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001f. photograph	re: Whitney (1 page)	n.d.	b(6)
001g. letter	Constituent to Members of the Drug Advisory Committee re: personal AID's story (1 page)	11/12/1996	b(6)
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American Academy of Pediatrics

Testimony By

THE AMERICAN ACADEMY OF PEDIATRICS

Before the

Subcommittee on Human Resources and Intergovernmental Relations
Government Reform and Oversight Committee
U.S. House of Representatives

"Off-Label Drug Use and FDA Review of Supplemental Drug Applications"

September 12, 1996

Department of Government Liaison
The Homer Building
601 Thirteenth Street, N.W.
Suite 400 North
Washington, D.C. 20005
202-347-8600 / 800-336-5475 / FAX: 202-393-6137

Good Morning. I am Ralph Kauffman, MD, Professor of Pediatrics and Pharmacology at the University of Missouri, Kansas City and Director of Medical Research at the Children's Mercy Hospital in Kansas City, Missouri. I am pleased to be here this morning on behalf of the American Academy of Pediatrics, an organization representing 50,000 pediatricians dedicated to the health, safety, and well-being of infants, children, adolescents, and young adults. I spent 16 years as either a member of or consultant to the American Academy of Pediatrics Committee on Drugs, including four years as Chairman. I should also add that I currently serve as a member of the Pediatric Advisory Committee of the US Pharmacopoeia. I have devoted virtually my entire professional career to the development of medications for the safe and effective treatment of diseases affecting infants and children.

A critical issue and a high priority of pediatricians for the past 30 years has been the approval and labeling of medications for use by infants, children and adolescents. It is shocking to note that few drugs -- only approximately 20 percent of all drugs marketed in the United States -- have been labeled for use by infants and children. Eighty percent or more of drugs approved since 1962 have been approved and labeled for use in adults with a disclaimer in the labeling that they are not approved for use by children.

Approval of a drug for human use requires proof of efficacy and safety for its specific intended use in human beings established by well controlled clinical trials. Once approved for specific indications, the drug is labeled for interstate commerce. The labeling contains the approved prescribing information including indications, contraindications, precautions, warnings, adverse reactions, and dosage recommendations.

The Kefauver-Harris amendments to the Food and Drug Act passed in 1962 require that drugs be demonstrated by well-controlled studies to be effective for their intended uses as well as safe. While this provision has been applied to approval of drugs for use by adult patients it has not been extended to use by infants and children in the labeling of a majority of drugs. This is particularly ironic since several key Food and Drug statutes were passed in the aftermath of therapeutic catastrophes involving children. The tragic deaths of 107 children from ingestion of elixir of sulfanilamide brought about the passage of the Federal Food, Drug and Cosmetic Act of 1938, and later the tragic malformations of infants caused by maternal use of thalidomide during pregnancy led to the 1962 Kefauver amendments to the Act.

Lack of pediatric labeling does not mean that the drugs are necessarily harmful, ineffective, or contraindicated in children but simply that the clinical trials which satisfy the FDA requirements for labeling were not conducted in children. Because of this, children have not shared in therapeutic advances to the extent adult patients have nor have they been provided the same protections afforded adult patients under the 1962 Kefauver-Harris amendments to the Food and Drug statutes. Though there has been modest progress in the labeling of marketed drugs for pediatric use, it remains sporadic and incompletely addressed.

Many reasons have been advanced for not studying and labeling drugs for use by children and adolescents, but the leading issues are regulatory impediments, economic disincentives, and

reluctance on the part of the FDA to make studies in children a requirement for a new drug unless the primary use of the drug will be in children. With the exception of antibiotics, medications for fever, vaccines, and a few other therapeutic categories, pediatric use represents a relatively small segment of the total market for a drug. Companies frequently are reluctant to expend the additional time and resources to do pediatric studies with little promise of additional market potential.

CHILDREN ARE NOT SIMPLY SMALL ADULTS

It is important to understand why drugs must be studied in children to establish their safe and effective use in children. In other words, why can't studies in adults provide sufficient information for use of a drug in children? No animal model or study in adults adequately predicts the effect of drugs on children of various ages and stages of development. The dynamics of growth and maturation of various organs, the changes in metabolism throughout infancy and childhood, changes in body proportions, and other developmental changes result in significant differences between children and adults. As a result, the elimination of drugs from a child's system, the dosage required and the safety and effectiveness of a pharmacologic agent need to be studied at critical developmental stages in the pediatric population.

Even within the pediatric population there is great diversity. There may be a need to study the same drug in several pediatric groups (i.e., neonates, infants, young children and adolescents) in order to determine drug efficacy, dosing, toxicity, and appropriate formulations for each subpopulation.

OFF-LABEL USES OF DRUGS IN CHILDREN AND ADOLESCENTS

An off-label use, also known as an "unapproved" use of an approved drug, refers to a use that is not included or that is disclaimed in the approved labeling. It is important to emphasize that "unapproved use" or "off-label" use does not imply an improper or illegal use. Indeed, this off-label use may represent the only, or best, treatment available for a specific illness in a child.

As mentioned, only a minority of currently marketed drugs have undergone pediatric clinical trials and have approved labeling for use in children. These include common antimicrobial agents, medications for fever, vaccines and some asthma and allergy medications. However, most drugs used to treat illnesses in children have never been formally tested or approved for pediatric use and lack even basic dosage recommendations for children in their labeling. These include such routinely used medications as dopamine (used to treat shock), cisapride (used to treat abnormal regurgitation of stomach contents in infants and small children), ketorolac (the only available injectable non-narcotic pain reliever), midazolam (used as a sedative and to treat convulsions), and adenosine (used to treat life threatening abnormal heart beats).and the list is much longer.

Lack of studies to support labeling of the majority of drugs for use by children places the physician caring for children in the untenable position of either prescribing without adequate labeling or denying pediatric patients access to important therapeutic agents. When confronted with this dilemma the physician invariably elects to prescribe a medication without adequate pediatric labeling. As a result, off-label use of medications has, by default, become an established standard of care for children. From the patient's perspective, infants and children frequently are exposed to

medications without the benefit of adequate studies to document safety and efficacy or establish doses appropriate for their age.

A related problem is that medications not approved for use by children are not manufactured in dosage forms which can be readily administered to children. For example, many medications are provided in capsule or tablet forms which cannot be swallowed by small children and are not available in small enough dosage increments to give the proper dose to children.

CHILDREN REMAIN THERAPEUTIC ORPHANS

In a 1994 hearing before the House Subcommittee on Health and the Environment, Sumner J. Yaffe, M.D., Director of the Center for Research for Mothers and Children at the National Institutes of Health, reported that only approximately 20 percent of all drugs marketed in the United States have had clinical trials performed in children which satisfy the FDA requirements for being labeled as safe and effective for use in infants and children. He further reported, "The FDA has suggested that of the 80 drugs most frequently used to treat newborns and infants in U.S. hospitals, only five are labeled for use by children. This does not imply that 80 percent of our drugs are contraindicated, unsafe, or disapproved for use in infants and children. Rather, it means that necessary testing has not been done to produce the data that would enable the Food and Drug Administration to grant approval status for specific clinical indications and uses in pediatric populations[1]."

Drugs which need to be labeled for pediatric use may be divided into 3 categories based on their position in the approval process and market place: 1) new drugs in clinical trials, not yet approved for general marketing; 2)drugs approved for adult use but not labeled for children and still under patent protection; and 3) drugs labeled for adult but not pediatric use which are off-patent and may be marketed as generic products by multiple companies. There is at least some potential economic incentive to include pediatric clinical trials in the premarketing development of new drugs. However, once a drug is marketed for an adult indication, the economic incentive to do additional studies to include pediatric labeling is markedly reduced because the drug may be prescribed off label. In the case of drugs which are off patent, there is absolutely no economic incentive to invest in studies to expand labeling because a single sponsor can no longer benefit from such an investment due to lack of exclusivity protection of the drug.

An examination of new molecular entities, which represent the most innovative new medications, approved by the FDA from 1984 through 1995 showed that approximately 80% of these medications were approved without labeling for children, although many of them are widely used to treat illness in children. An AAP survey of the 28 new drugs approved by the FDA in 1995, indicated that only four have pediatric labeling. The sponsors of 10 have indicated pediatric studies are in progress or will done in the future, and sponsors of the remaining 14 drugs have indicated studies are not needed, since it is not likely that those drugs will be used in children. However, several of these 14 drugs undoubtedly will be used in children. For example, the sponsor of dirithromycin, a new macrolide

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[1]Statement by Summer Y. Jaffe, MD, Director, Center for Research for Mothers and Children, National Institute of Child Health and Human Development, National Institute of Health, before the Subcommittee on Health and the Environment, House Committee on Energy and Commerce. February 8, 1994.

antibiotic approved in 1995, has indicated a pediatric study is not needed or planned although it is highly likely this antibiotic will be used by physicians to treat infections in children as well as adults.

LACK OF LABELING FOR USE OF DRUGS DURING PREGNANCY AND LACTATION

Two other disenfranchised populations of patients with respect to drug labeling are women who are pregnant and those who are breast feeding their infants. Pregnant and lactating women are routinely excluded from clinical trials of new drugs. Consequently, the labeling for very few drugs includes definitive information on or an assessment of risks associated with maternal use of the drug. This impacts the health of children because of the unknown risk to the unborn child and the unknown effects on the nursing child when the mother uses medication.

FDA EFFORTS AT PEDIATRIC LABELING

In 1979 FDA published regulations pertaining to the specific content and format of prescription drug labeling that stipulate that pediatric labeling be based on adequate, well-controlled studies involving children. The intention of these regulations was to encourage drug labeling that would regularly provide adequate information about the use of drugs in children. However, the result was not more adequately labeled drugs; rather labels simply state that the drug's safety and effectiveness in children have not been established. Eighty percent of the prescription drugs currently marketed in the United States are labeled with such disclaimers.

In an attempt to remedy this situation the FDA published regulations on December 13, 1994, aimed at increasing pediatric information in drug labeling and facilitating addition of pediatric indications to drug labeling. The 1994 regulations recognize several methods of establishing substantial evidence to support pediatric labeling claims. These include 1) allowing inclusion of published pediatric information in the labeling and 2) approval of pediatric use based on adult efficacy studies where the disease for which the drug is to be used is substantially the same in children and adults thereby allowing pediatric studies to focus on dosing and safety data for children. The regulations respond to concerns that current prescription drug labeling too often does not contain adequate information about the uses of drugs in children and are meant to provide the physician with more complete and useful information when prescribing for children. Though the new regulations have been in effect for almost two years, it is not yet apparent that they have resulted in any increase in new drug labeling for children.

RECOMMENDATIONS:

While we commend the efforts of the FDA at internally reforming the agency, we are concerned that the regulations of December, 1994 meant to encourage the inclusion of pediatric data in FDA-approved labeling, have failed to achieve their goal. The American Academy of Pediatrics believes additional steps must be taken to augment the FDA initiatives and supports the following measures to overcome some of the principal obstacles to labeling medications for children:

- AAP recommends that Congress provide the FDA with specific statutory authority and responsibility to make studies in appropriate pediatric populations a requirement during clinical trials of each newdrug with potential use by children, unless it is determined by a panel of experts in pediatric medicine that there will be no use of that drug in children and/or adolescents.

- The Congress should establish an independent panel of experts in pediatric medicine, composed of experts from the American Academy of Pediatrics, the Pediatric Pharmacology Research Unit Network, U.S. Pharmacopoeia, as well as other experts in pediatric research with authority to:

  - advise FDA which new drugs would have pediatric applications and the types of studies required in specific pediatric populations;

  - determine the need for studies of specific marketed drugs in the pediatric population;

  - advise the FDA on the approvability of specific NDA's;

- FDA should establish age definitions for children to be used for regulatory purposes as the standard throughout the Agency. The AAP recommends the following age breakdown:

  - child means a neonate, infant, young child, or adolescent;

  - neonate means a child from birth to the age of one month (30 days);

  - infant means a child from the age of one month to the age of two years;

  - young child means a child from the age of two years to the age of twelve years;

  - adolescent means a child front the age of twelve to the age of eighteen years.

- The FDA should, in consultation with the independent panel of experts in pediatric medicine, develop, prioritize and publish from the compendium of already approved and patented drugs, an initial list of drugs for which pediatric labeling is necessary.

- The FDA should be authorized, in consultation with the independent panel of experts in pediatric medicine, to identify, prioritize, and publish a list of off-patent drugs for which

pediatric labeling is necessary and be authorized to fund studies required to accomplish pediatric labeling of those drugs.

- The FDA should develop guidelines for the inclusion of pregnant and/or lactating women in clinical trials of new drugs and request such studies be performed when there is a high probability the drug will be used in these populations.

- The Academy supports consideration of proposals to provide economic incentives, if necessary, to companies who conduct pediatric studies and who provide pediatric dosage formulations for new drugs as well as already approved and off-patent drugs. Consideration should be given to patent extension for companies who complete pediatric studies which lead to pediatric labeling.

The American Academy of Pediatrics is anxious to work with Members of Congress to develop the best and most far-reaching protections for infants, children, adolescents and young adults. We welcome the opportunity to continue this dialogue.

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SECTION: COMMENTARIES

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TITLE: Is the "Therapeutic Orphan" About to Be Adopted?

AUTHOR: CHARLES J. COTE, MD, Department of Anesthesia, Children's Memorial Hospital, Northwestern University Medical School, Chicago, IL 60614, RALPH E. KAUFFMAN, MD, Departments of Pediatrics and Pharmacology, Children's Mercy Hospital, Kansas City, MO 64108, GLORIA J. TROENDLE, MD, Division of Metabolic and Endocrine Drug Products, Food and Drug Administration, Rockville, MD 20857, GEORGE H. LAMBERT, MD, Department of Pediatrics, Clinical Research Center, University of Medicine and Dentistry of New Jersey, Piscataway, NJ 08855

TEXT:

In this issue of Pediatrics, the Committee on Drugs (COD) has examined the continued problem of the "unapproved" use of "approved" medications in pediatrics. [n1] This commentary will expand on the issues that have restricted drug research in children and describe current initiatives to facilitate and encourage such research to achieve the necessary drug labeling to reduce unapproved uses of medications in children.

BACKGROUND

Physicians who treat infants and children frequently prescribe medications that have never been approved by the Food and Drug Administration (FDA) for pediatric patients; unfortunately, many drugs are released without labels for pediatric use and often with pediatric disclaimers. The need for specific pediatric studies to document safety and efficacy before widespread exposure of children to a new drug has been well documented. [n2] Generally recognized examples of catastrophes arising from the lack of such studies include tetracycline-induced dental dysplasia and neonatal deaths attributed to chloramphenicol-induced "gray baby" syndrome. [n3,n4] From an ethical and moral perspective, children of all ages deserve the same proof as adults that the medications they use are safe and efficacious. However, most new medications and the vast majority of older medications have not been labeled as safe and efficacious for pediatric use, because the research that meets FDA standards for establishing their safety and efficacy in children has not been carried out. [n5]

Clinical trial data submitted to the FDA as part of a New Drug Application (NDA) form the basis for FDA approval and labeling of the drug. Phase I and II premarketing clinical trials are typically limited to adult subjects (usually men) 20 to 40 years of age, followed by phase III investigations in a larger adult population, which may include the elderly. Children are not included in the majority of premarketing clinical studies. Even when a pediatric application

of a new (or old) medication is investigated, it frequently is carried out in a limited pediatric age range, thus leaving out the majority of children. Typically, phase III is the earliest point in the clinical drug development process that the FDA requests that pediatric studies be performed.

Until recently, the FDA has not assumed a proactive stance to ask nor did it have the regulatory authority to force manufacturers to perform pediatric studies. Most new drugs have been labeled with disclaimers for pediatric use. [n6] As a result, the labeling for many important newly approved drugs and the majority of old drugs contains pediatric disclaimers (Table). Significant segments of the patient population are left without the benefit of appropriate age-specific research to document a drug's safety, efficacy, or metabolic and kinetic profiles. With the absence of FDA-approved prescribing information, the selection and dosing of these drugs is left to the discretion of the individual physician. For the vast majority of indications, even in young pediatric patients, the benefits of using many of these medications "off-label" outweigh the risks of not using them. [n7]

Drugs commonly used to treat mental or physical pain in children, (morphine, meperidine, fentanyl, midazolam, bupivacaine, and ketorolac) illustrate the problem. Morphine and meperidine are commonly prescribed opioids for postoperative analgesia. The package insert of one manufacturer of patient-controlled analgesia (PCA) opioid formulations states that for morphine, "the intravenous route via the... PCA infuser is not recommended for use in individuals younger than 12 years" (Baxter morphine sulfate injection, United States Pharmacopoeia [USP] package insert for PCA formulation, July 1994) The same manufacturer states that meperidine "administered by the intravenous route via a compatible infusion device is not recommended for use in individuals younger than 19 years" (Baxter meperidine hydrochloride injection, USP package insert for PCA formulation, July 1994). Fentanyl, because of its minimal adverse cardiovascular effects, is perhaps the opioid of choice in critically ill premature and term neonates. However, the fentanyl label states that "safety and efficacy in children under two years has not been established" (Janssen fentanyl citrate [Sublimaze] injection package insert, September 1992).

The importance of developing age-specific drug kinetic data is well recognized from many therapeutic misadventures, some of which ended in patient death ("gray baby" syndrome with chloramphenicol). [n3,n4] Despite these misadventures, potent drugs used in sick children are not adequately studied. An excellent example is fentanyl, as described above, despite the knowledge that the pharmacokinetics of fentanyl is significantly altered by age-specific activity of enzymatic metabolism and neonatal hepatic blood flow. [n8-n10]

Children also have been left out of the picture with other frequently prescribed medications, such as medications to treat asthma, seizures, psychiatric disorders, and gastrointestinal motility problems, sedatives, and others (Table). [n2,n11] One of these commonly prescribed medications not labeled for pediatric use, cisapride (Janssen cisapride [Propulsid] package insert, January 1995), has recently been described as causing potentially life-threatening bradycardia and prolonged QT interval in a 2-month-old infant. [n12] Adenosine is now the drug of choice to treat pediatric supraventricular tachycardia (S. Mithani, personal communication, Bureau of Human Prescription Drugs Health Protection Branch, Canada, 1996), but "no controlled studies have been conducted in pediatric patients" (Fujisawa adenosine [Adenocard]

intravenous package insert, May 1994). Even older vasoactive medications such as dopamine (American Regent, dopamine hydrochloride injection, August 1992) and dobutamine (Lilly dobutamine hydrochloride solution [Dobutrex] injection, November 1993) have pediatric disclaimers.

