agency has an appeal mechanism through which they can routinely be addressed.

PhRMA recommends that the FDA ensure that a mechanism exists by which sponsors can appeal reviewers' decisions arising from efforts to implement the pediatric labeling goals. Arguably, the appeal should not be to the FDA staff member's supervisor, but to a group with a broader view, a group that understands the general need for pediatric use information, the specific need for pediatric use information for the compound (i.e., whether this represents a new treatment for an untreated condition or simply another treatment option), and the difficulties inherent in developing pediatric use information. An appeal mechanism involving a group with a broader view of pediatric uses of drugs would also allow for consistency in application of appeal criteria across reviewing divisions. In light of the confidential nature of the communications between the Agency and the sponsor of a new compound, the appeal mechanism must be structured to protect the sponsor's confidential information. Alternatively, the FDA could apply the chain-of-command appeal mechanism already established in its general operating procedures. See 21 CFR § 314.103.

While an appeal mechanism would add to the Agency's workload, PhRMA anticipates that a limited number of appeals would be filed and that resolution of the first few appeals would provide guidance to the Agency and the industry, further limiting the number of instances where the Agency and the sponsor disagree about the need for pediatric studies.

PhRMA offers to work with the FDA to develop alternatives for such an appeal mechanism.

#### FDA Lacks Legal Authority to Impose a Mandate for Pediatric Labeling

PhRMA questions, as do many others, whether FDA has the legal authority to require a sponsor to study and label a medicine for any age group, or for any indication, for which the sponsor does not choose to market the product. Despite the FDA's references to various sections of the FDCA, the FDCA does not authorize the FDA to require that manufacturers conduct pediatric studies either for new compounds or for drugs already on the market.

Indeed, an individual thoroughly knowledgeable about the FDCA, former Commissioner Kessler, explicitly acknowledged that the FDA does not have the authority to require sponsors of new drug applications to include pediatric uses in proposed labeling.

Despite the ardent desire of the FDA to increase pediatric indications, I need to acknowledge the limits of FDA's authority. It is our job to review drug applications for the indications suggested by the manufacturer. We do not have the authority to require manufacturers to seek approval for indications which they have not studied.... Thus, as a matter of law, if an application contains indications only for adults, we're stuck.<sup>4</sup>

Dr. Kessler's statement represents a consistent position for the Agency. As far back as 1967 the FDA said:

It should be noted that the burden of proving the safety and effectiveness of a new drug – or of new uses of an already approved drug – rests on the manufacturer. It is the manufacturer who chooses the indications to be investigated and determines the dosage level for which he will seek FDA approval. It is the duty of the Food and Drug Administration under the

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<sup>4</sup> Remarks by David A. Kessler, M.D., at the Annual Meeting of the American Academy of Pediatrics (October 14, 1992) at 1.

law to decide that proposed usages and levels are both safe and effective, based on the data submitted by the manufacturer.<sup>5</sup>

As to new drugs, the FDCA provides only for Agency reviews of applications filed by industry. The FDCA requires the FDA to determine whether a drug is safe and effective for the use(s) that the manufacturer proposes in the labeling that the manufacturer submits with the application. FDCA § 505(b)(1), 21 USC § 355(b). The FDCA does not authorize the FDA to require manufacturers to submit proposed labeling, and therefore to conduct studies of the compound's safety and effectiveness, for uses not selected by the manufacturer.

As authority for this Proposed Rule as applied to new drug applications, the FDA cites its authority to prohibit misleading product labeling. The FDA then asserts that a new drug's label would be misleading if it did not include material information about the drug's use under "customary or usual" conditions of use. It is not clear how the Agency proposes to know a drug's customary and usual conditions of use before a drug is legally marketed. The manufacturer knows the uses for which it intends to market the product, because the manufacturer has identified those uses in its proposed labeling. The manufacturer does not know – indeed, is not able to know – what uses may, over time, become "customary and usual" within some portion of the medical profession.

As to already-approved drugs, the FDCA authorizes the FDA to take action against a product when its labeling is false or misleading. In this Proposed Rule the FDA defines "misleading" to include the absence of material information about both labeled uses (uses intended by the manufacturer) and customary and usual conditions of use ("off-label" uses, according to the FDA). The Agency argues that if the manufacturer knows of an off-label use of its product, the manufacturer has an obligation to provide adequate directions for that off-label use. But this argument would encompass much more than pediatric uses, because manufacturers may learn of a variety of off-label uses, ranging from use by a single physician to use throughout a medical specialty.

The Agency clearly can't require that manufacturers conduct studies of all off-label uses they become aware of, just because those uses are customary and usual within some group of physicians. The FDA does not have the authority to restrict physicians to the uses approved by the FDA and developments in medical treatments occur when physicians try varied treatments. Even with unlimited resources, manufacturers can't study all the varied uses that physicians might make of prescription drug products. And resources are not unlimited. Such a requirement would force manufacturers to divert

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<sup>5</sup> The next statement reiterates the point: "Thus, when a new drug passes into the hands of the physician, the package insert information he receives is based on data the manufacturer has submitted to the Food and Drug Administration as his proof that the drug is safe and effective in the uses for which the manufacturer wishes to market the drug." John Jennings, M.D., "The Rx Label: Basis for all Prescribing Information," 1 FDA Papers 15-16 (November 1967).

resources for vital research and development programs into studies of off-label uses, even when the uses encompassed by the original research and development program might be particularly promising for the treatment of life-threatening diseases.

The FDA also asserts that, because the FDCA grants it authority to issue regulations for the efficient enforcement of the Act, the Agency has authority to impose on a drug's manufacturer new requirements for studies for uses not intended by the manufacturer. PhRMA notes that this argument would vastly expand the Agency's authority; the Agency's grant of authority to enforce the FDCA does not include a grant of authority to enforce requirements beyond those imposed by the FDCA.

**Specific Comments** (Section headings are copied from the Proposed Rule, with citation to page numbers.)

### **III. Results of Actions to Date and Need for Additional Steps (pg. 43902)**

**“...comment on whether there are other ways to assure that manufacturers reliably conduct pre- or post-approval studies in pediatric patients.” (pg. 43902)**

PhRMA questions whether the FDA is encountering problems with manufacturers conducting agreed-upon studies, either before or after the FDA has approved a product for use in adults. The Proposed Rule asks for assistance on assuring that manufacturers comply but does not describe the Agency's present experience with manufacturers' compliance.

The most effective way to assure that manufacturers reliably conduct appropriate pediatric studies is for the Agency to continue its present policy of working individually and flexibly with sponsors throughout the drug development process. In addition, it would be helpful if the Agency narrowed the focus of its efforts to classes of drugs where there is a more urgent need for pediatric dosing data. PhRMA recommends that the FDA convene an Advisory Committee, as recommended by the witnesses at the October 27 FDA-AAP public hearing. We note that the provision of incentives in the form of increased product exclusivity, priority review for drugs with a compelling need for pediatric information, and waiver of user fees will assist in achieving the goal underlying the Proposed Rule, more extensive pediatric use information for more prescription drugs.

PhRMA recommends that FDA substitute for the Proposed Rule a more flexible approach under which it would work with each NDA sponsor to develop an acceptable plan for clinical trials, if warranted, and provide incentives for development of data to support supplemental NDAs for marketed products. Once the Agency and the sponsor agree that such studies are worthwhile, the Agency could follow the progress of the pediatric clinical trials as part of the Agency's Phase IV tracking program.

## **V. Description of Proposed Rule (pg. 43902)**

### **A. Scope (pg. 43903)**

**“...comment on whether the requirement should apply more broadly, e.g., to applications for minor chemical variations of approved products, new indications, new dosage forms or new routes of administration...” (pg. 43903)**

New routes of administration and new dosage forms will necessitate supportive bioequivalence data, as they do now. It may be particularly important to consider pediatric studies when a new formulation is developed that would be uniquely suited to children, such as a chewable tablet or a liquid that contains no alcohol.

Other than those situations, the Proposed Rule should not be applied to minor changes in approved products. It would be a waste of FDA resources to review and the pharmaceutical industry's resources to prepare and submit supplemental applications if the Agency were to apply a rigid policy to all minor changes. Because many changes would apply in the same manner to adult and pediatric uses, flexibility is essential when dealing with minor changes to approved products.

### **B: Not-Yet-Marketed Drug and Biological Products (pg. 43903)**

#### **3. Sections 314.50(g)(2), 314.81(b)(2)(vii), and 601.27(b) – Deferred Submission and Postmarketing Reports (pg. 43904)**

**“...the circumstances in which FDA should permit deferral.” (pg. 43904)**

A variety of factors make it inappropriate and unreasonable to delay drug development or approval for adults until pediatric labeling could be approved concurrently. These factors include:

- The pediatric population with a specific disease may be quite small in comparison to the adult cohort for whom the drug is intended – so small that enrollment and completion of the pediatric trial cannot be accomplished in parallel with the adult program.
- If the natural course of the adult and pediatric disease are sufficiently different, it may be impossible for the pediatric and adult study programs to progress at the same pace.

- There are drugs for which analytic tools and clinical methodologies cannot be easily adapted to the pediatric population.
- The development of drugs which have complex pharmacokinetic properties (e.g., nonlinear properties) in adults will usually have to progress more slowly in pediatric patients. For example, if the pharmacokinetic properties of a compound are nonlinear, it is not possible to extrapolate from the adult dose range information to determine doses for pediatric age groups.
- There are drugs for which the scope and nature of nonclinical studies only support clinical studies in adults.
- Because of the difficulties in development of pediatric formulations for some compounds, the degree of need for pediatric information about a drug should be reviewed when two or more attempts to develop a satisfactory pediatric formulation have been unsuccessful.
- There are drugs for which unique drug-drug or drug-food interactions (e.g., drug-milk interactions) in the pediatric population confound the drug development process.