TABLE. Drugs with Widespread use in Children and Their Pediatric Disclaimers n1

Generic Name	Manufacturer's Name	Pediatric Disclaimer
Adenosine	Adenocard	No controlled studies have been conducted in pediatric patients (Fujisawa, package insert, May 1994)
Albuterol	Ventolin	Safety and effectiveness have not been established in children <12 y of age for Ventolin inhalation solution and Ventolin nebules inhalation solution; in children <4 y for Ventolin inhalation aerosol and Ventolin Rotacaps for inhalation; and children <2 y for Ventolin syrup (Glaxo, package insert, March 1995)
Bupivacaine hydrochloride	Sensorcaine	Not recommended in children <12 y due to limited experience in controlled clinical trials (Astra, package insert, February 1995)
Cisapride	Propulsid	Safety and effectiveness in children have not been established (Janssen, package insert, January 1995)
Meperidine hydrochloride injection (PCA)	Demerol (PCA)	Not recommended for use in individuals younger than 19 y (Baxter, package insert, July 1994)
Dobutamine	Dobutrex solution	Safety and effectiveness in children have not been established (Lilly, package insert, November 1993)
Dopamine	Dopamine hydrochloride injection	Safety and effectiveness in children have not been established (American Regent, package insert, August 1992)

Fentanyl citrate	Sublimaze	Safety and efficacy of Sublimaze in children under 2 y has not been established (Janssen, package insert, September 1992)
Flumazenil	Romazicon	Not recommended for use in children, as no clinical studies have been performed to determine risks, benefits, and dosages to be used (Hoffmann-La Roche, package insert, October 1994)
Fluoxetine hydrochloride	Prozac	Safety and effectiveness in children have not been established (Lilly, package insert, March 1995)
Gabapentin	Neurontin	Safety and effectiveness in children below the age of 12 y have not been established (Parke-Davis, package insert, December 1994)
Ketorolac tromethamine	Toradol	Safety and efficacy in children (<16 y) have not been established; therefore, use of Toradol in children is not recommended (Syntex, package insert, March 1995)
Mexiletine hydrochloride	Mexitil	Safety and effectiveness in children have not been established (Boehringer Ingelheim, package insert, October 1993)
Morphine (PCA)	Morphine sulfate injection (PCA)	Not recommended for use in individuals <12 y Baxter, package insert, April 1994)
Midazolam hydrochloride	Versed	Safety and effectiveness of Versed in children below the age of 18 y have not been established (Roche, package insert, June 1994)
Nicardipine hydrochloride	Cardene	Safety and efficacy in children <18 y have not been established (Syntex, package insert, September 1993)
Terbutaline sulfate	Brethine	Brethine is not recommended for patients under

	the age of 12 y because of insufficient clinical data to establish safety and effectiveness (Ciba-Geigy, package insert, August 1992)

n1 This table is not meant to be an all inclusive list, nor is any drug or manufacturer meant to be singled out. Data were abstracted from package inserts. Some manufacturers may have since submitted new labeling to the Food and Drug Administration.

It is a cause of deep concern that so many medications lack the developmental metabolic, pharmacokinetic, and pharmacodynamic data needed for their safe and effective use in children. Children should not be denied the benefit of these or any medications simply because of their age. The importance of developing such information cannot be overemphaszed. The use of medications inadequately studied in children has contributed to a variety of adverse outcomes, including seizures and cardiac arrest caused by bupivacaine toxicity, prolonged narcotic effects caused by altered hepatic blood flow, intermediate-acting muscle relaxants becoming long acting in neonates, benzodiazepine withdrawal, and interactions with antibiotics and other sedatives. [n7,n8-n10,n13-n19] These are but a few examples of why pediatric pharmacologic research is important. However, the funds needed to conduct such studies are difficult to obtain, particularly for older drugs, which are no longer patented. [n7,n20] Most manufacturers are not interested in financing the studies necessary to develop appropriate pediatric labeling for off-patent drugs, because they have no financial incentive to do so. Therefore, the pediatric patient is often a "therapeutic orphan." [n21] If the necessary studies are to be carried out, they likely will require funding from sources other than industry.

A recent example of the importance of pediatric studies is the new inhaled anesthetic agent desflurane. In preclinical studies and clinical adult trials, desflurane seemed ideal for pediatric application because of its gas partition coefficient and lack of metabolic degradation. However, the pharmaceutical company-supported and FDA-approved pediatric studies conducted before approval in adults found an unexpected and unacceptably high incidence of airway-related complications, particularly larynogospasm. [n22] This observation resulted in pediatric-specific labeling clearly stating that desflurane may be associated with airway-related complications. Serious injury may have resulted had the appropriate studies not been carried out in the hands of experienced pediatric clinical investigators. In this situation, the pharmaceutical company, the FDA, and the academic and medical community together fulfilled their obligations to investigate this new drug in children. Serious adverse effects in children and potential litigious losses would probably have resulted had the drug been released without proper pediatric labeling. The drug is presently recognized to be safe for use in children after induction and control of the airway.

Several factors contribute to the lack of appropriate pediatric studies: relatively small market share, fear of legal liability, potential long-term adverse effects, the reluctance of parents to give permission to allow their children to be research subjects, and the lack of adequate research funding from government, industry, and health care providers. [n20] Although legal liability is often an expressed concern, the actual number of such lawsuits arising from

pediatric clinical trials is negligible. [n20,n23] Another factor that has impeded pediatric clinical trials in the past is that the FDA relied on the manufacturer to advise the FDA whether a drug had a pediatric indication rather than independently assessing potential pediatric use.

Shirkey, who originally coined the term "therapeutic orphan," [n21] pointed out that the lack of financial support by government and industry for pediatric drug investigation is particularly ironic, because most of the major laws that support the FDA's role in regulating drugs have been passed in response to drug-induced adverse effects occurring in the pediatric population (ethylene glycol poisoning in 1938 and thalidomide in 1962). [n24-n26] Is it true that more than two decades after Shirkey's editorial, the pediatric patient continues to be a therapeutic orphan?

INITIATIVES TO SOLVE THE PROBLEM

The COD of the American Academy of Pediatrics (AAP) prepared a report for the FDA in 1979 that documented the absence of pediatric labeling for several hundred drugs used in pediatric patients. In 1982 the AAP COD published an additional report for the FDA, "General Considerations for the Clinical Evaluation of Drugs in Infants and Children." In 1984 a list of 103 parenteral drugs administered to neonates, but without neonatal labeling, was prepared by the AAP COD; this was followed in 1985 by a list of the top 10 drugs widely used in neonates for which there were published data (ranked according to use and availability of data) but that were not labeled for pediatric use. Despite good intentions, few of these drugs subsequently have had their labels revised for use by infants and children.

The Orphan Drug Act of 1982 was primarily designed to provide financial incentives to encourage the development of drugs with applications to small patient populations so that drugs with proven applicability might be developed and released to a limited market (<200000 patients per year). [n20] However, the Orphan Drug Act was not targeted specifically at pediatric patients. Although children with rare diseases have benefited from the Orphan Drug Act, the act has not stimulated or facilitated studies to obtain pediatric labeling for drugs widely used in adults. This failure is evidenced in part by the marked delay in FDA approval of zidovudine for children, because the appropriate pediatric studies were not carried out concurrently with clinical trials in adults.

In 1984, the Drug Price Competition and Patent Term Restoration Act modified the process for approval of abbreviated NDAs, allowing more rapid approval based on bioequivalency studies and extending patent rights to encourage studies of new indications for approved drugs. However, this act has not facilitated labeling of drugs for children.

Despite the concerns for children voiced by the industry through the Pharmaceutical Manufacturers Association, [n27] a survey of drug labeling in the 1990 Physicians' Desk Reference [n6] revealed that for 91% of 491 medications for which disclaimers or precautions against their use in children were cited, the disclaimers or precautions were based on a lack of adequate data. Approximately 80% of new chemical entity drugs approved between 1984 and 1989 were not labeled for use in children. This proportion has not changed; 92 (71%) of 130 new drugs approved from 1991 to 1995 did not have pediatric labeling at the time of approval. (At the time of this writing, complete data for 1995 were

not available.) However, at the request of the FDA, the manufacturers of 43 (33%) of these new drugs committed to or are conducting pediatric studies. The manufacturers of 49 (38%) of the new drugs told the FDA that these drugs would have no pediatric indications, although at least 21 will likely have some pediatric use, and another is currently one of the most commonly prescribed drugs for the treatment of gastroesophageal reflux in children of all ages (G. Troendle, personal communication, 1996; Janssen cisapride [Propulsid] tablets package insert, January 1995).

DEVELOPING SOLUTIONS

In 1988 a meeting of the AAP COD, with representatives of the FDA and the pharmaceutical industry, was held for the purpose of discussing the issues and problems associated with pediatric drug investigation. At the time, the role proposed for the FDA was to encourage drug companies to sponsor pediatric research, "if applicable," by making pediatric studies a priority: (1) if a new drug had a unique pediatric application; or (2) if a drug would be used in adults but would also have an important pediatric application for the same indication. If there would be little therapeutic gain, but a drug may be "applicable" to pediatric patients, then "after approval" studies would be encouraged. The concept of a "pediatric studies page" for NDAs for new molecular entities was introduced. Also, the need for incentives to the industry to sponsor pediatric studies was discussed by representatives of the FDA familiar with the problems related to drug development for children. However, it was recognized that the FDA did not have any legal means of compelling drug companies to perform pediatric research, even if the drug had a recognized, important pediatric application.

In April 1990 the Forum on Drug Development of the Institute of Medicine, National Academy of Sciences, sponsored a workshop, "Drug Development and the Pediatric Population." [n28] This meeting was convened to examine the issues that create barriers to drug testing in children. Input was enlisted from the FDA, the industry, the AAP, the National Institutes of Health (NIH), and many pediatric pharmacologists and toxicologists. The problems cited were numerous and somewhat specific to each group of individuals, depending on its perspective. [n28] A plea was made to the research community to develop more innovative and cost-effective research protocols with better statistical designs, to avoid arbitrary age restrictions, and to develop a greater sense of community between parties interested in pediatric research. FDA representatives indicated that regulatory changes were being explored to improve pediatric labeling, such as: (1) including peer-reviewed, published information on the pediatric use of drugs in drug labeling in addition to the information from FDA-approved clinical trials; (2) establishing a policy of identifying the need for pediatric studies in every NDA for new molecular entities; and (3) removing the FDA requirement for additional randomized and double-blind efficacy studies when the disease is the same in children as in adults and when information required for infants and children is primarily for dose and adverse effects rather than efficacy. The need for practical endpoints for long-term follow-up studies was also described. It was pointed out that support for long-term follow-up would likely need to come from government rather than industry.

Representatives from the industry stated that the greatest obstacle to industry-supported drug research was the potential for litigation and ethical problems encountered when carrying out research in children. This concern seems incongruent with the fact that few such lawsuits have occurred, and ethical

guidelines for drug research in children have existed since 1977 and have been revised recently. [n23,n29] The financial discrepancy between monetary return and the investment in pediatric research required to support pediatric studies was described. The need to develop legislation to provide economic incentives for investigating in pediatric clinical trials was noted.

The workshop highlighted eight recommendations to be addressed by all concerned parties in a cooperative effort to promote and develop adequate pediatric labeling: (1) inclusion of available pediatric data in drug labeling, even if this provides only limited pediatric information; (2) the need for a new awareness within FDA of the importance of pediatric studies; (3) a de-emphasis of the need for long-term follow-up studies unless specifically indicated; (4) recognition of the cost and time required to carry out pediatric studies; (5) the need by industry, academia, and publishers of journals to provide better incentives to conduct and publish pediatric research; (6) the need for the pediatric community to identify drugs important to the care of pediatric patients that need further data in children (7) the need for the NIH to stimulate pediatric research by providing core funding for a recommended clinical trials network; and (8) the need for the pharmaceutical industry to consider pediatric studies at all levels of drug development. There was a consensus that the implementation of these recommendations could be achieved only by the combined effort of the industry, the federal government (FDA and NIH), the medical community, and the general public.

SOLUTIONS

It is gratifying and encouraging that several key recommendations from the 1990 Institute of Medicine workshop subsequently have been implemented. The FDA recently promulgated regulatory changes that allow available pediatric data to be included in labeling, even though the data may not meet FDA criteria for approval on the basis of safety and efficacy. If the disease for which the drug is indicated is substantially the same in children as adults, efficacy in children may be extrapolated from adult studies. However, dose-finding and pharmacokinetic studies to obtain information on appropriate doses and safety in children will be required. [n30] A pediatric studies page in the NDA has been implemented by the FDA and is being expanded to include drugs that already have approved indications if they are being evaluated for new indications or dose formulations. The pediatric studies page requires the FDA and sponsoring company to identify whether pediatric studies are being conducted or planned and, if not, to explain why. Manufacturers will be required to reexamine existing information on marketed drugs to determine whether the labeling can be modified to include pediatric information on the basis of adult studies and available pediatric data. If so, they will be required to submit applications for supplemental labeling within 2 years. In addition, the FDA has the authority under the new regulations to request specific pediatric use information when deemed necessary. Within the FDA, a special Pediatric Subcommittee of the Medical Policy Coordinating Committee of the Center for Drug Evaluation and Research, with representatives from each division, has been formed to track the implementation of the new regulations and to facilitate the inclusion of pediatric testing in the drug development process.

The USP also has begun to include the latest pediatric uses and drug doses in the USP Dispensing Information based on available literature and consultation with subspecialty experts. This provides a ready reference source for the

practitioner, although it does not address the lack of pediatric clinical trials with which official labeling can be supported. Nonetheless, inclusion of pediatric information will help address the reluctance of insurance carriers and other third-party payers to pay for the use of medications that are not labeled for children. Because the USP Dispensing Information is one of the compendia used to document accepted medication uses, this effort by the USP may help slow a reimbursement denial trend, which threatens the care of children.

The National Institute of Child Health and Human Development recently funded a network of pediatric pharmacology research units expressly to carry out pediatric pharmacologic research that will support pediatric labeling. The FDA is working closely with the pediatric pharmacology research unit network to conduct pediatric studies on selected therapies that otherwise would not be studied. [n31]

In 1994 legislation was sponsored by Senator Nancy Kassebaum, [n32] with a companion House bill sponsored by Representative Kreidler, [n33] which proposed extending the period of exclusivity of a drug if the sponsoring company conducted pediatric studies that supported labeling for children. Unfortunately, this legislation was not reported out of committee. If such a bill eventually becomes law, it will provide an economic incentive to conduct pediatric studies by enhancing the opportunity for companies to recover their investment in pediatric studies for drugs that are necessary for the treatment of childhood illnesses but have limited market potential in children.

The COD of the AAP continues to work closely with the FDA to foster the study and labeling of drugs for pediatric use. The committee recently submitted a list of six drugs to the FDA that are considered priorities for studies in children (fentanyl, bupivacaine, midazolam, cimetidine, albuterol, and metronidazole).

It is past time that all drugs with potential pediatric applications should be investigated in infants and children with appropriately designed industry-supported and FDA-approved studies. The unapproved or off-label use of drugs is not an acceptable alternative to documentation of the safety and efficacy of drugs used by the pediatric population. The pediatric academic and private practice communities must become more vocal in demanding support for pediatric studies and for greater cooperation between industry, government, and academia to conduct the necessary studies when new drugs that have potential to be of help in caring for children are introduced. There is a need to make the general public more aware of these issues to encourage voluntary participation in and the financial support necessary for studies in children. Children have the same medical, legal, and ethical rights as all other segments of the patient population to have clinically important drugs available to treat disease effectively and safely. Recent efforts by the AAP, FDA, USP, NIH, and Congress suggest that perhaps the drug development and approval process is changing in a positive direction for children. The recently announced FDA changes in regulations and the establishment of the Pediatric Subcommittee of the Medical Policy Coordinating Committee of the Center for Drug Evaluation and Research to track the implementation of new regulations regarding pediatric drug testing will specifically address the importance of pediatric studies within each of the FDA's 12 divisions. This should go a long way to increasing and improving pediatric pharmacologic research of new drugs and, it is hoped, in cooperation with the pediatric pharmacology research units funded by the NIH, should also address pediatric labeling problems for old drugs. [n34] Perhaps it is also time

for large purchasers of drugs, such as health care systems and managed-care organizations, to apply economic pressure by basing those purchases in part on the presence of pediatric labeling. Perhaps now, with the cooperation of the industry, USP, NIH, FDA, AAP, parents, children, and health care providers, children no longer will be therpeutic orphans.

SUPPLEMENTARY INFORMATION: Received for publication Mar 7, 1996; accepted Apr 4, 1996.

Reprint requests to (C.J.C.) Department of Anesthesia, Children's MemorialHospital, Northwestern University Medical School, 2300 Children's Plaza, Chicago, IL 60614.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 201

[Docket No. 92N-0165]

Specific Requirements on Content and Format of Labeling for Human Prescription Drugs; Revision of "Pediatric Use" Subsection in the Labeling

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending its regulations governing the content and format on labeling for human prescription drug products. The final rule revises the current "Pediatric use" subsection of the professional labeling requirements for prescription drugs to provide for the inclusion of more complete information about the use of a drug in the pediatric population (ages birth to 16 years). The final rule, which applies to prescription drug products (including biological prescription drug products), recognizes several methods of establishing substantial evidence to support pediatric labeling claims, including relying, in certain cases, on studies carried out in adults. This final rule also requires that if there is not substantial evidence to support any pediatric use or use in a particular pediatric population, the labeling shall state this. Sponsors must reexamine existing data to determine whether the "Pediatric use" subsection of the labeling can be modified based on adequate and well-controlled studies in adults, and other information supporting pediatric use, and, if appropriate, submit a supplemental application to comply with new § 201.57(f)(9)(iv) by December 13, 1996. This action responds to concerns in FDA and elsewhere that current prescription drug labeling often does not contain adequate information about the use of drugs in the pediatric population. This action promotes safer and more effective use of prescription drugs in the pediatric population.

DATES: Effective January 12, 1995. The agency will accept "pediatric use" information based on revised § 201.57(f)(9) (21 CFR 201.57(f)(9)) after January 12, 1995. Sponsors must reexamine existing data, and, if appropriate, submit a supplemental application to comply with new § 201.57(f)(9)(iv) by December 13, 1996

FOR FURTHER INFORMATION CONTACT: Erica L. Keys, Center for Drug Evaluation and Research (HFD-362), Food and Drug Administration, 7500 Standish Pl., Rockville, MD 20855, 301-594-1046.

SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of October 16, 1992 (57 FR 47423), FDA proposed to amend its regulations pertaining to the content and format of prescription drug labeling in § 201.57 by revising the current "Pediatric use" subsection (§ 201.57(f)(9)) to allow a broader basis for the inclusion of information about use of a drug in the pediatric population. The proposal would have allowed pediatric claims based not only on adequate and well-controlled studies in the pediatric population but also, in some cases, on such trials in adults. The proposed regulation described other data needed when pediatric claims are based on trials in adults and indicated specific labeling language and the location of various kinds of information.

FDA issued the current pediatric labeling requirements in 1979 (44 FR 37434, June 26, 1979). The current regulation, codified at § 201.57(f)(9), requires that specific pediatric indications, if any, be described under the "Indications and Usage" section of the labeling, with appropriate pediatric dosage provided under the "Dosage and Administration" section. The current regulation also requires that recommendations for pediatric use be based on substantial evidence derived from adequate and well-controlled studies in the pediatric population, unless that requirement is waived. If a drug's safety and effectiveness in the pediatric population cannot be established or if the drug's use in the pediatric population is associated with a specific hazard, the current regulation requires appropriate statements or details.

By establishing a "Pediatric use" subsection and describing its content and format, the 1979 regulation was intended to encourage drug labeling that would regularly provide adequate information about use of prescription drugs in pediatric patients. As stated in the preamble to the proposed rule on which this final rule is based, however, most prescription drug products still lack adequate information about their use in pediatric populations. For example, an informal survey done in 1990 by the American Academy of Pediatrics examined labeling of all new molecular entities approved between 1984 and 1989 and found that 80 percent had no information on pediatric use. Other surveys have shown that the labeling for many prescription drugs states that safety and effectiveness in children have not been established and contains no information on pediatric use, even for drugs that are commonly prescribed for pediatric patients.