**“...comment on factors that should be considered in determining whether a product is among those that should be studied in adults before children.” (pg. 43904)**

Unless there is compelling evidence to the contrary, studies in children should always be deferred until reasonable evidence of safety and efficacy of the test agent in adults has been established. This principal of graduated risk means that, by and large, pediatric studies will not be initiated until the end of adult Phase II or Phase III studies. The exceptions would be:

- Where the disease in children is life-threatening and alternative therapy is lacking.
- Drugs developed specifically for the treatment of diseases in children, or primarily for pediatrics but with a limited adult use as well.
- Drugs intended for both adult and pediatric use and without major safety limitations, e.g., topical anesthetics, certain anti-infective drugs.
- Drugs in classes that are already well-studied in children.
- Drugs for which a large amount of off-label use is anticipated.

**“...comment on the types of evidence FDA should examine to ensure that deferred studies are carried out in a timely fashion.” (pg. 43904)**

If the FDA institutes an adequate tracking system for the progress of pediatric studies and continues to meet periodically with the sponsor to discuss the progress of the pediatric program, the Agency will have adequate assurance that deferred studies are being carried out in a timely fashion. There is neither need, nor rationale, for new rules in this area. An initial discussion of whether the sponsor has plans for pediatric studies should be included in the pre-IND meeting. The clinical development plan within an IND should contain a statement of whether, and when, the sponsor will consider the possibility of pediatric uses, formulations, doses, and whether PK/PD studies or more extensive clinical trials are needed for pediatric populations. There should be a progress report on initial activities, such as formulation, at the End-of-Phase II meeting and, if appropriate, further discussions between the Agency and the sponsor on the need to conduct pediatric studies.

**4. Sections 314.50(g)(3) and 610.27(c) --Waivers (pg. 43904)**

**“...comment on the proposed grounds for waiving the pediatric study requirement and whether additional grounds may exist, such as whether cost should justify waiver of the pediatric study requirement.” (pg. 43905)**

The FDA proposes to create considerable unnecessary work as well as the potential for conflicts with sponsors by creating a situation in which the Agency mandates pediatric studies and then must be the arbiter of numerous waiver requests. Certainly there is justification for a waiver if the pediatric formulation problems are extensive; if the cost of the pediatric studies is prohibitive; if the proposed studies expose the sponsor to excessive liability; if there are unique safety risks in children; and if the compound is novel and lacks a body of evidence on safety. FDA should not place itself in the position of making a cost judgment about specific drug products, except for the larger cost/benefit analysis of weighing the adverse impact in the adult population and to the public health at large if a drug approval benefiting the adult population is delayed in deference to a limited pediatric use. Market incentives will drive the pharmaceutical industry to pursue pediatric studies and will obviate the need for Agency involvement in this area, other than to monitor progress.

If the FDA proceeds with a waiver system, the amount of work required by manufacturers and the Agency would be decreased if the Agency were to identify diseases that are not likely to occur in children, i.e., prostate cancer, or classes of drugs not likely to be used in children, and grant blanket waivers for those drugs. Such a blanket waiver would, of course, need to include an exception process when the Agency determined, as the drug moved through the development process, that the evidence indicated that the drug might be useful to treat a disease that occurs in children.

PhRMA recommends that the FDA not devote resources to creation of a system for waivers, which would require staff, development of regulations or, at a minimum, a guidance, and operation of a submission tracking system. Those resources could more productively be spent reviewing supplemental applications for pediatric labeling for approved products.

**“...comment on defining the term ‘meaningful therapeutic benefit.’” (pg. 43905)**

FDA has already defined this term in the Accelerated Approval Regulations, 21 CFR § 314 Subpart H. The reality is that a “meaningful therapeutic benefit” must be the decision of the sponsor. In today’s costly drug development environment, and in an intensely competitive marketplace, the anticipation that a compound will provide a “meaningful therapeutic benefit” is an important factor in the decision to proceed with product development. Compounds that might provide a “meaningful therapeutic benefit” are the only ones that have a chance for success. In the final analysis, however, health care providers should be the arbiters of the therapeutic benefit of a particular compound. Only after the product is on the market, and sometimes only after the product has been available, and used, for a period of time, is it possible to determine whether the compound actually provides a “meaningful therapeutic benefit.” The Agency is ill-advised to establish itself as the arbiter on this issue at any time in the life of a drug product, but especially not at a time when information from the drug’s use by health care providers is not yet available.

**“...comment on what should be considered a ‘substantial number’ of pediatric patients.” (pg. 43905)**

FDA’s logic is unsound in its approach to defining a “substantial number” of pediatric patients. Drug development for a disease with a patient population of 200,000 or less, out of the entire US population, is eligible for “orphan” status in an FDA review. Development of an orphan product is the choice of the sponsor. In the area of pediatrics, FDA has “tentatively concluded that 100,000 or more prescriptions or uses per year in all pediatric age groups would be considered a substantial number.” In many disease states there is the possibility that a prescription may have one or more refills within a year’s time. For example, a patient using an asthma drug may receive several prescriptions during the course of the year. Because the FDA used data that is several steps removed from the number of patients using the drug per year, the FDA’s proposal may be based on inflated estimates for its suggested number of 100,000 prescriptions per year. This means that the population deemed to constitute “substantial use,” and for which studies and labeling will be mandatory by regulation, is less than half of that in which the sponsor might seek orphan drug status for elective development. Even though the total universe of children in the US is smaller than the universe of people in the US, it makes no sense

to use a smaller group for purposes of mandatory pediatric testing than is used for application of the incentives for orphan drug development.

As an alternative to regulating the process through specific numbers and rigid criteria, PhRMA urges the Agency to work collaboratively with the American Academy of Pediatrics Committee on Drugs to delineate when clinical testing in pediatric patients is needed, and with the product sponsor on how these goals will be best achieved.

**“...comment on these methods of assessing expected pediatric exposure and on the specific numerical threshold suggested.” (pg. 43905)**

See comments immediately above.

**“...comment on whether it (FDA) should codify its authority to require the manufacturers of marketed drugs to conduct pediatric studies, and if so, the circumstances under which the agency should exercise that authority.” (pg. 43905)**

PhRMA believes that the FDA cannot codify its authority to require pediatric studies, because, as discussed in the general comments, the Agency lacks such authority. The evidence is that the FDA, through its recent increased emphasis on pediatric studies, has already stimulated a significant increase in the number of pediatric pharmaceutical development programs planned and in progress within the pharmaceutical industry. Furthermore, the FDA already has at its disposal adequate means to encourage sponsors to initiate a pediatric development program, when one is indicated.

**“... comment on the proposed grounds for waiving the pediatric study requirement for already marketed drugs and biological products and whether additional grounds may exist, such as whether cost should justify waiver of the pediatric study requirement.” (pg. 43905)**

Physicians caring for children use relatively few of the hundreds of drugs and biologics currently marketed. The FDA should appoint an Advisory Committee, including representatives of the Academy of Pediatrics Committee on Drugs, to identify those marketed products that require additional pediatric information and should then engage the Pediatric Pharmacology Research Units sponsored by the National Institutes of Child Health and Development to develop the required information. Under this approach, a waiver for all other products would not be necessary.

There is no incentive for the originating sponsor of a marketed product whose patent life is limited or gone to expend resources on additional studies. For drugs near the end of their patent life, patent extension, as in the case of orphan drugs, might be an alternate approach that provides an incentive for sponsors to do the requisite studies. If the Agency were interested in exploring such an incentive, PhRMA would be happy to

meet with the Agency to consider legislative options, recognizing that the FDA does not have the delegated authority to grant patent extensions.

As previously noted, the FDA should not place itself in the position of having to make cost decisions to grant a waiver.

**“...defining the term “very significant illness.” (pg. 43906)**

There is no satisfactory definition of the term “very significant illness,” from either a personal or a regulatory perspective. It could conceivably be defined by number of patients, by number of prescriptions, by length of illness, by potential threat to life, by rate of increase of the disease in the general population, or some combination of these and other factors. Ultimately, no definition will be completely satisfactory and dialogue with the product sponsor, rather than definition of the term, will be a more productive approach.

**D. Studies in Different Pediatric Age Groups (pg. 43906)**

**“...comment on the issues raised by requiring studies in this age group (neonates and young infants).” (pg. 43906)**

The Agency must realize that the vast majority of drug use in the premature and the neonate populations is for disease processes not easily extrapolated from the adult indication, or even from the disease as it exists in older children. Very little neonatal use of drugs will fit within this Proposed Rule. If the goal is to include use information for these very young infants and neonates in product labeling, other approaches need to be developed.

Age ranges for PK studies should be based on the application of knowledge of the ontogeny of clearance pathways for the drug, not on arbitrary age categories. Understanding of specific pathways of clearance from *in vitro* drug metabolism studies and studies in adults should be applied to planning PK studies in children. For PD or clinical trials, validated end-points and the ability to assess these by age should be determinant of how studies are done, rather than by applying arbitrary age definitions. Measures like blood pressure may be easier to assess across ages than measures requiring patient participation, such as FEV1. The 1994 rule may be helpful because it allows extrapolation of effectiveness data from older children, along with PK data, across pediatric age ranges where effectiveness may be more difficult to assess in younger children.

PhRMA is opposed to the exposure of infants and young children to new chemical entities (NCEs), for the same indication as for adults, before adult dose selection, safety and effectiveness data enable the manufacturer to make a go/no-go decision for the

development of the product. Only in the circumstance where the drug is specifically targeted to a pediatric indication (such as surfactant in the newborn), or where the condition being treated is devastating or life threatening and no other therapy exists, would exposure of pediatric patients to a new drug, in the absence of adult dose selection and a well-advanced adult development program, be warranted. To do otherwise would unnecessarily expose children to a drug with a relatively high chance of being without benefit to them, or to society as a whole.