FDA continues to be concerned that, without adequate information, practitioners may be reluctant to prescribe certain drugs for their pediatric patients, or may prescribe them inappropriately, choosing dosages, for instance, that are arbitrarily based on the child's age, body weight, or body surface area without specific information as to whether this is appropriate. As a result, pediatric patients may be exposed to an increased risk of adverse reactions, or decreased effectiveness of the drugs prescribed, or may be denied access to valuable therapeutic agents.

The continuing absence of pediatric use information in prescription drug labeling may be due in part to the impression, perhaps conveyed by the existing regulation, that pediatric claims must always be based on adequate and well-controlled studies conducted in the pediatric population. Given the many problems associated with the testing of drugs in the pediatric population (e.g., obtaining informed consent for tests not directly of benefit to the child, use of placebo controls in a vulnerable population), studies meeting this standard are often difficult to obtain. Existing FDA regulations do not, in fact, require that controlled trials always be conducted in the pediatric population to support a pediatric use. Under current § 201.57(f)(9), the need for such studies may be waived where other data can satisfy the requirements of law. The basis for granting such a waiver is not, however, clear in the existing regulation. Section 201.57(f)(9)(iv) of this final rule clarifies how the agency will determine that data from adequate and well-controlled studies with adult subjects can provide substantial evidence of effectiveness in the pediatric population.

In summary, this rule is intended to provide practitioners with more pediatric use information in the labeling of human prescription drug products so that practitioners will have more reliable information upon which to base a decision to prescribe a drug for use in their pediatric patients. The rule does this by encouraging manufacturers to provide more information on drug labels upon which practitioners can base their decisions. The rule does not, however, limit the manner in which a practitioner may prescribe an approved drug.

II. Highlights of the Final Rule

The final rule revises the current "Pediatric use" subsection of the professional labeling requirements for prescription drugs to provide for the inclusion of more comprehensive information about use of a drug in the pediatric population. Under the final rule, products may be labeled for pediatric use based on adequate and well-controlled studies in adults together with other information supporting pediatric use (e.g., pharmacokinetic data, safety data, pharmacodynamic data). Such reliance on studies in adults was possible under the waiver provision in the existing rule, but the waiver provision was not often used. Of course, products may also be labeled for pediatric use based on adequate and well-controlled studies in the pediatric population. The pediatric age group, birth to 16 years, includes pediatric age groups often called neonates, infants, children, and adolescents. In the final rule, because the term "children" can be interpreted as referring only to a particular subset of the pediatric population (ages 2 to 12 years), and to make clear that the provisions of this rule apply to the entire pediatric population, references to "children" in the proposed rule have been deleted and replaced by "pediatric population" or "pediatric patients."

The major provisions of the final rule are summarized as follows:

The final rule continues to permit a specific pediatric indication (i.e., an indication different from those approved in adults) supported by adequate and well-controlled studies in the appropriate pediatric population, to be described under the "Indications and Usage" section of the labeling, with the appropriate pediatric dosage given under the "Dosage and Administration" section of the labeling. The "Pediatric use" subsection of the labeling must include any limitations on the pediatric indication, need for specific monitoring, specific hazards of the drug, differences between pediatric and adult responses to the drug, and other information related to the safe and effective use of the drug in pediatric patients.

If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they must be summarized in the "Pediatric use" subsection of the labeling and discussed in more detail, if appropriate, under the "Clinical Pharmacology" and "Clinical Studies" sections. Appropriate pediatric dosage must be given under the "Dosage and Administration" section of the labeling. This subsection of the labeling must also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug.

A pediatric use statement may also be based on adequate and well-controlled studies in adults, provided that the agency concludes that the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Where needed, pharmacokinetic data to allow determination of an appropriate pediatric dosage, and additional pediatric safety information must also be submitted.

Where the requirements for a finding of substantial evidence to support a specific pediatric indication or a pediatric use statement have not been met for a particular pediatric subgroup, the "Pediatric use" subsection of the labeling must contain a statement that appropriately characterizes the limitation, such as "Safety and effectiveness in pediatric patients (below the age of (—) (years/months/weeks)) have not been established." If use of the drug is associated with a specific hazard in this pediatric subgroup, the "Pediatric use" subsection must contain information about this hazard, or, where appropriate, refer to a more complete description of the hazard in the "Contraindications" or "Warnings" section of the labeling.

Where the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, the "Pediatric use" subsection of the labeling must contain the following statement: "Safety and effectiveness in pediatric patients have not been established." If use of the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the "Pediatric use" subsection must contain information about this hazard, or, where appropriate, refer to a more complete description of the hazard in the "Contraindications" or "Warnings" section of the labeling.

Any sponsor who believes that no "Pediatric use" subsection is appropriate or relevant to the labeling of its particular drug product must provide FDA with reasons justifying its omission, and may propose alternative statement(s).

Finally, recognizing the hazards that inactive ingredients can pose to the pediatric population, the final rule requires that prescription drug labeling contain statements about inactive ingredients that might be toxic to the neonate or other pediatric subgroup.

III. General Comments on the Proposed Rule

FDA received 11 comments on the proposed rule from prescription drug manufacturers, prescribers, professional societies, organizations with special interests in the pediatric population, the lay public, and others. Most supported the proposed labeling change, calling it "timely and important," "an important * * * step to facilitate the inclusion of information about use of drugs in children in the approved labeling," "a significant step toward the goal of including infants and children in the drug approval process," and a way "to fill the gap of information that currently exists in the area of appropriate drug usage in children."

One comment, for example, stated that providing pediatric use information in labeling will help health professionals reach rational drug therapy decisions for pediatric patients. The comment added "any information that can be used by pharmacists to assure rational drug therapy in special populations will be a positive addition to drug information. * * * Such labeling will enhance the likelihood of positive outcomes in pediatric patients."

However, some comments were less supportive, including one that stated: "While * * * [we] commend the FDA on its initiatives to improve information available to physicians and their pediatric patients regarding prescription drug use, we remain concerned that this approach will not measurably assist physicians."

Most comments also raised specific issues for consideration by the agency. Those issues are described below.

A. Definition of "Pediatric"

1. Several comments suggested that age breakdowns within the pediatric population might be appropriate. The pediatric age range begins at birth, and may cover individuals as old as 18 years to 21 years, encompassing the subspecialties of neonatology and adolescent medicine. One comment suggested that the rule define "pediatric" as children under 12 years, because "it has been commonly accepted that ages 12 years to 18 years may be included without previous clinical work in that age group." The

comment also suggested that the rule s s the age group when pharmacokinetic studies should be done in order to extrapolate the results from infancy through adolescence, or state whether the age range will be broken into subgroups with testing required for each. Another comment said that a definition of "pediatric" would have to consider drug metabolism, pharmacokinetics, and interaction with various organs and other body systems. The comment suggested that a system by which distinct classes of drugs are considered differently may be more logical and appropriate.

Another comment noted that pediatric patients are not homogeneous, and that age groups show significant differences in functional and physiological functions. The comment suggested that information from clinical studies be subdivided by age groups and their respective responses to drugs, suggesting age categories of premature infant, newborn, children under 2 years of age, children 2 years to 13 years, and adolescents 13 years to 18 years.

Another comment said that individuals 16 years to 18 years of age pose particular problems and suggested consultation with the American Academy of Pediatrics' Committee on Drugs to consider defining age categories or groups for pediatric labeling.

The "Pediatric use" subsection of labeling is where information about use of a drug in pediatric patients is located, and § 201.57(f)(9) describes in general terms the kind of information that should be included. The "Pediatric use" subsection does not attempt to resolve the many difficult issues related to use of drugs in this population. What appears in this subsection (e.g., age groups covered) will depend on the data available, and the ability to define results for specific subgroups. As a general matter, however, the agency offers the following guidance and useful breakdowns. The following age categories for the pediatric population are commonly distinguished, although the distinctions are inevitably arbitrary: (1) Birth up to 1 month (neonates), (2) 1 month up to 2 years of age (infants), (3) 2 years up to 12 years (children), and (4) 12 years up to 16 years (adolescents). Where possible, data should be analyzed by these groups, but it should not usually be necessary to establish a drug product's effectiveness in each group. It may, on the other hand, be important to have some pharmacokinetic information in each group, especially the younger age groups, to guide dosing and additional information, such as a specific study in neonates, to establish safety.

Although the agency has determined that the term "pediatric patients" refers to individuals from birth to 16 years of age, the agency recognizes that for some drugs, adult studies may be applicable to pediatric patients under the age of 16 years who have passed puberty; indeed, a primary purpose of this rule is to allow pediatric labeling based on adult studies, when appropriate. Although in many cases, additional pharmacokinetic and safety data may be needed to support pediatric use statements, in other cases, particularly for pediatric patients in the 12-to 16-year age group, there may be less additional data needed.

B. Applicability of the Rule to Biological Drug Products

2. One comment said that it was unclear whether the rule applies to biological drug products.

The rule (as well as § 201.57 in general) applies to biological drug products.

C. Pediatric Studies

3. One comment noted that about 80 percent of drug labeling currently contains language excluding use of the drug in pediatric patients or limiting use only to specific age groups. The comment asked FDA to encourage sponsors to include pediatric patients in their clinical studies when the drug is likely to be effective for an indication in this population.

As stated in the preamble to the proposed rule, FDA encourages sponsors to include pediatric patients in their clinical studies, and analyzes investigational new drug applications and new drug applications (NDA's) to determine whether studies in this population should be done before the drug is approved (57 FR 47423 at 47424). Under certain circumstances, the agency may require that clinical studies in the pediatric population be conducted before marketing approval (see response to comment number 4 in section III.C. of this document). If a drug is likely to be effective for pediatric use, the agency is making it clear that labeling for pediatric use may sometimes be based on adequate and well-controlled studies in adults, with additional pediatric data. FDA intends that this rule will call further attention to the need for creating and reviewing data on pediatric use.

4. One comment asked whether FDA intended to require a sponsor to submit information for a specific pediatric indication or use if there are available data suggesting that such an indication or use would be permitted under the regulation. The comment said that there may be "good reasons" why a sponsor might not wish to seek a pediatric indication or use for a drug even when available evidence would support such a use. For example, the drug's benefit/risk ratio in the pediatric population might be different from that in adults, or there might be sufficient and better alternative therapies available for the pediatric use. Additionally, the comment expressed concern that a drug that has been tested in adults may not provide a sufficient legal defense against a claim for injury of a child. The comment said that a sponsor should not be forced to assume or be placed in the position of having to defend such an action unless the sponsor believes the data in support of the pediatric use are sufficient, and that a sponsor should not be mandated or forced by the rule to seek a pediatric use if the sponsor, for whatever reason, does not wish to do so.

Another comment expressed concern that FDA might delay approval of products that have good existing available data for safety and efficacy in adults while acceptable pediatric information is developed.

This rule does not add a new requirement that sponsors carry out new pediatric studies, nor does it require that sponsors submit labeling with claims that are inadequately supported. New § 201.57(f)(9)(iv) provides that a pediatric use statement may be based on adequate and well-controlled studies in adults, provided that the course of the disease and the drug effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. Sponsors are required to reexamine existing data to determine whether the "Pediatric use" subsection of the labeling can be modified based on adequate and well-controlled studies in adults, and other information supporting pediatric use, and, if safety and effectiveness for pediatric use have been demonstrated, submit a supplemental application to comply with new § 201.57(f)(9)(iv) by December 13, 1996. A sponsor who does not believe that the disease and drug effects are similar in the pediatric and adult populations, or who believes that use in pediatric patients is otherwise not adequately supported by data, should not propose revised labeling under this provision. Under new § 201.57(f)(9)(vi), the sponsor may propose labeling stating that safety and effectiveness in pediatric patients have not been established.

Additionally, under new § 201.57(f)(9)(vii), if the sponsor

believes that none of the statements described in paragraphs (f)(9)(ii) through (f)(9)(vi) of that section is appropriate or relevant to the labeling of a particular drug, the sponsor must provide reasons for omission of the statements and may propose alternative statement(s). In response to such a proposal, FDA may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling and that the alternative statement is accurate and appropriate. Section 201.57(f)(9)(vii) has been modified to make this explicit.

Although this rule does not add new requirements for conducting pediatric studies, various provisions of the Federal Food, Drug, and Cosmetic Act (the act), the Public Health Service Act (the PHS act), and existing regulations authorize FDA to require such studies under certain circumstances.

Under section 505(k) of the act (21 U.S.C. 355(k)), FDA may require NDA holders to establish records and submit reports to the agency on data relating to clinical experience or other data or information in order to determine whether there may be grounds for revoking the NDA approval. Such a requirement may be established either through regulation or through an order regarding the NDA (21 U.S.C. 355(k)(1)).

Existing regulations require application holders to report to the agency adverse experiences occurring in the course of use of the product in professional practice, as well as during clinical investigations (21 CFR 312.32, 314.80). In addition, approved application holders must submit as part of the annual report a summary of significant new information that might affect the safety, effectiveness, or labeling of the product, as well as copies of unpublished and published reports of studies of the drug (21 CFR 314.81(b)(2)(i), (b)(2)(v), and (b)(2)(vi)). The report also must contain a description of the action the company has taken or intends to take because of the new information, such as submission of a supplement, addition of a warning, or initiation of a new study (21 CFR 314.81(b)(2)(i)).

Section 505(e) of the act specifies grounds on which the agency may withdraw or suspend approval of an NDA. If there is an imminent hazard to the public health, approval of the NDA may be suspended immediately by the Secretary of the Department of Health and Human Services. In addition to other circumstances, approval of an NDA is to be withdrawn if clinical experience or other data show that the product is unsafe or not shown to be safe under the conditions of use upon the basis of which the application was approved. Moreover, the approval may be withdrawn if the labeling is false or misleading and not corrected within a reasonable time after notice of the matter.

Under section 502(a) of the act (21 U.S.C. 352(a)), a drug is considered misbranded if its labeling is false or misleading. Section 201(n) of the act (21 U.S.C. 321(n)) makes it clear that the "misleading" determination is to be based not only on representations made or suggested in the labeling, but also on failure to reveal material facts. Material facts include those which concern consequences which may result from use of the product under the labeled conditions of use or under customary or usual conditions of use. These conditions of use may include off-label uses prescribed by practitioners for their patients.

In addition, drugs are considered misbranded under section 502(f) of the act if the labeling fails to bear adequate directions for use. FDA regulations define adequate directions for use as directions under which the lay person can use a drug safely and for the purposes for which it is intended (21 CFR 201.5). "Intended uses" are further defined in the regulations to include uses other than the ones on the labeling (21 CFR 201.128). If a manufacturer knows that a drug is used for an off-label use, the manufacturer may be required to provide adequate labeling for that use (21 CFR 201.128).

Prescription drugs for human use are exempt from the requirement to carry adequate directions for lay use under certain circumstances, if labeled with the prescription legend (21 CFR 201.100). Among the exemption criteria is the requirement that the drug carry adequate labeling for the prescriber, as authorized by an approved application, for the intended use. In summary, the drug product is misbranded if the intended use is not approved in an NDA.

Drug products are also misbranded, under section 502(f)(2) of the act, if the labeling does not carry adequate warnings against unsafe use. Such unsafe use may include use by pediatric patients where the use may be dangerous to their health, or unsafe dosage or methods or duration of administration in the pediatric population.

Biological drug products are approved under authority of section 351 of the PHS act (42 U.S.C. 262). This provision authorizes the promulgation of regulations designed to ensure the continued safety, purity, and potency of the products (42 U.S.C. 262(d)(1)). An approved product license application (PLA) may be revoked if the product does not conform to applicable requirements in the regulations or is not safe and effective for all of its intended uses or is misbranded with respect to any such use (21 CFR 601.5(b)(4) through (b)(6)). If there is a danger to health, the Commissioner may suspend the product license (21 CFR 601.6). Under section 351(b) of the PHS act, no one may falsely label a biological product. Biological drug products are also subject to the applicable drug provisions of the Federal Food, Drug, and Cosmetic Act, as previously discussed.

Moreover, the agency has stated that an application for marketing approval should contain data on a reasonable sample of the patients likely to be given a drug once it is marketed (58 FR 39406 at 39409, July 22, 1993). This conclusion, stated explicitly in a guideline on the need for data in both genders, applies equally to age subgroups, including pediatric and geriatric populations. FDA may refuse to approve an application that fails to contain sufficient information to determine whether the product can be safely and effectively used in populations likely to receive it. In addition, for an approved drug, in certain cases (e.g., where the drug is widely used, represents a potential hazard, or is therapeutically important in pediatric patients), FDA may require further studies in pediatric populations and appropriate labeling changes. As previously discussed, an already approved drug may be considered illegally marketed if adequate information on safe and effective use in pediatric patients is not obtained and included in the labeling.

The agency thus expects sponsors to seek supplemental claims for pediatric uses that are supported by adequate data. This does not imply, however, that a sponsor should seek a claim for a pediatric use if the benefits of that use do not outweigh its risks; the determination of whether to include a pediatric use statement must be based on clinical data, and other use information, not on a vague concern about liability.

5. One comment said that although the desire to use potentially relevant data in the "Pediatric use" subsection of the labeling was "understandable," such data should not take the place of adequate and well-designed controlled studies in the pediatric population, and that FDA ultimately may have to require such studies. The comment stated that FDA should require manufacturers to

fund research projects regarding drug safety and efficacy, including short-term and long-term side effects, in pediatric patients.

FDA agrees that clinical studies regarding a drug's safety and effectiveness in pediatric patients are desirable, and the agency encourages such studies in appropriate cases. As discussed in comment 4 in section III.C. of this document, the agency has the authority to require such studies under certain circumstances. In some cases, such studies may be required prior to approval where pediatric use is important and where the adult and pediatric diseases cannot be considered sufficiently similar. In other cases, the controlled trials in adults, with pharmacokinetic and other data as needed, may support valid pediatric labeling.

6. One comment stated that FDA should consider other alternatives to the rule, including a formal review process that collects and analyzes available safety and efficacy data on a drug's use in the pediatric population both before and after marketing approval, which, through committee review, could recommend further testing of the drug after it is marketed if specific pediatric safety or efficacy concerns are found.

FDA believes that the comment has misinterpreted the purpose of the rule. The rule describes the kind of data and information that can be included in labeling for the pediatric population. In general, it is the sponsor's responsibility to collect, on a continuing basis, available data on safety and efficacy, propose revised labeling, and carry out [illegible]ed studies. In some circumstances, FDA has required pediatric studies prior to approval, elicited agreement by drug sponsors at the time of marketing approval to carry out additional pediatric studies after approval, or stimulated conduct of pediatric studies after approval. When appropriate, FDA makes use of its standing advisory committees to help decide whether and when pediatric studies are needed.

7. One comment stated that FDA should revise the rule to specify what data must be provided by manufacturers. The comment asked what number of pediatric patients would be sufficient to determine if there is a difference in age-related response, and how FDA will determine that all available information about the pediatric use of all available drugs has been included, including epidemiologic studies.

FDA declines to accept the comment's suggestion. The agency believes that specifying an exact number of pediatric patients to be studied would be impractical due to variations in the pediatric population and responses to different drugs. This is particularly true, given the various kinds of data that can be used under the rule to support pediatric labeling.

D. Drugs Currently Under Review

8. One comment suggested that drugs currently under development or under review by FDA should be given special consideration to avoid delays in development and approval associated with implementation of the rule.

FDA does not expect delays in review or approval as a result of this rule. FDA already examines available pediatric data under current labeling regulations. The principal change created by the revised regulation is the ability to rely on studies in adults to support pediatric efficacy in some situations.