**E. Pediatric Formulations (pg. 43906)**

**“...comment on whether it is appropriate to require a manufacturer to develop a pediatric formulation and, if so, the circumstances in which it would be appropriate to impose such a requirement.” (pg. 43906)**

Under the American economic system, the government does not determine what products a manufacturer must produce and market, and for whom they must be marketed. Therefore, the FDA does not have the authority to require a manufacturer to market a product for pediatric use. If the Agency were to successfully demonstrate that a significant public health problem exists and that all attempts to develop a voluntary solution have failed, then the Agency and other public health agencies could consider options that might be available. To date, however, such a situation has not occurred. Take the AIDS crisis, for example. Members of the pharmaceutical industry have been active since the early days in research and development of drug products. Research on the use of a drug in adults was essential to the development of a drug to prevent the transmission of the virus from mother to fetus, thereby drastically curtailing the incidence of pediatric AIDS cases. In addition, companies have been working to develop pediatric formulations of products approved for adult use. Several of those formulations (e.g., Retrovir, Epivir, Videx, and Ritonavir) have already been approved by the FDA.

As previously stated, a flexible FDA approach with ongoing interaction on pediatric issues between sponsor and Agency, and appropriate incentives, will gain requisite pediatric dosing information more rapidly and more successfully than will rigid regulation.

**“...comment on the appropriate design and methodology of such measurement” (benefit of the final rule). (pg. 43906)**

**“(1) Quantify the societal costs...” (pg. 43906)**

**“...(2) assess the proportion of these costs that would be eliminated by the new information that would result from the rule.” (pg. 43906)**

A cost/benefit analysis is an appropriate approach in assessing the value of a new therapy, a new health care program, or a new Proposed Rule. In the pharmaceutical industry, however, and in the health care field in general, the cost/benefit analysis is

performed before the new intervention is tried. PhRMA strongly urges FDA to answer these questions before the Agency considers proceeding with this Proposed Rule.

The FDA should consider the costs to patients waiting for new life-saving medicines if finite company research resources are diverted from the search for new therapies to conducting pediatric clinical trials for limited, and possibly inappropriate, uses of existing products.

Pediatric patients participating in some of that research would inappropriately be exposed to the risks of drug trials when manufacturers make the decision that the clinical trial data do not support submission of a New Drug Application, or the FDA makes the decision that the data submitted in the New Drug Application do not support approval for marketing. In addition, the time and attention of medical personnel involved in pediatric clinical trials would be diverted from trials involving drugs already on the market, or for which there is agreement that the drug will be approved for marketing. In such circumstances, the manufacturer's drug development resources would have been diverted unnecessarily.

PhRMA also notes that an additional societal cost, seldom noted in FDA calculations, is the increase in Agency staff resources to review the inevitable requests for waiver and deferral, as well as the data and the associated submissions in support of pediatric labeling of both new and already-approved products, and the associated potential for delay in review of New Drug Applications for uses in adults. Some portion of the FDA's resources would be diverted from review of pediatric supplements to the review of waiver requests. Even if the resources were diverted from something other than the review of pediatric supplements, implementing a mandatory rule and then developing a waiver program represents a misallocation of the Agency's resources.

In addition, part of the cost/benefit assessment must include the cost to industry of complying with the Proposed Rule. In the *Federal Register* notice, the FDA has grossly underestimated these costs, as noted in PhRMA's response to OMB on this issue, which is attached to this submission. Also included as part of the cost to industry, but which is not included in the PhRMA comments to OMB, is the cost of potential liability resulting from pediatric clinical trials, especially trials involving compounds that are not subsequently approved for marketing to adults. While there have not, to date, been many claims against manufacturers from participants in clinical trials, the FDA's proposed mandate for pediatric clinical trials early in drug development can be anticipated to increase the number of claims.

**F. Ethical Issues (pg. 43906)**

**"...ethical issues raised by this proposal." (pg. 43907)**

The American Academy of Pediatrics Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations addresses quite well the major concerns surrounding pediatric clinical trials. As previously stated, introduction of NCEs to children, without substantial safety and effectiveness data in adults, is in many instances not ethical and may preclude the possibility of manufacturers conducting the simultaneous drug development programs set forth in the Proposed Rule.

#### **G. Remedies (pg. 43907)**

**“...comment on appropriate remedies for failure to conduct a required pediatric study and the circumstances, if any, in which the agency should deny or withdraw approval of a drug product.” (pg. 43907)**

PhRMA agrees with the FDA proposal to require sponsors to file information pertinent to pediatric studies and pediatric labeling changes in the annual report. Accumulation of this information, along with an adequate tracking system within the FDA to follow the progress of pediatric studies and labeling claims, could preclude the need to finalize this Proposed Rule.

In reality, as the Agency noted in the *Federal Register* notice, FDA currently has adequate authority to take action against approved products as “misbranded” if the Agency genuinely believes that lack of pediatric information in the label misbrands the product. PhRMA disagrees, however, that the absence of pediatric use information causes a drug product to be misbranded.

#### **VII. Implementation Plan (pg. 43908)**

**“...comment on the proposed effective date and proposed compliance date.” (pg. 43909)**

Pending NDAs should be granted a full waiver and should be treated as marketed products under the Proposed Rule. When the Agency proposes a compliance date of 15 months for new product applications submitted on or after the effective date of the Final Rule, the FDA needs to clearly state what constitutes “compliance.” If compliance is the initiation of discussion with FDA concerning the sponsor’s proposed pediatric plan, 15 months is adequate. If compliance means completion of the pediatric studies, 15 months will usually be inadequate. If compliance means completion of pediatric studies and completion of the Agency’s review of the supplemental application, 15 months will almost always be inadequate. The special difficulties of pediatric clinical trials militate against any regulation designed to force manufacturers to conduct and analyze such studies under arbitrary time deadlines. It is certainly not in the interest of children that manufacturers rush through clinical studies involving children to meet an arbitrary deadline established by the regulatory agency that purports to be protecting children.

## **X. Analysis of Impacts (pg. 43909)**

### **C. Cost of Studies (pg. 43911)**

**“...comment on the estimate that four new formulations would be required per year.” (pg. 43911)**

The estimate that only four drugs per year will require new formulations is difficult to understand. The FDA example at 43911 focuses on 14 new drugs per year with some potential pediatric use that were available only in tablet or capsule form at the time of approval. Manufacturers of 4 of these 14 new drugs have since developed suspensions and FDA concludes that, “It seems reasonable, therefore, to assume that, of the 14 new drugs per year estimated to require additional pediatric research, about 4 might require new formulations.” The Agency’s assumption implies that the other 10 drugs will not require reformulation but can be studied in children in tablet or capsule form. This seems highly unlikely.

The study of drugs and biologics in children normally requires pediatric formulations, and often more than one formulation. Some companies have spent millions of dollars in the pursuit of a single pediatric formulation and some have given up the pursuit after multiple efforts to develop a pediatric formulation have failed. As Dr. Clemente noted in his statement to the October 27 FDA-AAP public hearing, the task of developing a new formulation is time-consuming, expensive, often frustrating, and may require unique skills and knowledge. The FDA estimate of four new formulations per year reflects a misunderstanding of either the reasons for the need for pediatric formulations or the problems involved in pediatric formulation work.

### **D. Other Impacts (pg. 43912)**

**“...comment on the best means to obtain adequate and timely pediatric information without slowing the process for bringing new drugs to market.” (pg. 43912)**

The best means to obtain adequate and timely pediatric information without slowing the process for bringing new drugs to market is to:

1. Work closely with the sponsor from the start of the drug or biologic development process to ascertain (1) if there is a reasonable expectation that this product will have extensive use among children, (2) what type of pediatric study program will be needed, and (3) how and when the pediatric formulations and studies and resultant labeling will be accomplished.

2. Be flexible in crafting a pediatric study program that recognizes the unique aspects of the drug or biologic and the pediatric age continuum.
3. Monitor the study program's progress and inform sponsors if progress is lagging.
4. Stimulate sponsors to comply through tangible incentives that help off-set the considerable expense of pediatric testing, e.g., expedited review of the adult NDA, patent extension, market exclusivity, and relief from user fees.

### Summary

In evaluating the Proposed Rule, PhRMA urges the FDA to consider carefully the following:

- The FDA's emphasis on pediatrics, resulting from the December 1994 rule and from the Agency's current practice, has, in fact, successfully increased the industry's drug and biologic development for children. The Proposed Rule is unnecessary.
- A flexible Agency approach, combined with newly-enacted market exclusivity and other incentives, will best achieve the goal of improving the information available to those who care for children.
- PhRMA urges the FDA to retain the principle of graduated risk, which requires that manufacturers not expose pediatric patients to clinical trial risks, for drugs to be used in adults, until adequate information has been developed about safety in adults.
- The timing of pediatric studies must not be mandated but, as with the provision just passed by Congress, developed cooperatively between the sponsor and the FDA. Timing will depend on multiple factors, including the nature of the disease in adults and children, its seriousness, the availability and effectiveness of other treatment options, and the difficulties in developing a pediatric formulation and designing pediatric clinical trials.
- The proposal to force a sponsor to study drug usage in populations as small as 100,000 prescription uses sets a dangerous precedent potentially damaging to the public health by diverting significant research resources away from drug research that is more beneficial to the general public.
- Pediatric studies and pediatric formulations may be, and often are, technologically difficult, time consuming and expensive. The FDA cost estimates are grossly inadequate and misleading. PhRMA urges the FDA to consider carefully the conclusions of the formulation workshop scheduled for 1998 to address problems associated with pediatric formulations of medical compounds.