E. Supplements for Drugs Already Approved

9. One comment suggested that FDA work with manufacturers of approved drugs to develop a method that allows the manufacturers to update their labeling in a quick and cost-effective manner. The comment also said that package inserts do not generally reflect current scientific literature because of the problems with current methods of updating labeling. The comment said that this had created situations where prescribers are making decisions on treatment modalities without the benefit of timely information.

FDA does not believe that changes in regulations are needed to allow timely updating of labeling. Under the current regulations, applicants can propose changes in their approved labeling. FDA normally reviews supplements subject to prior approval in the order received. Effectiveness supplements are rated as priority or standard and are subject to performance goals set in connection with the Prescription Drug User Fee Act of 1992.

10. One comment said that the filing and approval of pediatric labeling supplements from different sponsors on different timetables could mean that some labels for products considered to be substantially similar might be silent with regard to pediatric usage, while others might be detailed. The comment suggested that FDA and the American Academy of Pediatrics' Committee on Drugs could identify therapeutic classes to be relabeled first, so that FDA could review and approve pediatric use labeling for products from different companies and coordinate implementation of labeling changes for similar agents.

With respect to effectiveness claims, pharmacokinetics, and safety data, much information is drug specific and will be reviewed as it is submitted. Therefore, the agency is not adopting the comment's suggestions. The agency advises, however, that, in general, when a class of drug products is involved, FDA examines labeling as it applies to the class.

F. Impact on Industry

11. One comment claimed that the rule places NDA holders at a competitive disadvantage relative to abbreviated new drug application (ANDA) holders. The comment stated that the rule would give NDA holders the burden and responsibility for pediatric studies and literature searches, but not impose a similar burden and responsibility on ANDA holders.

FDA disagrees with the comment in part. The rule is directed to anyone marketing a prescription drug and is intended to encourage the inclusion of more complete information about use of a drug in the pediatric population and about hazards associated with this use. The rule permits a new basis for reference to pediatric uses, but it does not impose a new requirement to conduct studies in pediatric populations. To the extent that NDA holders have access to data not available to ANDA holders, they will have more data to examine and more likelihood of having a basis for proposing changes to the "Pediatric use" subsection of labeling. The agency believes this represents only a modest burden and, in any event, sees no other way to gain further pediatric information in labeling. ANDA holders cannot be required to examine data they do not possess. ANDA holders are not precluded from providing pediatric use data, and are expected to do so under this rule, if data are available. An ANDA applicant who believes new safety or effectiveness information should be added to a product's labeling should provide adequate supporting information to FDA, and FDA will determine whether the labeling for the generic and listed drugs should be revised.

G. Minor Editorial Changes

12. One comment said that labeling revisions that are editorial in nature and are used to reformat existing pediatric use labeling information to conform to the rule should be made in accordance with § 314.70(d) (21 CFR 314.70(d)) (changes described in the annual report). The comment said that this would also facilitate the agency's processing of minor changes.

FDA agrees with the comment. As stated in the preamble to the proposed rule, "[m]inor editorial changes may be made in accordance with § 314.70(d)" (57 FR 47423 at 47426). To comply with this rule, references to "children" in the "Pediatric use" subsection of the insert labeling of products already being marketed must be changed, where appropriate, to "pediatric population" or "pediatric patients." For products other than biological products, such changes are considered minor editorial changes.

As stated in the preamble to the proposed rule, for biological products, such changes are to be submitted in accordance with the procedures outlined in § 601.12 (21 CFR 601.12) (57 FR 47423 at 47426).

H. Format of Proposed Labeling

13. One comment said that it is impractical and impossible to list on the labeling all dosages and hazards for the pediatric population. The comment suggested placement of a general label on all adult prescription drugs stating that the medication should not be given to pediatric patients without a physician's instructions. The comment said that requiring overly complicated and lengthy information on labeling would discourage the prescribing of needed medications.

FDA believes that the comment misinterprets the proposed rule and the purpose of pediatric use labeling. The purpose of the rule is to encourage more pediatric use information in labeling and to provide practitioners with more information on pediatric use.

14. One comment said that for certain products, e.g., corticosteroids, where class labeling has been in effect, the agency will have to decide and communicate how the pediatric wording will be addressed.

In most cases, pediatric labeling will be drug specific. Where class labeling exists, FDA generally examines the labeling for those products as a whole.

IV. Specific Comments on the Proposed Rule

A. Section 201.57(f)(9)(i)

FDA, on its own initiative, has added a definition in § 201.57(f)(9)(i) to indicate that under paragraphs (f)(9)(ii) through (f)(9)(viii), the terms "pediatric population(s)" and "pediatric patient(s)" are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

B. Proposed § 201.57 (f)(9)(i) and (f)(9)(ii)

FDA received no comments on these provisions (renumbered as § 201.57(f)(9)(ii) and (f)(9)(iii)), and has finalized them without change.

C. Proposed § 201.57(f)(9)(iii)

Proposed § 201.57(f)(9)(iii) (renumbered as § 201.57(f)(9)(iv)) states, in part, that "FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drugs are sufficiently similar in children and adults to permit extrapolation from the adult data to children. The additional information supporting pediatric use must include data on the pharmacokinetics of the drug in children for determination of pediatric dosage. Other information, such as data from pharmacodynamic studies of the drug in children, controlled or uncontrolled studies confirming the safety or effectiveness of the drug in children, pertinent premarketing or postmarketing studies or experience, may be necessary to establish the applicability of the adult data to children."

15. One comment said FDA should revise proposed § 201.57(f)(9)(iii) to indicate that pharmacokinetic data are not mandatory in some situations. Another comment stated that pharmacokinetic data may not be the most appropriate way to determine pediatric dosing because the differences in metabolism or in distribution in pediatric patients may support dosing that will not necessarily be related to blood levels. Both comments stated that dosing for inhalation products should not be based on pharmacokinetics.

Another comment said that difficulties in obtaining informed consent, use of placebo controls, and obtaining adequate blood samples for pharmacokinetic analysis in pediatric patients are not serious impediments to performing studies necessary for appropriate pediatric labeling. The comment said there is a well-established ethical structure within which informed consent may be obtained and placebo controls used in the pediatric population, and that current technology requires only very small blood samples for measurement of most compounds. According to the comment, the primary impediments to doing adequate clinical trials in the pediatric population are the absence of a regulatory mandate and the existence of economic disincentives.

The agency recognizes that pharmacokinetic data are important sources of information, but may not always be the most appropriate method for determining pediatric dosing schedules and may be infeasible, unnecessary, or insufficient. Other types of data or experience may sometimes substitute for pharmacokinetic data, and other data or experience in the pediatric population may be needed in addition to pharmacokinetic data. The agency has modified the rule to state that the additional information supporting pediatric use must *ordinarily* include data on the pharmacokinetics of the drug in the pediatric population for determination of pediatric dosage.

As discussed in response to comment 4 in section III.C. of this document, this rule does not create a new requirement for pediatric studies, but the authority for requiring pediatric studies already exists. There are situations in which data on safe and effective use in pediatric patients may be necessary for approval or for continued marketing of a drug. Revised § 201.57(f)(9) does not create the requirement for pediatric studies, but is intended to encourage the inclusion of more comprehensive labeling about pediatric use by permitting use of adult data in establishing pediatric efficacy. Specifically, the rule allows the pediatric use statement to be based on adequate and well-controlled studies in adults when additional information exists to show that the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients to permit extrapolation from the adult efficacy data to pediatric populations.

FDA has, on its own initiative, amended proposed § 201.57(f)(9)(iii) to indicate that FDA's determination whether the effects of a drug are sufficiently similar in adults and pediatric patients will include an examination of the drug's beneficial and adverse effects. FDA has also amended § 201.57(f)(9)(iii) to make clear that other information besides pharmacokinetic data may be necessary not simply to "establish the applicability of the adult data to pediatric patients," but, more generally "to show that the drug can be used safely and effectively in pediatric patients." Section 201.57(f)(9)(iii) has also been modified to remove any potential misimpression that uncontrolled studies could demonstrate effectiveness.

16. One comment questioned the rule's language about extrapolating adult data to pediatric patients. The comment said that the exact mechanism

by which many psychiatric drugs work is not known, so that, for these drug products, extrapolation between adult and pediatric populations may be inaccurate and potentially hazardous. The comment noted that randomized controlled studies of tricyclic antidepressants in pediatric patients have raised questions regarding efficacy, while safety issues have been raised based on noncontrolled data indicating a potential risk, which might not have been clear based on adult data, of sudden cardiac death in pediatric patients using tricyclics.

FDA agrees that extrapolation from adult experience is inappropriate, and thus unacceptable, in some cases. Extrapolation is not necessary under the rule, but is an alternative to the conduct of adequate and well-controlled studies in pediatric patients. In those cases where the pediatric use statement is based primarily on adequate and well-controlled studies in adults, additional information supporting pediatric use is usually needed, ordinarily including data on the pharmacokinetics of the drug in the pediatric population for determination of pediatric dosage. Other information, such as data from pharmacodynamic studies of the drug in pediatric patients, data from other studies supporting the safety or effectiveness of the drug in pediatric patients, pertinent premarketing or postmarketing studies or experience, may be necessary also to show that the drug can be used safely and effectively in the pediatric population.

17. One comment said that the preamble to the final regulation should clarify that "other information" supporting pediatric use in proposed § 201.57(f)(9)(iii) need not be limited to data developed or sponsored by the NDA holder, but may include data such as reports of studies by academic researchers in peer-review journals that were prepared by persons who are not related to the NDA sponsor.

The agency believes that no change is needed in revised § 201.57(f)(9)(iv) because the section does not suggest that the data must have been developed or sponsored by the NDA holder.

D. Proposed § 201.57(f)(9)(iv)

FDA received no comments on this provision (renumbered as § 201.57(f)(9)(v)), and has finalized it without change.

E. Proposed § 201.57(f)(9)(v)

Proposed § 201.57(f)(9)(v) (renumbered as § 201.57(f)(9)(vi)) provides, in part, that "[i]f the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this subsection of the labeling shall contain the following statement: 'Safety and effectiveness in children have not been established.'"

18. One comment expressed concern that this provision may create disincentives for sponsors to develop better information on pediatric use of their drugs. The comment suggested that FDA require mandatory phased-in safety testing and appropriate clinical studies of pharmaceuticals in the pediatric population. Alternatively, the comment recommended that FDA and manufacturers work to develop agreements whereby the manufacturer consents to carry out additional postapproval pediatric studies.

FDA believes that the comment suggests actions beyond the scope of this rule. FDA encourages pediatric testing, and, as discussed in comment 4 in section III.C. of this document, has the authority to require pediatric studies. In some cases, FDA will require pediatric studies for approval or continued marketing. This rule, however, does not add new requirements for pediatric studies, but rather describes the kind of data that can be used to support labeling claims.

F. Proposed § 201.57(f)(9)(vi)

Proposed § 201.57(f)(9)(vi) (renumbered as § 201.57(f)(9)(vii)) provides "[i]f the sponsor believes that none of the statements described in paragraphs (f)(9)(i) through (f)(9)(v) (renumbered as (f)(9)(ii) through (f)(9)(vi)) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement."

19. One comment asserted that the proposal did not adequately address the problem of a large number of drugs that have been approved and marketed for years without pediatric usage information in their labeling, which are widely used in pediatric patients and for which there is substantial published literature regarding their pediatric use. The comment noted that proposed § 201.57(f)(9)(vi) would impose on the sponsor the responsibility for providing information that would promote the safe and effective use of prescription drugs in pediatric patients and noted that the sponsor may have complex reasons for not necessarily wanting to include pediatric information in the labeling. The comment recommended that the final rule include a mechanism that would allow summary information from authoritative published literature to be added to the labeling of currently marketed drugs so this information would be available to the pediatric prescriber. It suggested that the rule should provide an option permitting "recognized authoritative medical experts or groups of experts" to provide information to support pediatric information in the labeling in lieu of the sponsor.

Another comment urged the agency to provide for the incorporation of supplemental indications into drug labeling based solely on information submitted by persons other than the sponsor. The comment said that changes should be made based on studies reported in peer-reviewed medical literature, rather than relying on submissions by the sponsor. The comment stated that this was necessary to make the labeling of certain drugs, particularly anticancer agents, conform to the current state of medical knowledge. The comment noted that FDA restricts promotion of off-label uses, and third-party payers often take the position that agents that have no labeled indication for treatment of cancers in pediatric patients are experimental and therefore nonreimbursable, even though they may be safe and effective.

The sponsor is primarily responsible for bringing forth evidence to support labeling changes. A third party could, however, provide evidence to persuade the agency to direct the sponsor to submit a labeling supplement. A study need not have been conducted by or on behalf of the sponsor in order to support a labeling change. The evidence to support labeling should continue to be of the type and quality that would ordinarily support labeling statements. Published literature on pediatric use may contribute to this evidence, and authoritative groups may suggest approaches, but the views of authoritative groups do not themselves represent sufficient evidence of effectiveness. With respect to the comment concerning reimbursements, the agency advises that reimbursements to patients are beyond the scope of the rule and FDA authority. However, FDA agrees with the underlying concern that appropriate indications be on the label so that practitioners understand how best to prescribe the drug for the patient's medical benefit.

G. Proposed § 201.57(f)(9)(vii)

Proposed § 201.57(f)(9)(vii) (renumbered as § 201.57(f)(9)(viii)) states "[i]f the drug product contains one or more excipients that present an increased risk of toxic effects to

neonates or other pediatric subgroups, a special note of this risk, generally in the 'Contraindications,' 'Warnings,' or 'Precautions' section, shall be made."

20. Four comments expressed concern about this proposed requirement. One comment said that the data relating to the toxicity of excipients, including preservatives, are inconclusive, making the requirement inappropriate. The comment stated that FDA should encourage collection and analysis of data to enable specific determinations on the use of excipients and preservatives.

Another comment asked FDA to clarify whether the proposed requirement that labeling contain statements about excipients that present an increased risk of adverse effects to the neonate or other pediatric subgroups was intended to reflect published literature or to be based on studies designed to show whether an increased risk exists. It added that it was not clear how or by whom a determination of increased risk would be established. The comment suggested that the final rule state that a sponsor can rely on existing information and is not required to conduct additional studies. The comment also suggested that, if additional studies were necessary, animal data be used rather than requiring clinical studies in neonates. It suggested that a standardized list could be developed jointly by industry and FDA.

A third comment suggested that a requirement that any labeling identify any increased risk of toxic effects to neonates or other pediatric groups should not be interpreted as establishing a requirement that sponsors conduct toxicology or other studies to identify or quantify such risks. The comment also stated that the preamble to the final regulation should state whether the increased risk of toxic effects is limited to those established by human data or experience, or would also include those based on animal or in vitro models.

A fourth comment noted that ANDA holders may use excipients different from those used by the reference listed drug. The comment suggested that ANDA holders should be required to provide specific information regarding excipients used.

The final rule requires the labeling for a drug product containing one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups to note such risks in the "Contraindications," "Warnings," or "Precautions" section of the labeling. If toxicity data for the inactive ingredient(s) do not exist or are inconclusive, revised § 201.57(f)(9)(viii) would not require the labeling to contain a statement about an increased risk to neonates or other pediatric subgroups. However, in such cases, FDA encourages applicants to collect and analyze data on inactive ingredients and preservatives that could represent a pediatric risk. These data may include human data, animal data, or data derived from in vitro models.

FDA also notes that current regulations already require ANDA applicants whose inactive ingredients differ from those used in the reference listed drug to identify and characterize the inactive ingredients in a proposed drug product and to provide information demonstrating that such inactive ingredients do not affect the safety of the proposed drug product (see 21 CFR 314.94(a)(9)). Given these provisions, there is no reason to believe that the inactive ingredients used in a generic drug product are any less safe than those in the reference listed drug.

The agency has determined that, for the purposes of this final rule, the terms "excipient" and "inactive ingredient" have the same meaning. However, because the agency generally uses the term "inactive ingredient," the agency has, on its own initiative, amended proposed § 201.57(f)(9)(vii) to refer to "inactive ingredients" instead of "excipients."

V. Legal Authority

FDA's revision to the "Pediatric use" subsection of prescription drug labeling is authorized by the Federal Food, Drug, and Cosmetic Act (the act) and by the Public Health Service Act (the PHS act). Section 502(a) of the act prohibits false or misleading labeling of drugs, including, under section 201(n) of the act, failure to reveal material facts relating to potential consequences under customary conditions of use.

Section 502(f) of the act requires drug labeling to have adequate directions for use and adequate warnings against use by the pediatric population where its use may be dangerous to health, as well as adequate warnings against unsafe dosage or methods or duration of administration, as are necessary to protect users.

Section 502(j) of the act prohibits use of drugs that are dangerous to health when used in the manner suggested in their labeling. Drug products that do not meet the requirements of any paragraph of section 502 of the act are deemed to be misbranded.

In addition to the misbranding provisions, the premarket approval provisions of the act authorize FDA to require that prescription drug labeling provide the practitioner with adequate information to permit safe and effective use of the drug product. Under section 505 of the act, FDA will approve an NDA only if the drug is shown to be both safe and effective for its intended use under the conditions set forth in the drug's labeling. Section 701(a) of the act (21 U.S.C. 371(a)) authorizes FDA to issue regulations for the efficient enforcement of the act.

Under § 201.100(d) (21 CFR 201.100(d)) of FDA's labeling regulations, prescription drug products must bear labeling that contains adequate information under which licensed practitioners can use the drug safely for their intended uses. Section 201.57 describes specific categories of information, including information for drug use in selected subgroups of the general population, which must be present to meet the requirements of § 201.100.

In addition, under 21 CFR 314.125, FDA will not approve an NDA unless, among other things, there is adequate safety and effectiveness information for the labeled uses and the product labeling complies with the requirements of part 201 (21 CFR part 201).

Section 351 of the PHS act provides legal authority for the agency to regulate the labeling and shipment of biological products. Licenses for biological products are to be issued only upon a showing that they meet standards "designed to insure the continued safety, purity, and potency of such products" prescribed in regulations (42 U.S.C. 262(d)). The "potency" of a biological product includes its effectiveness (21 CFR 600.3(s)). Section 351(b) of the PHS act prohibits false labeling of a biological product. FDA's regulations in part 201 apply to all prescription drug products, including biological products.

A drug product that is not in compliance with § 201.57(f)(9) would be considered misbranded and an unapproved new drug under the act. A noncomplying product that is a biological product would, in addition, be considered falsely labeled and an unlicensed biological product under the PHS act.

VI. Implementation

The primary purpose of the proposed rule was to revise the existing pediatric labeling requirements by expanding the basis on which information about use of a drug in the pediatric population may be included. The proposed rule would have required sponsors to comply with the pediatric use provisions 1 year after the date of publication of a final rule in the Federal Register.

21. Several comments said that the proposed 1-year implementation period was too short. The comments claimed that extrapolating and reviewing data would be time consuming and that the agency would be unable to approve pediatric use labeling within 1 year. The comments suggested that the agency cooperate with industry to establish a 3-year implementation schedule, only require sponsors to submit revised labeling in 1 year, or make the rule effective in 2 years.

The agency has carefully considered the comments and has revised the implementation schedule for the final rule. The agency will accept pediatric use information based on revised § 201.57(f)(9) after January 12, 1995.

Sponsors have a continuing obligation to maintain labeling that is truthful and comprehensive in accordance with § 201.57, including § 201.57(f)(9). Section 201.57(f)(9) requires labeling to contain at least one of the statements under § 201.57(f)(9)(ii) through (f)(9)(vi), or to propose an alternative statement under § 201.57(f)(9)(vii). The statement must accurately describe available data.

Sponsors must, therefore, reexamine existing data to determine whether the "Pediatric use" subsection of the labeling can be modified based on adequate and well-controlled studies in adults and other information supporting pediatric use, and, if appropriate, submit a supplemental application to comply with new § 201.57(f)(9)(iv) by December 13, 1996. A sponsor who does not believe that the disease and drug effects are similar in the pediatric and adult populations, or who believes that use in pediatric patients is otherwise not adequately supported by data, should not propose revised labeling under new § 201.57(f)(9)(iv), and need not inform the agency of this conclusion.

Therefore, FDA expects sponsors to examine available information and update pediatric labeling for their products, if appropriate. Sponsors should also examine data on the extent and nature of use of their products in pediatric patients. If FDA concludes that a particular drug is widely used, represents a safety hazard, or is therapeutically important in the pediatric population, and the drug sponsor has not submitted any pediatric use information, then the agency may require that the sponsor develop and/or submit pediatric use information.

If FDA has made a specific request for the submission of pediatric use information because of expected or identified pediatric use, and the sponsor fails to provide such information, the agency may consider the product to be a misbranded drug under section 502 of the act, or a falsely labeled biological product under section 351 of the PHS Act, as well as an unapproved new drug or unlicensed biological product. (See 21 U.S.C. 355 and 42 U.S.C. 262).

Under the final rule, any new or revised pediatric indications, or statements on pediatric indications, or statements on pediatric use under the provisions of § 201.57(f)(9)(ii) through (f)(9)(iv) would require FDA approval of a supplemental application in accordance with § 314.70(b) or § 601.12. Other changes to proposed § 201.57(f)(9)(ii) through (f)(9)(iv) to add or strengthen precautions, contraindications, warnings, or adverse reactions or to add or strengthen dosage and administration instructions to increase a product's safety (for products other than biological products) could be put into effect at the time a supplement covering the change is submitted to FDA in accordance with § 314.70(c). Minor editorial changes to products other than biological products may be made in accordance with § 314.70(d).

To comply with this rule, references to "children" in the "Pediatric use" subsection of the insert labeling of products already being marketed must be changed, where appropriate, to "Pediatric population" or "pediatric patients." The agency advises that after January 12, 1995, such changes must be made, no later than the first time that labeling is sent to the printers or ordered for reprinting to replenish old stocks of labeling. Such changes for products other than biological products are considered minor editorial changes and may be submitted in an annual report in accordance with § 314.70(d).

Any new or revised statement under § 201.57(f)(9)(viii) regarding inactive ingredients that may be toxic to the neonate or other pediatric subgroup should be made in accordance with the provisions of § 314.70(c) or § 601.12 (21 CFR 601.12), as appropriate.

All supplements containing pediatric use information and their mailing covers should be plainly marked "Pediatric supplements."

For those products subject to section 351 of the PHS act, labeling changes should be made in accordance with § 601.12. Persons who have questions regarding such changes and need guidance on whether a supplement is necessary should contact one of the following three divisions as appropriate: Office of Therapeutics Research and Review, Division of Application Review and Policy (HFM-585), 301-594-5109; Office of Vaccine Research and Review, Division of Vaccine and Related Product Applications (HFM-475), 301-594-2090; or Office of Blood Research and Review, Division of Blood Applications (HFM-370), 301-594-2012; at the following address: Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852.

22. One comment suggested that the rule would have a substantial economic impact, particularly if the agency adheres to the proposed 1-year implementation period. The comment said that there are cost factors arising from the extensive resources required to reevaluate the available clinical study data and literature to extrapolate adult safety data to the pediatric age group or groups. The comment noted that drug studies in pediatric patients have additional costs not experienced with the adult population, and may, in some cases, require inpatient studies. The comment also claimed that encouraging pediatric studies prior to approval or as a Phase 4 commitment could lengthen the development process, slow drug approval, and thereby have an additional economic impact.

The agency has considered the comment and has revised the implementation schedule for this final rule. The implementation schedule is discussed in section VI. of this document.

The agency stresses that this rule does not require sponsors to conduct pediatric studies. The authority to require studies is found in the act and regulations already promulgated. Rather, this rule recognizes alternative methods of establishing substantial evidence to support pediatric labeling claims. Where a finding of substantial evidence to support a pediatric indication or a pediatric use statement has not been met for a specific subgroup or for any pediatric population, the sponsor must instead indicate that no data are available. If a sponsor believes that a pediatric use statement would be inappropriate or irrelevant to the labeling of a particular drug, it must provide a reason for omitting the statement. This rule does not affect any determination by the agency that pediatric studies are needed before or after approval for a new drug.

VII. Environmental Impact

The agency has determined under 21 CFR 25.24(a)(8) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VIII. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and the Regulatory Flexibility Act (Pub. L. 96–354). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The agency believes that this final rule is consistent with the principles set out in the Executive Order. In addition, the final rule is not a significant regulatory action as defined by the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the final rule does not impose additional requirements for sponsors to conduct pediatric studies, the agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required.

List of Subjects in 21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 201 is amended as follows:

PART 201—LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 508, 510, 512, 530–542, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 358, 360, 360b, 360gg–360ss, 371, 374, 379e); secs. 215, 301, 351 361 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 264).

2. Section 201.57 is amended by revising paragraph (f)(9) to read as follows:

§ 201.57 Specific requirements on content and format of labeling for human prescription drugs.

* * * * *

(f) * * *

(9) Pediatric use:

(i) Pediatric population(s)/pediatric patient(s): For the purposes of paragraphs (f)(9)(ii) through (f)(9)(viii) of this setion, the terms "pediatric population(s)" and "pediatric patient(s)" are defined as the pediatric age group, from birth to 16 years, including age groups often called neonates, infants, children, and adolescents.

(ii) If there is a specific pediatric indication (i.e., an indication different from those approved for adults) that is supported by adequate and well-controlled studies in the pediatric population, it shall be described under the "Indications and Usage" section of the labeling, and appropriate pediatric dosage information shall be given under the "Dosage and Administration" section of the labeling. The "Pediatric use" subsection shall cite any limitations on the pediatric indication, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. Data summarized in this subsection of the labeling should be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or "Clinical Studies" section. As appropriate, this information shall also be contained in the "Contraindications," "Warnings," and elsewhere in the "Precautions" sections.

(iii) If there are specific statements on pediatric use of the drug for an indication also approved for adults that are based on adequate and well-controlled studies in the pediatric population, they shall be summarized in the "Pediatric use" subsection of the labeling and discussed in more detail, if appropriate, under the "Clinical Pharmacology" and "Clinical Studies" sections. Appropriate pediatric dosage shall be given under the "Dosage and Administration" section of the labeling. The "Pediatric use" subsection of the labeling shall also cite any limitations on the pediatric use statement, need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population (e.g., neonates), differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. As appropriate, this information shall also be contained in the "Contraindications," "Warnings," and elsewhere in the "Precautions" sections.

(iv) FDA may approve a drug for pediatric use based on adequate and well-controlled studies in adults, with other information supporting pediatric use. In such cases, the agency will have concluded that the course of the disease and the effects of the drug, both beneficial and adverse, are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult efficacy data to pediatric patients. The additional information supporting pediatric use must ordinarily include data on the pharmacokinetics of the drug in the pediatric population for determination of appropriate dosage. Other information, such as data from pharmacodynamic studies of the drug in the pediatric population, data from other studies supporting the safety or effectiveness of the drug in pediatric patients, pertinent premarketing or postmarketing studies or experience, may be necessary to show that the drug can be used safely and effectively in pediatric patients. When a drug is approved for pediatric use based on adequate and well-controlled studies in adults with other information supporting pediatric use, the "Pediatric use" subsection of the labeling shall contain either the following statement, or a reasonable alternative: "The safety and effectiveness of (*drug name*) have been established in the age groups — to — (note any limitations, e.g., no data for pediatric patients under 2, or only applicable to certain indications approved in adults). Use of (*drug name*) in these age groups is supported by evidence from adequate and well-controlled studies of (*drug name*) in adults with additional data (insert wording that accurately describes the data submitted to support a finding of substantial evidence of effectiveness in the pediatric population)." Data summarized in the preceding prescribed statement in this subsection of the labeling shall be discussed in more detail, if appropriate, under the "Clinical Pharmacology" or the "Clinical Studies" section. For example, pediatric pharmacokinetic or pharmacodynamic studies and dose-response information should be described in the "Clinical Pharmacology" section. Pediatric dosing instructions shall be included in the "Dosage and Administration" section of the labeling. Any differences between pediatric and adult responses, need for specific monitoring, dosing adjustments, and any other information related to safe and effective use of the drug in pediatric patients shall be cited briefly in the "Pediatric use" subsection and, as appropriate, in the "Contraindications," "Warnings," "Precautions," and "Dosage and Administration" sections.

(v) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for a particular pediatric population, the

"Pediatric use" subsection of the labeling shall contain an appropriate statement such as "Safety and effectiveness in pediatric patients below the age of (—) have not been established." If use of the drug in this pediatric population is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the "Contraindications" or "Warnings" section of the labeling and this subsection shall refer to it.

(vi) If the requirements for a finding of substantial evidence to support a pediatric indication or a pediatric use statement have not been met for any pediatric population, this subsection of the labeling shall contain the following statement: "Safety and effectiveness in pediatric patients have not been established." If use of the drug in premature or neonatal infants, or other pediatric subgroups, is associated with a specific hazard, the hazard shall be described in this subsection of the labeling, or, if appropriate, the hazard shall be stated in the "Contraindications" or "Warnings" section of the labeling and this subsection shall refer to it.

(vii) If the sponsor believes that none of the statements described in paragraphs (f)(9)(ii) through (f)(9)(vi) of this section is appropriate or relevant to the labeling of a particular drug, the sponsor shall provide reasons for omission of the statements and may propose alternative statement(s). FDA may permit use of an alternative statement if FDA determines that no statement described in those paragraphs is appropriate or relevant to the drug's labeling and that the alternative statement is accurate and appropriate.

(viii) If the drug product contains one or more inactive ingredients that present an increased risk of toxic effects to neonates or other pediatric subgroups, a special note of this risk shall be made, generally in the "Contraindications," "Warnings," or "Precautions" section.

* * * * *

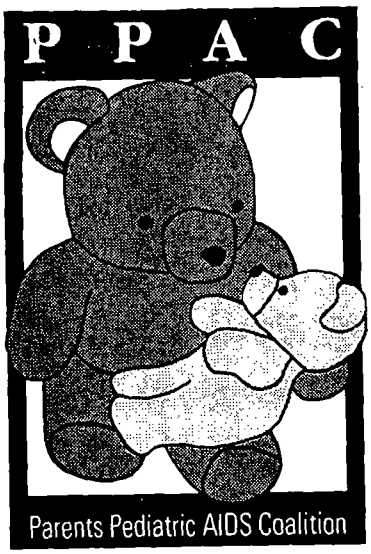
Dated: November 15, 1994.

David A. Kessler,

Commissioner of Food and Drugs.

[FR Doc. 94-30238 Filed 12-12-94; 8:45 am]

BILLING CODE 4160-01-F



Joan Milne, Director

December 21, 1996

FYI
-Pauline

Last month, the FDA began approval hearings on another new drug for AIDS patients. If approved, it would have made the tenth drug available for general use for adults with AIDS. While applauding the progress being made in AIDS research, myself, and a few other parents from Northern California, are extremely upset that none of this research is filtering down to our children. Are you aware that, out of the nine drugs already having FDA approval, only three are approved for use in children? And of those three, only two are approved for infants?

We, as parents of children with AIDS, got together to formulate a list of demands for the FDA and the drug companies. We then started a letter writing campaign aimed at informing the FDA of our dissatisfaction. We asked the parents of some of the children, as well as the children, themselves, to write about this issue. We also requested some input from other organizations dealing with childrenwith AIDS. Attached is the product of our collective frustrations.

We were also able to send one of the parents and her son back to Washington, in order to testify before the FDA. A packet containing this information was given to each of the panel members, and any media that were present. While I was on the Internet a few days later, I found an AP release of the FDA hearings, including a summary of Deb's statement. Much to my amzement, I found the following quote. "The panel issued a stern warning to drug makers not to seekapproval for any more AIDS therapies without at least preliminary testing in children". This is exactly what we hoped to accomplish. However, this is only the beginning. We still need to follow through and make sure the the drug manufacturers adhere to the warning.

I wanted you to be aware of the issues surronding all our children, and hope that we can count on you for your continuing support on this matter.

Sincerely,

Joan Milne
2724 Oak Rd #119
Walnut Creek, CA 94596
(510) 945-7735

CHILDREN WITH HIV/AIDS NEED EQUAL ACCESS TO ALL AVAILABLE MEDICATIONS

PARENT'S DEMANDS
REGARDING PEDIATRIC DRUG APPROVAL

As mothers of children with HIV and AIDS, we have an extremely tough fight on our hands. Not only must we deal with the physical and emotional impact of this disease in our children, but we are faced with an uncaring and unwilling pharmaceutical industry which for years has ignored our plight.

Presently, there are nine antiretrovirals approved to fight HIV. Approval on a tenth is anticipated. Of these ten drugs, only three are labeled for use in children, only two for infants. The World Health Organization estimates that by the year 2000, there will be ten million children infected with the AIDS virus worldwide.

WE THEREFORE DEMAND:

□ **Safety studies in children** must begin immediately upon preliminary efficacy data in adults with pediatric studies written no later that the initiation of adult Phase II studies. These studies should begin regardless of formulation. If a company does not currently have a suspension, they must **initiate research in children able to take pills and capsules.**

□ Only **conditional approval should be given by the FDA to drugs when the pharmaceutical sponsor seeks approval without pediatric data**. We do not wish to delay access to adults with HIV and AIDS. However, the pharmaceutical industry must be held accountable to children's needs as well and full approval should be contingent upon presentation of pediatric data.

□ Industry sponsors should **approach the FDA for revised labeling as soon as safety data are available** on any pediatric population.

□ The pharmaceutical sponsors should **seek more palatable suspensions** or ways of making them more tolerable especially for young children. The technology for this already exists and should be used.

□ A task force has already met to discuss existing pediatric viral load data and make recommendations for its use in clinical practice. We insist that **recommendations regarding viral load monitoring in children** are quickly and directly distributed to pediatricians, community based organizations and community newsletters; as well as the standard publications and journals.

With the support of others in the HIV community, we are certain to achieve our goal of insuring equal and early access for children to promising therapies for the treatment of HIV and other pediatric life-threatening diseases.

Parents of children in Northern California:
Deb, Dorothy, Joan, Linda, and Marilyn

SUPPORTING ORGANIZATIONS LIST IN FORMATION:
Parents' Pediatric AIDS Coalition
Pediatric Advocacy Network
Sunburst Projects
Positively Kids
ACT UP Golden Gate

Statement by Deborah L. Scheer

Food and Drug Administration
Drug Advisory Committee Hearing

November 22, 1996

My lively and wondrous son, Dillon, and I live on the Russian River in Sonoma County in Northern California. Sonoma County has the largest population of people living with AIDS in any rural county in America. I chose to live there because my son has HIV, and I felt that the services and the community would help support both of us. As it's happened, we've been embraced and surrounded by many people with deep compassion and direction.

Our new friends, our new family, are pro-active and front-runners with the relatively new HIV treatment therapies. From the studies done with adults on the new drugs, their doctors are informed about the drugs' efficacy, dosing, side effects, etc. and therefore better able to help their patients make treatment decisions. Their doctors understand viral load testing results and use it as an important diagnostic tool in keeping the virus under control. With the viral load test and combination therapy, our friends are doing a lot better. Through the passing summer, Dillon and I watched our friends feel stronger and more hopeful. For many of them, it's the first time since their diagnoses that they are thinking about their futures and the possibility of growing old. It was a truly joyous summer, and Dillon and I enjoyed and shared the excitement with our friends.

But then came the end of summer, and I learned that our children and their families can't and don't have the hope that the adult community has. Our children have only three drugs approved for pediatric use. This is less than one third the availability for adults. The drug that we want approved today, delaviridine, will be the tenth drug used to fight HIV. However, even this drug has no pediatric data. And while they've been doing viral load testing on children for awhile, the pediatric HIV doctors haven't been informed of their findings and what this means in children.

My son, Dillon, is a very bright and active child with few symptoms thus far. He had a wonderful summer, and I hope he has many, many more. But, Dillon has already lost several young friends and a foster baby brother to HIV. And, at the end of the summer, I learned that three of

Dillon's closest friends, Sam, Josh, and Sammy, had rising viral loads and their CD-4 counts were dropping.

Sam's mother shared with me her conversation with Sam's doctor. The doctor was crying with her over the results of Sam's lab tests. What could possibly make this doctor cry? Could it have been she didn't have new drugs to treat Sam? Sam had already exhausted the only three drugs available to him. Or, perhaps it was her fear of treating Sam with drugs that have not yet been tested on kids and, therefore, she could be taking an incredible risk with his life? Or, was it that she could see his end coming because she didn't have anything to offer him, and it was tearing her apart?

Josh's parents have chosen not to disclose his diagnosis to him to protect him from additional stress in his already complicated life. His mother has been frantic over the last couple of years. Josh has a T-Cell count of under 40 and a rising viral load. I'm sure to ease his mother's absolute dread, Josh's doctor readily points to the fact that they really don't know what viral load results mean in children, and that clinically he looks great. Well...I need to ask, "would or could a doctor who's treating a child with leukemia tell his mother that though his lab tests were showing disease progression, not to worry because the child looks great?" I don't think so! Josh deserves and needs combination therapy, but his doctor won't put him on any of the other five or six approved drugs because they haven't been tested for dosage, side effects and efficacy on children.

The grandmother of another one of Dillon's friends, Sammy, drives him eight hours a month for lab tests. She returns home with horrifying results and with the same treatment that has been failing to stop the virus from further destroying his immune system. Sammy is a bright and beautiful six year old boy who goes to the schools in his community to talk about HIV, how it impacts him, and how the students can protect themselves. He and his grandmother are well known and loved in their community. Little Sammy is a hero. And he is going to die.

My son is strong and healthy right now. I love him with all my heart! But love will not stop the virus. I can't protect him alone. I know this personally from having loved and lost Justin, Dillon's foster brother. All my love could not protect him. HIV claimed his life on his fifth month birthday. With so few treatment options for children, Dillon is not walking far behind Sam and Josh and Sammy. Without major changes in our whole system now, we are setting up Dillon and his friends and many other children for very, very short lives. This is unacceptable to me and families

across the nation. Let alone all those families from other countries who look to the United States for therapies and direction. Even if you could be persuaded to act now, start making changes now, I hope to God it's not too late for Sam and Josh and Sammy.

We need six different things to happen to save Sam, Josh, Sammy, Dillon and all the other HIV+ children:

1. We need safety studies in children that begin immediately upon preliminary efficacy data in adults, regardless of formulation. For example, if a company doesn't have a suspension, it can still start research with young children who can swallow pills and capsules.

2. Our children need equal and early access to promising therapies through expanded access programs such as compassionate use and parallel track.