- Any FDA actions involving pediatric labeling, including a Final Rule if the Agency decides to proceed with one, should be harmonized with pediatric study requirements internationally and allow for the continued increase of sponsors' voluntary pediatric programs.
- The Agency should accept the unanimous recommendation of speakers at the October 27 FDA-AAP hearing of the pediatric labeling Proposed Rule and convene an advisory group of parents, the American Academy of Pediatricians, the Pediatric Pharmacology Research Units funded by the National Institutes of Child Health and Development, the pharmaceutical industry, and the FDA to identify the specific diseases for which pediatric medicines are especially needed and those already-approved drugs for which pediatric studies are needed. PhRMA offers to assist the FDA in any way we can to convene such a meeting as soon as possible.
- PhRMA doubts that the FDA has the legal authority to mandate that sponsors conduct clinical trials or seek approval of labeling for indications or population subgroups beyond those proposed by the sponsor in the New Drug Application.

\* \* \* \* \*

PhRMA appreciates the opportunity to comment on this important Proposed Rule and is eager to work with the Agency toward the goal of improved health for all citizens, children and adults.

Enclosure

John D. Siegfried, M.D., PhRMA letter to OMB, dated  
September 15, 1997

John D. Siegfried, M.D.  
DEPUTY VICE PRESIDENT  
REGULATORY AND SCIENTIFIC AFFAIRS



September 15, 1997

Office of Information and Regulatory Affairs  
OMB  
New Executive Office Bldg.  
725 17<sup>th</sup> Street, N.W., Room 10235  
Washington, D.C. 20503  
Attn: Desk Officer for FDA

RE: FDA Proposed Rule "Requiring Manufacturers to Assess Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients," 62 *Fed. Reg.* 43900 (August 15, 1997).

Dear OMB Desk Officer for FDA:

The Food and Drug Administration (FDA) has published a proposed rule that would require manufacturers to conduct, and report to the FDA, studies of the safety and effectiveness of drugs in pediatric populations. 62 *Fed. Reg.* 43900 (August 15, 1997). In that proposed rule, the FDA sets forth its estimates of the annual burden of the reporting requirements on manufacturers. *Id.* at 43909. The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to submit these comments on the FDA's estimates of the reporting burden that would be imposed by this rule, if it were promulgated as proposed.

These comments relate to the FDA's estimates of the annual reporting burden, as required by the Paperwork Reduction Act of 1995. PhRMA will provide comments on the substance of the FDA's proposed rule to the FDA within the 90-day comment period that the FDA has provided.

While the 30-day comment period to OMB has not provided sufficient time for PhRMA to conduct more than a very cursory survey of its member companies, PhRMA has obtained from some members estimates of the time that would be required to complete the annual reports proposed by the FDA.

The FDA has underestimated the time required to comply with the annual reporting requirements. This underestimation of the reporting time affects the Agency's estimate of both the burden on manufacturers to submit reports and the burden on the Agency to review and evaluate the information to be submitted. PhRMA urges the OMB to direct the FDA, first, to prepare a more accurate estimate of the reporting burden and, second, to review the level of resources that the Agency would be required to allocate to reviewing and making use of the information that would be submitted if this proposed rule were to be promulgated as a final rule.

*Pharmaceutical Research and Manufacturers of America*

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One specific estimate may illustrate the FDA's underestimation of the annual burden. The FDA proposes, in § 314.50(d)(7), that each manufacturer submit, as part of a New Drug Application, an "integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations," with references to the full descriptions of such studies. The FDA estimates that, each year, 150 manufacturers would submit such an integrated summary and that it would require 8 hours for a single company to compile the summary information. Thus, the annual reporting burden, according to the FDA, would require 1,200 hours.

The FDA assumes that only brief summaries will be needed because full descriptions of clinical studies conducted by or for the manufacturer will already have been submitted in the New Drug Application (as required by § 314.50(d)(3)) and that all other relevant information, i.e., information from one or more searches of the published literature, will have been submitted in the New Drug Application (as required by § 314.50(d)(5)). However, as the manufacturer prepares the New Drug Application, specifically the section on possible pediatric use for the drug, if the manufacturer has not conducted clinical studies, the manufacturer will have to review and summarize all independently-conducted clinical studies published in the medical literature. To follow the letter as well as the spirit of the FDA proposed pediatric rule, all of those studies would have to be read, evaluated, summarized, and reported, at least for the first such annual report following the effective date of the rule.

One company estimates that, to date for one pediatric reporting project, medical staff have spent at least 118 hours reviewing the medical literature and summarizing the findings. This represents a 150 percent increase over the FDA's estimate of time required to complete this reporting task. In other words, the FDA's estimate of 1,200 hours should be increased to approximately 18,000 hours. In addition, the company used a contract research firm to find, sort, read, evaluate and summarize the findings from a thorough literature search. If the time burden of the contracted work were added, the burden could be increased at least ten-fold from the FDA's estimate.