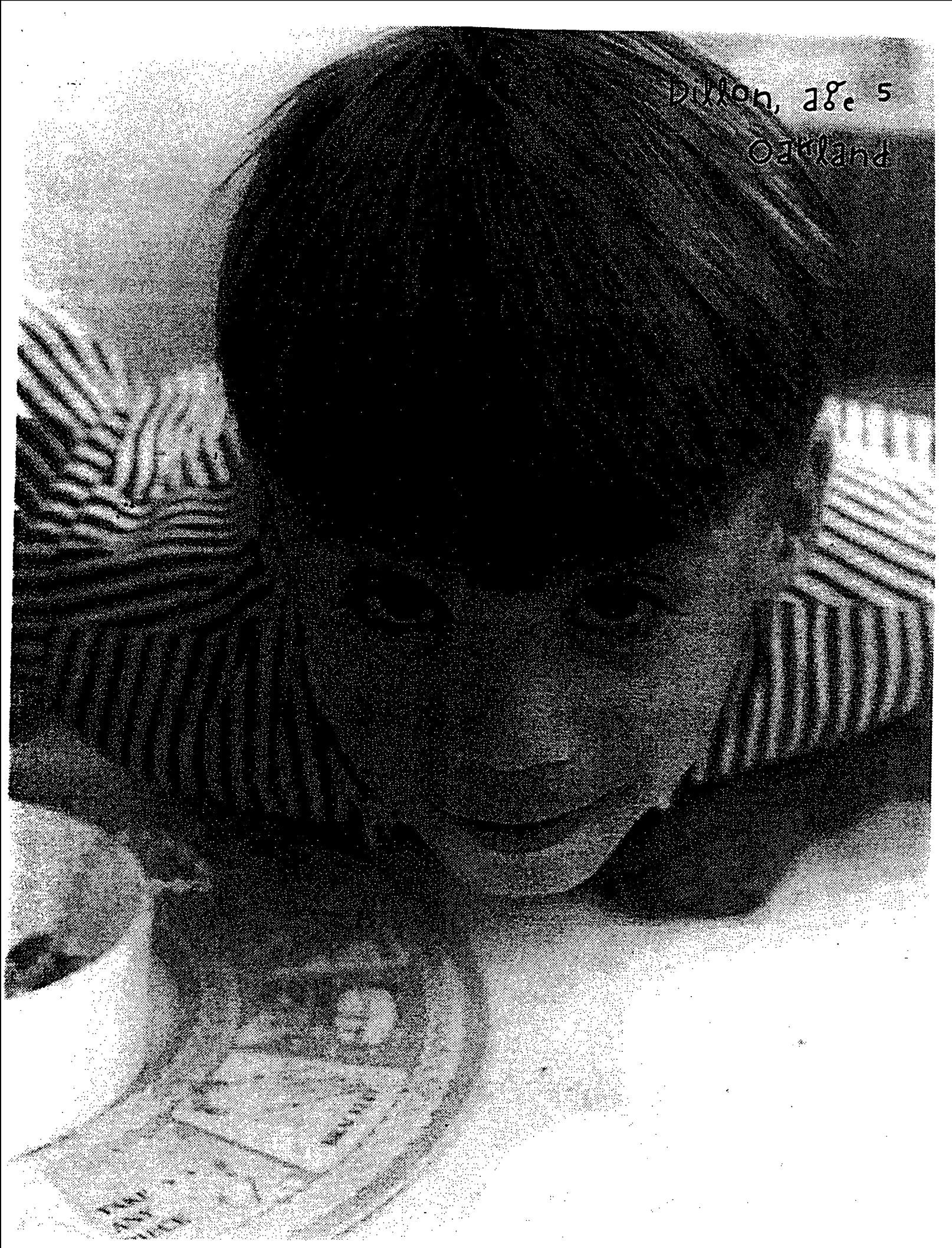
3. We need industry sponsors to approach the FDA for revised labeling as soon as safety data is available on any pediatric population.

4. We want conditional approval given to drugs when a sponsor seeks approval without pediatric data.

5. Using existing technology, pharmaceutical sponsors should seek more palatable suspensions or ways of making them more tolerable, especially for young children.

6. So that pediatricians will have a better understanding of the practical application of viral load results as a monitoring tool, the Secretary of Health and Human Services should convene a task force to compile, interpret and disseminate existing pediatric viral load data.

On behalf of my son, and all the children with AIDS in America, I thank you for your attention and urge you to address these issues with speed and compassion.


Dijon, age 5
Oakland

fUA

DIE VRW S DIE

DILLON

written by:
Gerald
HW postcwz
child

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DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
001a. letter	constituent to Drug Advisory Committee Members re: personal AID's story (1 page)	11/13/1996	b(6)

COLLECTION:
Clinton Presidential Records
Domestic Policy Council
Elizabeth Drye
OA/Box Number: 10452

FOLDER TITLE:
Pediatric Uses [2]

2014-0046-S
rc1371

RESTRICTION CODES

Presidential Records Act - [44 U.S.C. 2204(a)]

P1 National Security Classified Information [(a)(1) of the PRA]
P2 Relating to the appointment to Federal office [(a)(2) of the PRA]
P3 Release would violate a Federal statute [(a)(3) of the PRA]
P4 Release would disclose trade secrets or confidential commercial or financial information [(a)(4) of the PRA]
P5 Release would disclose confidential advice between the President and his advisors, or between such advisors [a)(5) of the PRA]
P6 Release would constitute a clearly unwarranted invasion of personal privacy [(a)(6) of the PRA]

C. Closed in accordance with restrictions contained in donor's deed of gift.
PRM. Personal record misfile defined in accordance with 44 U.S.C. 2201(3).
RR. Document will be reviewed upon request.

Freedom of Information Act - [5 U.S.C. 552(b)]

b(1) National security classified information [(b)(1) of the FOIA]
b(2) Release would disclose internal personnel rules and practices of an agency [(b)(2) of the FOIA]
b(3) Release would violate a Federal statute [(b)(3) of the FOIA]
b(4) Release would disclose trade secrets or confidential or financial information [(b)(4) of the FOIA]
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b(7) Release would disclose information compiled for law enforcement purposes [(b)(7) of the FOIA]
b(8) Release would disclose information concerning the regulation of financial institutions [(b)(8) of the FOIA]
b(9) Release would disclose geological or geophysical information concerning wells [(b)(9) of the FOIA]

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DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
001b. letter	constituent to FDA re: personal AID's story (1 page)	11/13/1996	b(6)

COLLECTION:
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Domestic Policy Council
Elizabeth Drye
OA/Box Number: 10452

FOLDER TITLE:
Pediatric Uses [2]

2014-0046-S
rc1371

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001c. photograph	re: Sam (1 page)	n.d.	b(6)

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OA/Box Number: 10452

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COLLECTION:
Clinton Presidential Records
Domestic Policy Council
Elizabeth Drye
OA/Box Number: 10452

FOLDER TITLE:
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COLLECTION:
Clinton Presidential Records
Domestic Policy Council
Elizabeth Drye
OA/Box Number: 10452

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b(9) Release would disclose geological or geophysical information concerning wells [(b)(9) of the FOIA]

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DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
001f. photograph	re: Whitney (1 page)	n.d.	b(6)

COLLECTION:
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Domestic Policy Council
Elizabeth Drye
OA/Box Number: 10452

FOLDER TITLE:
Pediatric Uses [2]

2014-0046-S
rc1371

RESTRICTION CODES

Presidential Records Act - [44 U.S.C. 2204(a)]

P1 National Security Classified Information [(a)(1) of the PRA]
P2 Relating to the appointment to Federal office [(a)(2) of the PRA]
P3 Release would violate a Federal statute [(a)(3) of the PRA]
P4 Release would disclose trade secrets or confidential commercial or financial information [(a)(4) of the PRA]
P5 Release would disclose confidential advice between the President and his advisors, or between such advisors [a)(5) of the PRA]
P6 Release would constitute a clearly unwarranted invasion of personal privacy [(a)(6) of the PRA]

C. Closed in accordance with restrictions contained in donor's deed of gift.
PRM. Personal record misfile defined in accordance with 44 U.S.C. 2201(3).
RR. Document will be reviewed upon request.

Freedom of Information Act - [5 U.S.C. 552(b)]

b(1) National security classified information [(b)(1) of the FOIA]
b(2) Release would disclose internal personnel rules and practices of an agency [(b)(2) of the FOIA]
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DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
001g. letter	Constituent to Members of the Drug Advisory Committee re: personal AID's story (1 page)	11/12/1996	b(6)

COLLECTION:
Clinton Presidential Records
Domestic Policy Council
Elizabeth Drye
OA/Box Number: 10452

FOLDER TITLE:
Pediatric Uses [2]

2014-0046-S
rc1371

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DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
001h. letter	Constituent to FDA re: personal AID's story (1 page)	n.d.	b(6)

COLLECTION:
Clinton Presidential Records
Domestic Policy Council
Elizabeth Drye
OA/Box Number: 10452

FOLDER TITLE:
Pediatric Uses [2]

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001i. letter	From Constituent re: personal AID's story (1 page)	n.d.	b(6)

COLLECTION:
Clinton Presidential Records
Domestic Policy Council
Elizabeth Drye
OA/Box Number: 10452

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The Legal Community's Caring Response to AIDS

ALRP
AIDS LEGAL REFERRAL PANEL

November 15, 1996

Drug Advisory Committee
Center for Drug Evaluation and Research
HFD-21, Food and Drug Administration
5600 Fisher's Lane
Rockville, MD
20857

Dear Advisory Panel Members:

We are pleased to have the occasion of the review of delavirdine before the FDA Drug Advisory Panel to write to you. We fully support the approval of new non-nucleoside analogs to broaden the treatment options available to people living with HIV disease. However, we must insist that *all* drugs approved by the FDA for the treatment of HIV, including delavirdine, be accessible to *all* people with HIV.

The approval of delavirdine will bring the latest in medical technologies only to those who have been represented in the clinical trials to date. Tragically, it does not result in more treatment options for pregnant women, who are currently only offered AZT monotherapy as an FDA-approved treatment. Single drug treatment for HIV is no longer acceptable, given the potential comparative efficacy of combination therapy. In no other population is AZT monotherapy now considered standard treatment. The FDA's continued neglect of the growing numbers of pregnant women with HIV in the face of promising therapies is causing HIV to become an illness whose course is defined by the availability, or lack, of these therapies for different populations. The discrepancy between the choices available for pregnant women and adults in general constitutes nothing less than discrimination. The FDA must enroll pregnant women in clinical trials as soon as possible.

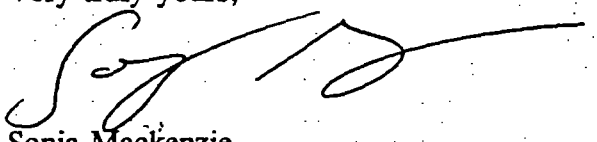
Similarly, children, who are in desperate need of the most effective drugs possible, will not benefit from the approval of delavirdine without the development of clinical trials. HIV disease typically progresses more quickly to an AIDS diagnosis in children, and they need FDA-approved protease inhibitors available to them, in addition to the three other types of drugs currently available. This makes it all the more imperative that the FDA also enroll children in clinical trials as soon as possible. An often-cited reason in defense of the lack of drug trials involving children is the claim that there are not enough infants and children to enroll in these clinical trials. However, there are thousands of children across the country who are being seen by the 60 lead and 350 affiliate care centers funded through Title IV of the Ryan White CARE Act, and are fully eligible for participation in clinical trials.

582 Market Street • Suite 912 • San Francisco, CA • 94104-5310

FDA Drug Advisory Committee
November 15, 1996

Given this oversight of these populations, the FDA is failing to fulfill its responsibility to provide approved therapies for all people living with this illness. We urge you to consider the impact that this neglect is having on women, children, and families across the country who are living with the knowledge that they are being denied treatments as others are rightfully offered the opportunity to live healthier lives. Pregnant women and children cannot live without these treatments.

Very truly yours,



Sonja Mackenzie
Public Policy Assistant

SUNBURST PROJECTS
POST OFFICE BOX 2824
PETALUMA, CA 94953
FAX (707) 769-0780
TEL (707) 769-0169

Serving Children and Families Living with HIV/AIDS

CAMP SUNBURST

SUNBURST NATIONAL AIDS PROJECT

EDUCATIONAL OUTREACH

COUNSELING SERVICES

ADVOCACY

Those who bring sunshine to the lives of others cannot keep it from themselves

November 14, 1996

Food and Drug Administration
5600 Fishers Lane
Rockville MD 20857

Re: Application #20-705 (Delaviridine - Pharmacia-Upjohn)

Dear Panel Members:

We are writing to express our deep concern about the lack of efficient and rapid formulation of well-designed research protocols that include all ages of children within the HIV/AIDS pediatric population. Time is of the essence in evaluating new drugs for children, and safety studies in children must begin immediately upon the availability of preliminary efficacy data in adults. Today, with modern technology, pharmaceutical sponsors should not be grappling with ways to make medications more tolerable to children. Perhaps the issue of a special pediatric formulation is just an excuse to further limit studies to adult populations.

AIDS Clinical Trials Groups need to be increased so as to facilitate the evaluation of promising new agents for the treatment of HIV infection in children at the same time these clinical trails are being conducted for the adult population. These investigational treatment programs should be located in areas of the country where children with HIV/AIDS are most heavily concentrated, thus expanding child client access to compassionate use therapies.

Despite the cost crisis facing people living with HIV/AIDS in accessing promising protease inhibitors------

OUR NATION'S CHILDREN SHOULD HAVE EQUAL ACCESS TO THESE PROTEASE INHIBITORS AS WELL AS OTHER DRUGS APPROVED FOR ADULTS LIVING WITH HIV/AIDS.

THESE PRODUCTS SHOULD BE DEVELOPED IN CONCERT WITH ADULT RESEARCH.

We urge you to take responsibility so that our children are ensured quality pediatric care. Thank you for your leadership on behalf of our nation's children.

Sincerely,

Geri Brooks, Ph.D.
Executive Director
SUNBURST PROJECTS

Drug Advisory Committee
Center for Drug Evaluation and Research
HFD-21, Food and Drug Administration
5600 Fisher's Lane
Rockville, MD 20857

Dear Advisory Panel Members,

You have the honor of reviewing delavirdine, a drug which promises to allow those living with HIV and AIDS to step further into their own lives and to reclaim their futures. With the discovery of protease inhibitors and the powerful proof of combination therapies, the past years have indeed seemed to bring a new wave of hope into our communities. Those who were diagnosed as positive years ago and were told to put aside the rest of their life so that they could die, are now slowly beginning to pick up the pieces and learn how to live, again. The ripples of hope and newly-lit optimism are making their way into our media and, as the newspapers, magazines, and televisions tote the era of an AIDS "cure," our psyches are slowly becoming accustomed to these ideas. Yet, where children, pregnant women, low-income and homeless individuals are concerned, there is a profound silence. We must begin to address this silence.

You sit here today to review the approval of delavirdine, which, if passed, would exist as the tenth approved drug available for those living with HIV and AIDS. *Adult, non-pregnant, well-provided for* people living with HIV and AIDS. As of this date, only three drugs have been approved for pediatric use: AZT, ddI, and 3TC. As the doors of health are finally opening wider for much of this nations populace, children - born and unborn- and pregnant women are simply being squeezed out. This ever-growing chasm of opportunity is simply unacceptable.

The argument for equal health care seems simple, yet as we all know, the approval of safe drugs involves the cooperation, participation, and energy of many experts in many different fields. In a recent "Wall Street Journal" article, the dearth of approved pediatric drugs was aptly attributed to the economy: "The attitude of the drug companies is that it's not economically feasible or profitable because there are a limited number of children" (11/15/96). There are <u>thousands</u> of young children today who are HIV positive and whose viral count, because of the lack of access to drugs, is increasing at a rapid rate. How many more infected children will it take before the drug companies consider the project of prolonging their lives as something which is economically profitable??

I write to you as an HIV Services Specialist working at a non-profit clinic in San Francisco. Here, we run our services based on the premise that health care for all is a right, not a privilege. I hope that you take this message forward today and lend a voice to all those children and pregnant women who could not be here. Your input could make a real difference - it could even mean that women and children take one more step into the horizon of future living.

Very sincerely,

Katherine Gergen

Katherine Gergen
HIV Services Specialist

4:06 PM (ET) 11/22

FDA Advisers Mull AIDS Drug

GAITHERSBURG, Md. (AP) -- Scientific advisers deadlocked Friday over whether to allow AIDS patients to buy a new drug, citing conflicting evidence over whether it works and who should use it.

Pharmacia & Upjohn had argued that delavirdine would help kill the HIV virus in early-stage patients' blood and slightly boost their immune system when used in combination with older medicines.

But the improvement was so slight -- and the drug failed to do any good for late-stage patients -- that advisers to the Food and Drug Administration were left wondering how any doctor would know how to prescribe delavirdine.

"We're in a tough position," said Dr. Wayne Greaves of Howard University Hospital, before the panel voted 4-4 on whether the drug should be approved. "There are still patients who need additional drugs."

"A year ago, I would have viewed this very differently," said Dr. Christopher Mathews of the University of California, San Diego, who questioned approving a drug that showed such minimal effect when just this year three powerful new medicines began selling, promising patients significant improvement.

But the panel urged the FDA not to make a final decision until doctors finish analyzing an additional study to confirm the drug's impact, data due to be completed in mid-January.

The tie vote came after mothers tearfully protested that Pharmacia, like almost every AIDS drug manufacturer, had not even begun testing to determine whether delavirdine would help HIV-infected children.

Of the nine AIDS drugs sold Friday, only three are approved for children's use -- and they do not include the newest, most potent AIDS therapies. The mothers accused drug makers and the FDA of ignoring children's desperate need in the race to sell AIDS medicines to adults.

"Love will not stop the virus," said Deborah Scheer of Sonoma County, Calif., as her HIV-infected son, Dylan, gazed at the panelists. "I cannot protect him alone and I need your help."

The panel issued a stern warning to drug makers not to seek approval for any more AIDS therapies without at least preliminary testing in children.

But for delavirdine, the issue was whether the drug even works in adults.

One study of 720 patients showed it modestly helped adults who were not yet seriously ill, when used in combination with the oldest AIDS drug, AZT. Patients who took both drugs saw a slight rise in important immune cells called CD4s, gaining about 30 cells per milliliter of blood after a year of therapy while those who took AZT alone lost CD4 cells. The delavirdine patients also lost about twice as much of the virus floating in their blood as did those who took just AZT.

But a study of severely ill patients found delavirdine taken with another older medicine, ddI, found that small benefit lasted only 12 weeks. By year's end, not only were delavirdine patients doing no better but 66 of them had died, compared with 61 who took ddI alone.

Worse, the scientists said, delavirdine hasn't been tested in combination with the three newest AIDS drugs, a new class of drugs called protease inhibitors that has proved so potent that a three-drug combination including one of these medicines has become standard care for advanced patients.

Delavirdine doesn't attack the HIV virus in the same manner as protease inhibitors, working instead more similarly to AZT.

But Pharmacia argued delavirdine does have potential. Genetics testing of 34 patients suggested when the drug is combined with AZT, it can halt or even reverse the AIDS virus' dangerous ability to mutate until AZT is useless. That study showed delavirdine caused an 85-fold increase in patients' susceptibility to AZT treatment.

And the panelists agreed that delavirdine is "leaps and bounds safer" than most other AIDS drugs. Its chief side effect was a skin rash.

Hope for Children with AIDS

Pediatric AIDS Foundation

PEDIATRIC STUDIES IN PHARMACEUTICALS URGENTLY NEEDED

THE PROBLEM

Approximately 80% of all pharmaceuticals now on the market have not been tested for safety and effectiveness in children.

- Pediatricians, pharmacists, and parents are generally forced to guess about the safety and dosing of such drugs for children, even when the drug is the only known therapy for a serious disease.
- FDA has tried to encourage drug companies to conduct pediatric studies, but generally without success.
- FDA maintains that it has no means by which to compel pediatric research.

The problem seems to be getting worse.

- None of the new AIDS therapies has pediatric data, even though there is every theoretical reason to believe that the drugs would be as effective in children as in adults. Despite drug company promises to FDA that they would start research in children after the drug is approved for adults, such trials have not begun, delaying pediatric use by years.
- A survey of pediatric AIDS patients has shown that very few of these children are taking the new therapies, despite access to good medical care. Surveys of similarly situated adults would show that many are getting such drugs.

Distinct pediatric data are needed. Children are not just "little adults;" they often metabolize drugs very differently from adults and dosages are dependent on both metabolism and size.

- There are classic cases of drugs that are safe in adults being toxic--even lethal--for children.

Drug companies do not gather pediatric data for a number of possible reasons.

- Children are a very small market for most drugs. Research on children will not provide the enormous returns that research on adults will.
- Drug companies sometimes believe that children are difficult to recruit for trials (although when such trials are actually begun such problems are rare).
- Drug companies sometimes believe that a side effect or bad reaction by a child in research may slow FDA approval of the therapy for adults. (Companies also may fear that if they do pediatric trials and their competitors do not, such an adverse reaction may put them at a competitive disadvantage with similar companies who do not do such research.)

CO-FOUNDERS: Susan DeLaurentis/Elizabeth Glaser/Susan Zeegen
1311 Colorado Avenue, Santa Monica, California 90404
TEL: (310) 395-9051 FAX: (310) 395-5149

THE PROPOSAL

FIRST, FDA should require that all <u>new</u> drug applications (for drugs for which children are foreseeable users) contain pediatric safety and dosing data as a condition for approval.

- Such a requirement is supported by the law.
- The Food, Drug, and Cosmetic Act requires that drugs be "safe and effective," not "safe and effective for adults only."
- The legislative history of the Act is filled with clear Congressional intent to protect children.

Such a requirement for pediatric data will not slow approval of drugs.

- Pediatric safety and dosing studies can be done *at the same time* as adult studies on effectiveness. Since safety and dosing are relatively brief when compared to effectiveness studies, they can be completed long before effectiveness trials are completed and ready for submission to the FDA.
- Under revised regulations (December 1994), drug companies are *not required to conduct the more time-consuming effectiveness trials in children.* FDA will generally allow companies to extrapolate adult effectiveness trials to show effectiveness in children, so long as safety and dosing studies are done.
- Safety and dosing studies are generally relatively brief (3-12 months) and relatively small (30-60 patients) and are, therefore, relatively inexpensive.

SECOND, FDA should require manufacturers of already-approved drugs (that are determined to be significantly needed by children) to conduct pediatric trials over a reasonable period of phase-in or have the drug withdrawn as mislabeled.

- An immediate enforcement of a requirement of pediatric studies would be unfair and unworkable for already approved drugs.
- Such pediatric data are, nonetheless, needed, both because some doctors prescribe such drugs for children (even without data) and because some doctors do not prescribe such drugs (because of the lack of data).
- Since effectiveness trials are generally not required for children, these trials can be relatively small and relatively brief, and, therefore, relatively inexpensive.

EXPECTED RESPONSE

Some drug companies will protest that the requirement of pediatric data will cost them money.

- But note that the requirements for safety and dosing data can be met by doing relatively brief, small, and inexpensive studies.

- And note that drug companies will be forced to argue against a pediatric data requirement *without an alternative proposal* for gathering such data and *with a very bad past history* of ignoring the issue.

Some drug companies and Members of Congress may propose to create quasi-patent incentives for doing pediatric studies rather than requirements.

- Such legislation was discussed in both the 103rd and 104th Congress, but with no action.

- But note that such incentives are not efficient (only the biggest drugs will be tested) and are expensive (because market exclusivity delays the advent of cheaper generic drugs).

Pediatric groups (ranging from generalities (such as the American Academy of Pediatrics) to specialists such as the Pediatric AIDS Foundation) will actively support the new requirements.

Press interest will be high.

Prepared by the Georgetown Federal Legislation Clinic on behalf of the Pediatric AIDS Foundation (c:\wpdocs\cp\tp)

Corey Smoor
1/7/97

FDA - Simplified requirements for approval
- POUFA - may waive Fees

Meeting w/UP - microbicides, vaccines
- followed by keystone grp.
- annual budget 500,000

licensed drugs - carb. ratsma, pediatric
- free drugs
- govt protocols
- 3rd party payers
- providers provide patients

vaccines - new evaluation — Separate — {expedited licensing
pediatric applications — other drugs
microbicides - (pre research)

Padwa - Parents Pediatric AIDS organizations

Hope for Children with AIDS

Pediatric AIDS Foundation

PROPOSED ACTION PLAN

- During the week of December 16, the President would issue an Executive Order and accompanying statement, directing the FDA to take immediate regulatory action to ensure that all drugs be proven safe and effective for use by children prior to their approval by the FDA.

- The Executive Order would:

  - ***Describe the dire need for pediatric data.*** The Order would explain that 80% of all drugs currently on the market have not been proven safe and effective for use by children. The order would explain the ramifications of this situation, namely that (1) children are being denied life-saving therapies because physicians are afraid to prescribe potentially toxic drugs that have not been approved for use by children, and (2) children may be exposed to an increased risk of adverse reactions or decreased effectiveness of the drugs prescribed because pediatricians do not have appropriate dosage data.

  - ***Explain that FDA has the statutory authority to require pediatric data prior to its approval of a new drug.*** The Order would explain that pursuant to the approval and labeling requirements of the Food, Drug, and Cosmetic Act, the FDA has the authority to require pediatric data.

  - ***Direct the FDA to promulgate regulations, as a condition of approval for all new drugs for which children are foreseeable users, that pharmaceutical manufacturers submit pediatric safety data, and, as appropriate, pediatric efficacy data.***[1] The Order would direct the FDA to promulgate new regulations in accordance with the "notice and comment" procedures of the Administrative Procedure Act.

  - ***Direct the FDA to issue the proposed regulations as soon as possible.*** The Order would direct the FDA to publish, within 90 days, new proposed regulations for public comment.

---

1. In most instances, efficacy data for use by children can be extrapolated from adult efficacy data.

CO-FOUNDERS: Susan DeLaurentis/Elizabeth Glaser/Susan Zeegen
1311 Colorado Avenue, Santa Monica, California 90404
TEL: (310) 395-9051 FAX: (310) 395-5149

- The statement accompanying the Executive Order would:
  - ***Describe the urgent need for pediatric data.***
  - ***Declare that drugs should be safe and effective for all foreseeable users, not just adults.***
  - ***Speak about the need to ensure that children share in and benefit from therapeutic progress.***
  - ***Dedicate this action to Elizabeth Glaser, and her work to improve child health.*** (Note: December 3rd was the 2nd anniversary of Elizabeth's death from AIDS-related complications.)
- Prior to issuance of the Executive Order, David Kessler and Bill Schultz (as well as PAF representatives) would be consulted about the wording of the Order to ensure that it is on clear legal footing.
- Children, pediatricians, scientists, and advocates would be present when the President signs the Order. Attendees would include:
  - Representatives from the Pediatric AIDS Foundation
  - Children with life-threatening illnesses, such as AIDS and cancer
  - Parents of children with life-threatening illnesses who have been denied needed therapies because of the lack of pediatric data
  - Pediatricians and scientists who have advocated for the need for pediatric data
- Pediatric AIDS Foundation and other child advocacy organizations would issue press releases lauding the President's efforts to protect the health and safety of American children.

Office of HIV/AIDS Policy

Office of the Assistant Secretary for Health
U.S. Public Health Service/DHHS
200 Independence Avenue, S.W.
Washington, D.C. 20201
Tel. (202) 690-5560

☐ Room 733-E
Fax. (202) 690-6584

☐ Room 730-E
Fax. (202) 690-7560

Deliver to: Elizabeth Dorr

Fax: 456-7028
Tel: 456-5573

From: Deborah von Zinkernagel
Date: 1/8 : ____

This fax contains 2 pages + cover

If transmission problems occur, please call ____

Comments: NIH is sending additional stuff in the hour. If other materials are helpful, I will fax them for your file.

Status Report of NIH Studies on Protease Inhibitors in Reducing Perinatal Transmission

The National Institutes of Health (NIH) is currently developing several clinical trial protocols to evaluate three protease inhibitors in combination with other agents in HIV-infected pregnant women and children. These studies will be conducted by the Pediatric AIDS Clinical Trials Group (PACTG), which is sponsored by the National Institute of Allergy and Infectious Diseases and the National Institute of Child Health and Human Development. These are phase I clinical trials to evaluate the safety, pharmacokinetics, and tolerance to ritonavir, indinavir and nelfinavir in combination with AZT and lamivudine (3TC). It is anticipated that enrollment into these trials will begin in the second quarter of fiscal year (FY) 1997. While the three protease inhibitors have been previously tested in HIV-infected adults, these studies will be the first clinical trials evaluating the effects of the agents in potentially reducing maternal viral load in HIV-infected pregnant women.

These agents also will be evaluated among HIV-exposed neonates and infants. A clinical study, designated ACTG 345, is currently being developed as a phase I protocol to evaluate the safety and pharmacokinetics of ritonavir in young HIV-infected infants. It is anticipated that this clinical trial will open for enrollment in the next few months. At present, there are no plans to study indinavir in neonates due to the lack of an appropriate liquid formulation and because of drug-associated hyperbilirubinemia and potential risk for kernicterus in the newborn. A clinical protocol to evaluate nelfinavir in neonates is planned in the near future.

Following the completion of these phase I studies, a phase III clinical trial of combination therapy that includes a protease inhibitor is planned for testing in HIV-infected pregnant women and possibly in newborns. The selection of which protease inhibitor to be evaluated will be based on the phase I/II tolerance, safety and pharmacokinetics studies; the currently planned study is to compare the ACTG 076 AZT regimen, AZT/3TC, AZT/protease inhibitor, and AZT/3TC/protease inhibitor combinations. It is anticipated that this study will be open for enrollment during FY 1998.

Prepared by the NIH/Office of AIDS Research
October 3, 1996

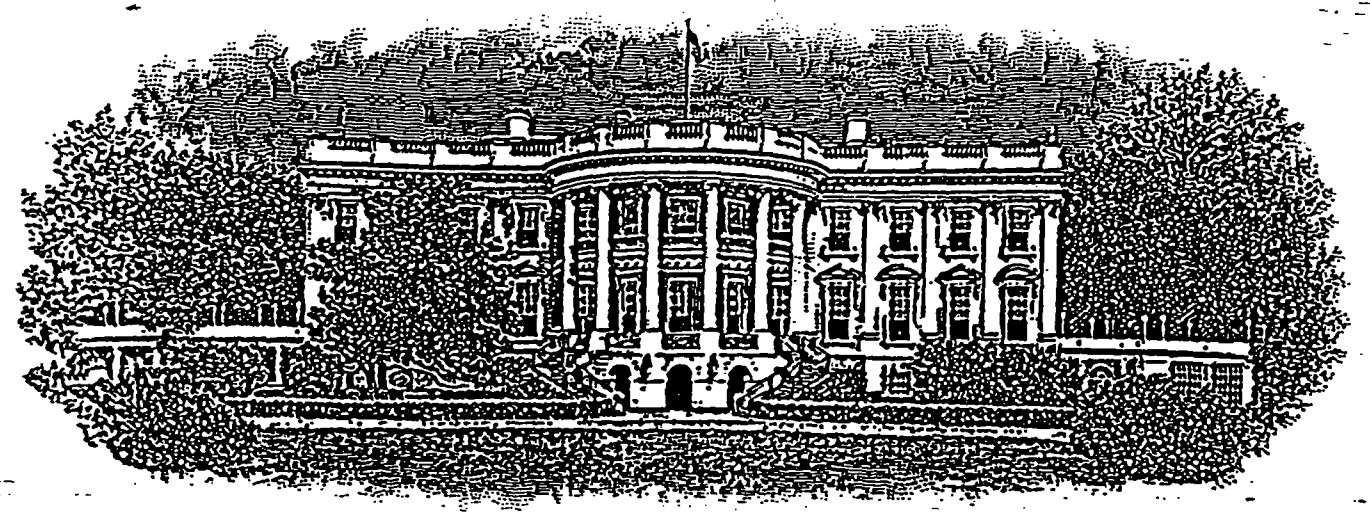
There are currently no formal obstetric guidelines for the use of protease inhibitors outside of clinical trials among pregnant HIV-infected women. The lack of phase I safety and pharmacokinetics data makes the development of such guidelines difficult to develop at this time. However, previous obstetric guidelines for HIV-infected pregnant women have used the principle that treatment of pregnant women should be essentially the same as for non-pregnant women unless there were known fetal toxicities that outweighed the benefit for the mother.

In the clinical setting, some obstetricians are already initiating combination therapy including protease inhibitors for maternal indications--not for reduction of transmission--in pregnant HIV-infected women with high or increasing viral load or clinical deterioration despite treatment with other antiretroviral agents. However, due to the lack of safety information and the lack of data regarding transplacental transfer of these drugs, many obstetricians are opting to wait until pregnancy is completed prior to initiating the use of protease inhibitors for their patients.

The findings from these proposed clinical trials may resolve the drug safety issues and prove useful in identifying additional therapeutic regimens that can further reduce perinatal transmission of HIV infection, thus building on the critical clinical findings of the ACTG 076 study. ACTG 076 previously demonstrated the significant reduction by 67 percent of perinatal transmission due to the administration of AZT to HIV-infected pregnant women during the second and third trimester of gestation and delivery and to the newborn for six weeks following birth.

Prepared by the NIH/Office of AIDS Research
October 3, 1996

The White House



DOMESTIC POLICY

FACSIMILE TRANSMISSION COVER SHEET

TO: Bill Corr

FAX NUMBER: 401-5783

TELEPHONE NUMBER: _____

FROM: Elizabeth Drye

TELEPHONE NUMBER: 456-5573

PAGES (INCLUDING COVER): _____

COMMENTS: _____

AIDS Policy Center
For Children, Youth & Families

December 6, 1996

The Vice-President
The White House
1600 Pennsylvania Avenue, NW
Washington, DC 20500

Dear Vice-President Gore:

We are writing to request a meeting with you concerning access to new HIV/AIDS combination therapies for pregnant women and children. As you know, Congress addressed this issue in the FY 1997 omnibus funding bill by encouringing expedited clinical trials on new combination therapies for pregnant women and children with HIV/AIDS, and requiring that the Secretary of Health & Human Services prepare a report to the appropriations committees on these initiatives by December 31, 1996.

AIDS Policy Center was instrumental in securing this report language and has been monitoring the administration's response to this request. We are very concerned about the lack of response to date on this important issue and want to meet with you and members of your staff to discuss the administration's plans.

In a letter to AIDS Policy Center from President Clinton October 23, 1996, we were informed that you had been asked to work with the FDA commissioner to make recommendations on this matter. We enclose a copy of this letter.

Please have your staff contact David Harvey to confirm arrangements for a meeting. Thank you for your attention to this important matter.

Sincerely,

Sheri Saltzberg
President, Board of Directors

David C. Harvey
Executive Director

918 Sixteenth Street, NW
Suite 201
Washington, DC 20006
Tel: (202) 785-3564
Fax: (202) 785-3579
E-mail: APCCYF@aol.com

THE WHITE HOUSE

WASHINGTON

October 23, 1996

Ms. Sheri Saltzberg
Mr. David C. Harvey
AIDS Policy Center for
Children, Youth and Families
Suite 422
910 17th Street, N.W.
Washington, D.C. 20006

Dear Sheri and David:

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This is indeed a very important issue, and the Vice President has asked the FDA Commissioner to make recommendations on this matter. We will continue to keep your perspective in mind -- working together, I know we can defeat AIDS.

I appreciate your active involvement in this important matter. Keep up the good work.

Sincerely,

Bill Clinton

Building Public Trust:

Actions to Respond to The Advisory Committee on Human Radiation Experiments

E X E C U T I V E O F F I C E O F T H E P R E S I D E N T

06-Jan-1997 05:06pm

TO: Jennings_C

FROM: Nickandtim

SUBJECT: Pediatric Drugs

To Chris Jennings
From Tim Westmoreland

Well, while you're having record-breaking heat waves, we're having record-breaking cold spells. I would be happy if I could get my living room up to 60 degrees.

Word has it that Greg Simon and you may be meeting with David Harvey of the AIDS Policy Center for Children, Youth and Families about drugs for children. If I may, I'd make a couple of suggestions.

First, don't say anything you wouldn't want published; David is not a good repository for secrets, and I would be very concerned that the industry lobbyists could hear about any proposed actions before you want them to. Second, please don't tell him about the work that we (either Georgetown or the Pediatric AIDS Foundation) have been doing with FDA and/or other Administration types; I had planned to share this with him only after it was ripe. And third, don't expect much depth in the discussion; David has several times told me that he will rely on me to tell him what to do on pharmaceutical issues because he doesn't know FDA law; I have so far told him only to press for action to ensure that pediatric drug research is done, and he has circulated some background work about the problem that I wrote.

Having said that, the APC constituents serve a lot of kids with AIDS who have a great need. They are a health care services group and they will have a compelling story.

I hope all else is well.

Tim

FAX

To: Toby Donenfeld

Fax: 202-456-6231

From: Christa Singleton

AIDS Policy Center
For Children, Youth & Families
918 Sixteenth Street, NW, Suite #201
Washington, D.C. 20006
Phone:(202)785-3564
Fax: (202)785-3579

APC

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Bill Clinton

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CATCHALL SPENDING BILL COMPLETED

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October 2, 1996

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Also through the efforts of AIDS Policy Center, the full Senate Labor/HHS Committee omnibus report addressed issues of access to new combination drug therapies by pregnant women and children with HIV/AIDS. The omnibus bill conference report states:

> "The conferees are aware that the new HIV drug combinations therapies have not yet been approved for pregnant women and children and that adolescents are experiencing problems in accessing the new therapies. The conferees strongly encourage the Secretary and the pharmaceutical industry to expedite clinical trials for pregnant women and children with HIV/AIDS, and report to the Committees on these initiatives by December 31, 1996, including providing access to the new drugs for adolescents."

IMMIGRATION SERVICES TO CONTINUE FOR LEGAL IMMIGRANT CHILDREN AND FAMILIES

In another section of the omnibus bill, Congress passed HR 2202, which was designed to address federal efforts to combat illegal immigration. Late last week, the bill contained a provision to deny medical services for HIV for legal immigrants; however, efforts from multiple advocacy organizations, including AIDS Policy Center and the National Organizations Responding to AIDS coalition, resulted in this provision being removed from the final bill signed by the President.

Please see attached page for a final summary of federal funding to AIDS programs. Please also note that this will be the last legislative alert until after the November 1996 elections.