The FDA's estimate for the annual reporting burden for other reporting obligations are equally unrealistic. For example, the FDA proposes that manufacturers submitting New Drug Applications for new molecular entities submit "data ... adequate to assess the safety and effectiveness of the drug product for the claimed indications in pediatric populations." Proposed § 314.50(g)(1). The FDA estimates that 10 companies per year would be submitting New Drug Applications for new molecular entities. This is another underestimation, even if this number is combined with the FDA's estimate of the number of manufacturers requesting deferral of the submission of pediatric safety and effectiveness data, proposed § 314.50(g)(2), discussed below. The number of New Drug Applications for new molecular entities has increased for each of

the past three years, from 22 in 1994, 28 in 1995, to 53 in 1996. Only if the FDA uses the lowest number in the 1990s, 22, would its estimate of 19 companies submitting pediatric use data or requesting deferral of submission of such data be reasonable. Likewise, the FDA has estimated that a single manufacturer would require 16 hours to prepare the report of the data supporting the safety and effectiveness of the drug for that indication for the pediatric population. But clinical study data, or data from published literature, can't be summarized quickly. Two working days for one staff member may be sufficient for an FDA reviewer to review the summary of the pediatric data; it is not sufficient time to create the summary.

The FDA has proposed that manufacturers submitting New Drug Applications could, under some circumstances, request that they be allowed to "defer submission of some or all assessments of safety and effectiveness ... until after approval of the drug product for use in adults." Proposed § 314.50(g)(2). The FDA estimates that 9 manufacturers submitting New Drug Applications in any single year will request a deferral of the submission of pediatric study data, and that it will take each manufacturer 8 hours to complete the submission requesting the deferral. Again, this may be an unrealistic estimate of the number of manufacturers submitting New Drug Applications who will need, for any of several reasons, to request deferral of the submission of pediatric data. Likewise, the estimate that a manufacturer could prepare a request for a deferral within 8 hours is completely unrealistic. For manufacturers that have encountered difficulties in developing an acceptable pediatric formulation, the task of describing the problems encountered in the formulation effort could, by itself, take more than one staff working day.

The FDA's estimates also include annual post-approval reporting, and the Agency has substantially underestimated the reporting burden. For example, in § 314.81(b)(2)(i), the FDA proposes to require companies marketing approved drugs for which pediatric data have not been submitted to the FDA to file pediatric information annually for each such drug. The annual report would include information about "whether new studies in the pediatric population ... have been initiated" and "an estimate of patient exposure to the drug product, with special reference to the pediatric population." The FDA estimates that 650 such reports would be required annually. It is hard to determine whether that number represents the number of manufacturers who would be required to file such reports (assuming reports would be required of both innovator and generic companies) or the number of drugs for which such reports would be required. If the estimate is for the number of drugs, it might be realistic; PhRMA reports that the FDA has approved for marketing approximately 290 new molecular entities in the past 11 years. Once again, however, the FDA's estimate of the number of staff hours, 1.5, to prepare such a report is unrealistic. Just the collection of information about the extent of use of the drug product would require more than 1.5 hours. While a manufacturer would have information about the number of units of a drug shipped to wholesalers, the manufacturer would not routinely have information

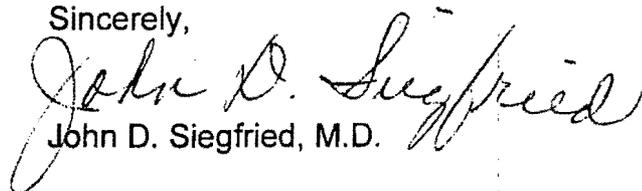
about how many of those units were dispensed for pediatric use. Thus, the manufacturer would have to consult one or more other sources to compile that information for reporting to the FDA.

The FDA has also underestimated the time required for the annual reporting of the "analysis of available safety and efficacy data conducted or obtained ... in the pediatric population and changes proposed in the label based on this information." § 314.81(c). The Agency has estimated that 650 respondents would spend 1.5 hours each year preparing such reports. While, as noted above, the number of respondents might be accurate, the time estimate is very low. It is completely unrealistic for an agency with any claim to scientific expertise to estimate that a staff member could summarize the results of safety and effectiveness studies in a pediatric population in 1.5 hours, let alone report proposed labeling changes based on the summarized information within the same 1.5 hours. Even multiplying the FDA's time estimate by 10 results in an unreasonably low time estimate of 15 hours.

Because the FDA has both underestimated the number of manufacturers that would be required to submit reports in any year under the proposed rule and underestimated the time required to prepare such reports, the FDA's estimates of the annual reporting burden that would be imposed by the proposed rule are substantially underestimated. PhRMA urges the OMB to return the proposed rule to the FDA with a request that the FDA provide a more realistic estimate of the annual reporting burden.

The Pharmaceutical Research and Manufacturers of America represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, happier, healthier and more productive lives. Investing nearly \$19 billion a year in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

Sincerely,

  
John D. Siegfried, M.D.