Federal AIDS Program
Funding Summary 1996-1997
(updated 10-2-96)

Federal HIV/AIDS Program	FY 1996	FY 1997 President's Budget Request	FY 1997 House Passed Bill	FY 1997 Senate Labor/HHS Subcommittee Passed Bill	FY 1997 Omnibus Spending Bill
CDC-Prevention	$584.5m	$617.0m (+32.5m)	$599.1m ($15.0m)	$589.08 (+5.6m)	$617.0 (+32.5m)
HRSA-Ryan White Care Act Total	$757.3m	$895.7m (+139m)	$812.3m (+54.9m)	$854.2m (+96.9m)	$996.3m (+239m)
Title I	$391.7m.	$423.9m (+32.2m)	$401.7m (+10.0m)	$401.7m (+10.0m)	$449.9m (+58.2m)
Title II	$260.8m	$350.0m (+89.2m) (+24 Title II) (+65 ADAP)	$290.8m (+30m) (+7 Title II) (+23 ADAP)	$332.8m (+72m) (+7 Title II) (+65 ADAP)	$416.8m (+156m) (+41 Title II) (+115 ADAP)
Title IIIb	$56.9m	$64.6m (+7.7m)	$61.9m (+5.0m)	$61.9m (+5.0m)	$69.6m (+12.7m)
Title IV	$29.0m	$34.0m (+5.0m)	$34.0m (+5.0m)	$34.0m (+5.0m)	$36.0m (+7.0 m)
Title V - Acts Title V - Dental Reimbursement	$12.0m $6.9m	$16.3m (+4.3m) $7.5m (0.6m)	$16.3m (+4.3m) $7.5m (0.6m)	$16.3m (+4.3m) $7.5m (0.6m)	$16.3m (+4.3m) $7.5m (0.6m)
NIH - Research	$1,407.8m	$1,431.9m (+24.1m)	$1499.5 (+91.5)	$1,499.5m (+91.5)	1,501.7m (+93.9m)
HUD - HOPWA	$171.0m	$196.0m (+25.0m)	$171.0m (+0.00)	$196.0m (+25.0m)	$196.0m (+25.0m)

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The conferees expect the General Accounting Office to review the Department's implementation activities to determine whether these efforts will achieve the goal of improving the timeliness, accuracy and reliability of Davis-Bacon wage determinations. The General Accounting Office shall report its findings to the Appropriations Committees after it has made its review.

The conferees agree with the directive in the Senate Report with respect to black lung field offices.

OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION

SALARIES AND EXPENSES

The conference agreement includes $325,734,000, instead of $297,734,000 as proposed by the House in H.R. 3755 and $329,194,000 as proposed by the Senate in H.R. 3755 as reported from Committee. The agreement includes language as proposed by the Senate that authorizes OSHA to collect and retain fees for services provided to nationally recognized testing laboratories and to use such sums to administer laboratory recognition programs that ensure the safety of equipment and products used in the workplace. The House bill had no similar provision.

The conferees are concerned about the enforcement of States occupational safety and health standards by States operating OSHA-approved State plans, particularly where such standards differ significantly from Federal standards and may impose an undue burden on interstate commerce. The conferees believe that California's enforcement of its hazard communication standard, which incorporates portions of proposition 65, may impose such a burden. OSHA is directed to expedite its review and approval, or rejection, of California's hazard communication/proposition 65 standard, and to provide a report to the Appropriations Committees on this matter, by no later than January 1, 1997.

MINE SAFETY AND HEALTH ADMINISTRATION

SALARIES AND EXPENSES

The conference agreement includes $197,810,000, instead of $191,810,000 as proposed by the House in H.R. 3755 and $196,726,000 as proposed by the Senate in H.R. 3755 as reported from Committee.

BUREAU OF LABOR STATISTICS

SALARIES AND EXPENSES

The conference agreement includes $361,700,000, instead of $354,700,000 as proposed by the House in H.R. 3756 and $351,339,000 as proposed by the Senate in H.R. 3755 as reported from Committee. This includes $309,647,000 in Federal funds, instead of $302,647,000 as proposed by the House and $299,685,000 as proposed by the Senate, and $52,053,000 from the Unemployment Trust Fund as proposed by the House instead of $51,665,000 as proposed by the Senate.

DEPARTMENTAL MANAGEMENT

SALARIES AND EXPENSES

The conference agreement includes $144,588,000, instead of $142,508,000 as proposed by the Senate in H.R. 3755 as reported from Committee and $137,801,000 as proposed by the House in H.R. 3755. The conferees agree with the allocation of funds in the Senate Report with respect to international child labor issues.

The agreement includes language as proposed by the Senate to require that any decision under the Longshore and Harbor Workers' Compensation Act that has been pending before the Benefits Review Board for more than 12 months shall be considered affirmed by the Board and shall be considered the final order of the Board. The House bill had no similar provision. With respect to the Inspector General of the Department, the conferees endorse the language in the House Report concerning quarterly reporting on actual savings resulting from his efforts and on "funds put to better use".

ASSISTANT SECRETARY FOR VETERANS' EMPLOYMENT AND TRAINING

The conference agreement includes $181,940,000 as proposed by the House in H.R. 3755 instead of $174,225,000 as proposed by the Senate in H.R. 3755 as reported from Committee.

GENERAL PROVISIONS

The conference agreement includes a general provision proposed by the House in H.R. 3755 modified to provide that effective January 1, 1997 no Department of Labor funds shall be disbursed without the approval of the Department's Chief Financial Officer or his delegatee. The Senate bill had no similar provision.

The conference agreement does not include House language in H.R. 3755 that would have permitted employees who are 16 and 17 years of age to load materials into a cardboard baler or a compactor that is in compliance with the current safety standard promulgated by the American National Standards Institute. This matter has now been resolved in Public Law 104-174 which was signed by the President on August 6, 1996. The Senate bill had no similar provision.

The conference agreement does not include House language in H.R. 3755 that would have prohibited the enforcement of Hazardous Occupation Order No. 2 with respect to incidental and occasional driving by minors on the job, unless the Secretary finds that the operation of a motor vehicle is the primary duty of the minor's employment. The Senate bill had no similar provision.

The conference agreement does not include a general provision proposed by the Senate in H.R. 3755 as reported from Committee to exempt certain work performed by prison inmates from minimum wage and overtime requirements of the Fair Labor Standards Act under certain circumstances. This would have been a permanent change in the law. The House bill had no similar provision. The conferees believe that the provision is not necessary. The courts have uniformly held that a prisoner who is required to perform labor which serves the prison institution is not an employee of the prison or of the State and is not entitled to the minimum wage.

The conference agreement includes a general provision to allow the Secretary of Labor to waive various sections of the Job Training Partnership Act to improve intergovernmental service delivery systems. This would involve a State that has executed a memorandum of understanding with several Federal agencies, including the Department of Labor. The waivers of JTPA provisions would involve such things as definitions, planning and procurement requirements, cost categories and cost limitations, and program design requirements. This provision was not included in either the House or the Senate version of H.R. 3755 but is the same as a proviso in the fiscal year 1996 appropriations act.

TITLE II—DEPARTMENT OF HEALTH AND HUMAN SERVICES

HEALTH RESOURCES AND SERVICES ADMINISTRATION

HEALTH RESOURCES AND SERVICES

The conference agreement includes $3,405,019,000 instead of $3,082,199,000 as proposed by the House in H.R. 3755 and $3,713,096,000 as proposed by the Senate in H.R. 3755 as reported from Committee.

The conference agreement does not include the legal citation for the Pacific Basin program as proposed by the Senate. The House bill did not include the citation. The conferees have agreed to terminate the Pacific Basin program but encourage consideration of the region's needs in other Health Resources and Services Administration (HRSA) programs, as appropriate.

The conference agreement includes the legal citation for the Native Hawaiian Health Care program as proposed by the Senate. The House bill did not include the citation. The conferees have increased funding for the consolidated health centers line in part so that health care activities funding under the Native Hawaiian Health Care program can be supported under the broader health centers line if the agency feels it is appropriate.

The conference agreement includes $828,000 for facilities renovations at the Gillis W. Long Hansen's Disease Center as proposed by the Senate rather than $2,828,000 as proposed by the House.

The conference agreement includes $198,452,000 for the family planning program as proposed by the Senate rather than $192,592,000 as proposed by the House.

The conference agreement earmarks $167,000,000 for the Ryan White Title II State AIDS drug assistance programs rather than $117,000,000 as proposed by the Senate and $75,000,000 as proposed by the House. Total funding for the Ryan White programs has been increased by $238,850,000 from the fiscal year 1996 level to a total of $896,252,000. Funding increases are included for all Ryan White titles in recognition of the costs of drug purchases, particularly the new protease inhibitors, viral load testing, caseload increases and AZT therapy for pregnant women.

The conferees are aware that the new HIV drug combination therapies have not yet been approved for pregnant women and children, and that adolescents are experiencing problems in accessing these therapies. The conferees encourage the Secretary and the pharmaceutical industry to expedite clinical trials for pregnant women and children with HIV/AIDS, and to report to the Committees on these efforts by December 31, 1996, including providing access to the new drugs for adolescents.

The conferees expect that all States receiving AIDS drug assistance funding will employ cost-saving strategies to maximize assistance to HIV patients. HRSA should assure that each State seeks the best possible price for AIDS drug purchases. Such strategies might include one or more of the following: the Veterans' Health Care Act Office of Drug Pricing Program, manufacturers' voluntary rebates and discounts to States, and pharmacy discounts.

The conference agreement includes language proposed by the Senate permitting the use of funds provided to continue operating the Council on Graduate Medical Education. The House bill had no similar provision.

The conference agreement includes language proposed by the Senate allocating up to $8,000,000 of the funds provided for consolidated health centers for loan guarantees for the construction and renovation of community and migrant health centers and, if authorized, for loans made for the costs of developing managed care networks. The House bill had no similar provision.

The conference agreement includes language designating $103,609,000 of the funds provided for the Maternal and Child Health block grant for special projects of regional and national significance (SPRANS). This designation will provide $2,857,000 more for SPRANS activities than would otherwise be the case under the statutory formula. The conferees intend that this amount be used for the traumatic brain injury State demonstration projects recently authorized under title XII of the Public Health Service Act. This provision was not included in either House or Senate bill. The Senate bill

AIDS Policy Center
For Children, Youth & Families

December 2, 1996

The President
The White House
1600 Pennsylvania Avenue, NW
Washington, D.C. 20500

Dear Mr. President:

On behalf of 338 affiliate care projects serving 50,000 infected and affected children, youth and families living with HIV/AIDS, we are writing to strongly urge increased funding for Title IV of the Ryan White CARE Act in the President's FY 1998 budget request.

We understand that the budget request is under final consideration, and are certainly aware of the federal budget constraints. However, in a year of enormous focus by The White House on the growing needs of youth who are at-risk or infected with HIV/AIDS, it is imperative that Title IV of the Act, which supports youth-focused services and primary medical care, be an absolute priority for additional funding.

As The White House report on Youth & HIV/AIDS states, *"large numbers of young people are uninsured or underinsured, and the sources for funds to pay for necessary services are limited.... Title IV of the Ryan White CARE Act provides support for the development of innovative models that link systems of comprehensive primary/community-based research, medical, and social services for children, adolescents, and families"* (page 10).

In addition, this last year we witnessed an unprecedented focus by Congress to reduce perinatal HIV transmission. It is imperative that Title IV of the Act, which supports services and primary medical care for pregnant women and children aimed at reducing perinatal HIV transmission, be an absolute priority for additional funding.

Specifically, we recommend that the President's FY 1998 budget request include an additional $25 million for Title IV programs over the FY 1997 funding level of $36 million. This request reflects three priorities in FY 1998: (1) $10 million to expand social services and primary medical care to reduce perinatal HIV transmission through new therapy options; (2) $10 million to expand outreach services and primary medical care for youth infected with HIV/AIDS; (3) $5 million to support a basic program increase for existing Title IV projects.

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We also strongly encourage that the funding needs of all titles of the Ryan White CARE Act be considered in the FY 1998 budget request, in addition to other federal AIDS programs that include prevention, research and housing. Attached is additional information and a funding rationale for Title IV of the Ryan White CARE Act.

Thank you for your consideration of this request.

Sincerely,

Sheri Saltzberg
President

David C. Harvey
Executive Director

AIDS Policy Center
For Children, Youth & Families

RYAN WHITE CARE ACT TITLE IV

FY 1998 Funding Rationale Additional Primary Care Needs

Memorandum

- Title IV supports coordinated social services, primary medical care, and access to research for children, youth, women and families.
- Over 75% of Title IV projects provide direct primary medical care to children, youth, at-risk youth, and pregnant women with HIV and AIDS. Medicaid does not fully reimburse Title IV projects for the costs of primary medical care.
- Over 65% of Title IV projects are the principal source of primary medical care for children, youth, at-risk youth, and pregnant women with HIV and AIDS living in their geographic area.
- Title IV reaches 338 sites in 27 states, the District of Columbia, and Puerto Rico. Title IV is administered by the Maternal & Child Health Bureau of HRSA.
- Title IV sites serve an estimated 50,000 HIV infected and affected children, youth, at-risk youth, women, men and families. Demand for services has tripled during the past three years.

Funding Rationale

- Women and youth are the fastest growing population infected and affected with HIV in the United States and need greater access to Title IV projects.
- Additional funding for Title IV will support increased primary medical care and participation in clinical research by children, youth, and women with HIV, particularly African-Americans and Hispanics.
- $25 million in additional Title IV funds are needed to (1) prevent perinatal HIV transmission, (2) expand youth focused HIV care programs, and (3) expand existing programs.

FY 1998 Title IV Budget Request Summary

I. Prevention of Perinatal HIV Transmission	$10 million
II. Adolescent Special Initiative	$10 million
III. Basic Program Increase	$5 million
FY '98 Subtotal	$ 25 million
FY '97 Appropriation	$36 million
FY '98 Total Request	$61 million

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> "The conferees are aware that the new HIV drug combinations therapies have not yet been approved for pregnant women and children and that adolescents are experiencing problems in accessing the new therapies. The conferees strongly encourage the Secretary and the pharmaceutical industry to expedite clinical trials for pregnant women and children with HIV/AIDS, and report to the Committees on these initiatives by December 31, 1996, including providing access to the new drugs for adolescents."

IMMIGRATION SERVICES TO CONTINUE FOR LEGAL IMMIGRANT CHILDREN AND FAMILIES

In another section of the omnibus bill, Congress passed HR 2202, which was designed to address federal efforts to combat illegal immigration. Late last week, the bill contained a provision to deny medical services for HIV for legal immigrants; however, efforts from multiple advocacy organizations, including AIDS Policy Center and the National Organizations Responding to AIDS coalition, resulted in this provision being removed from the final bill signed by the President.

Please see attached page for a final summary of federal funding to AIDS programs. Please also note that this will be the last legislative alert until after the November 1996 elections.

Federal AIDS Program
Funding Summary 1996-1997
(updated 10-2-96)

Federal HIV/AIDS Program	FY 1996	FY 1997 President's Budget Request	FY 1997 House Passed Bill	FY 1997 Senate Labor/HHS Subcommittee Passed Bill	FY 1997 Omnibus Spending Bill
CDC-Prevention	$584.5m	$617.0m (+32.5m)	$599.1m ($15.0m)	$589.08 (+5.6m)	$617.0 (+32.5m)
HRSA-Ryan White Care Act Total	$757.3m	$895.7m (+139m)	$812.3m (+54.9m)	$854.2m (+96.9m)	$996.3m (+239m)
Title I	$391.7m.	$423.9m (+32.2m)	$401.7m (+10.0m)	$401.7m (+10.0m)	$449.9m (+58.2m)
Title II	$260.8m	$350.0m (+89.2m) (+24 Title II) (+65 ADAP)	$290.8m (+30m) (+7 Title II) (+23 ADAP)	$332.8m (+72m) (+7 Title II) (+65 ADAP)	$416.8m (+156m) (+41 Title II) (+115 ADAP)
Title IIIb	$56.9m	$64.6m (+7.7m)	$61.9m (+5.0m)	$61.9m (+5.0m)	$69.6m (+12.7m)
Title IV	$29.0m	$34.0m (+5.0m)	$34.0m (+5.0m)	$34.0m (+5.0m)	$36.0m (+7.0 m)
Title V - Acts Title V - Dental Reimbursement	$12.0m $6.9m	$16.3m (+4.3m) $7.5m (0.6m)	$16.3m (+4.3m) $7.5m (0.6m)	$16.3m (+4.3m) $7.5m (0.6m)	$16.3m (+4.3m) $7.5m (0.6m)
NIH - Research	$1,407.8m	$1,431.9m (+24.1m)	$1499.5 (+91.5)	$1,499.5m (+91.5)	1,501.7m (+93.9m)
HUD - HOPWA	$171.0m	$196.0m (+25.0m)	$171.0m (+0.00)	$196.0m (+25.0m)	$196.0m (+25.0m)

AIDS Policy Center for Children, Youth and Families
918 Sixteenth Street, NW
Suite 201
Washington, DC 20006
Phone: (202) 785-3564
Fax: (202) 785-3579
Email: apccyf@aol.com

The conferees expect the General Accounting Office to review the Department's implementation activities to determine whether these efforts will achieve the goal of improving the timeliness, accuracy and reliability of Davis-Bacon wage determinations. The General Accounting Office shall report its findings to the Appropriations Committees after it has made its review.

The conferees agree with the directive in the Senate Report with respect to black lung field offices.

OCCUPATIONAL SAFETY AND HEALTH ADMINISTRATION

SALARIES AND EXPENSES

The conference agreement includes $325,734,000, instead of $327,734,000 as proposed by the House in H.R. 3755 and $269,194,000 as proposed by the Senate in H.R. 3755 as reported from Committee. The agreement includes language as proposed by the Senate that authorizes OSHA to collect and retain fees for services provided to nationally recognized testing laboratories and to use such sums to administer laboratory recognition programs that ensure the safety of equipment and products used in the workplace. The House bill had no similar provision.

The conferees are concerned about the enforcement of State occupational safety and health standards by States operating OSHA-approved State plans, particularly where such standards differ significantly from Federal standards and may impose an undue burden on interstate commerce. The conferees believe that California's enforcement of its hazard communication standard, which incorporates portions of proposition 65, may impose such a burden. OSHA is directed to expedite its review and approval, or rejection, of California's hazard communication/proposition 65 standard, and to provide a report to the Appropriations Committees on this matter, by no later than January 1, 1997.

MINE SAFETY AND HEALTH ADMINISTRATION

SALARIES AND EXPENSES

The conference agreement includes $197,810,000, instead of $191,810,000 as proposed by the House in H.R. 3755 and $196,726,000 as proposed by the Senate in H.R. 3755 as reported from Committee.

BUREAU OF LABOR STATISTICS

SALARIES AND EXPENSES

The conference agreement includes $361,700,000, instead of $354,700,000 as proposed by the House in H.R. 3755 and $351,839,000 as proposed by the Senate in H.R. 3755 as reported from Committee. This includes $309,647,000 in Federal funds, instead of $302,647,000 as proposed by the House and $299,585,000 as proposed by the Senate, and $52,053,000 from the Unemployment Trust Fund as proposed by the House instead of $51,965,000 as proposed by the Senate.

DEPARTMENTAL MANAGEMENT

SALARIES AND EXPENSES

The conference agreement includes $144,569,000, instead of $142,508,000 as proposed by the Senate in H.R. 3755 as reported from Committee and $137,801,000 as proposed by the House in H.R. 3755. The conferees agree with the allocation of funds in the Senate Report with respect to international child labor issues.

The agreement includes language as proposed by the Senate to require that any decision under the Longshore and Harbor Workers' Compensation Act that has been pending before the Benefits Review Board for more than 12 months shall be considered affirmed by the Board and shall be considered the final order of the Board. The House bill had no similar provision. With respect to the Inspector General of the Department, the conferees endorse the language in the House Report concerning quarterly reporting on actual savings resulting from his efforts and on "funds put to better use".

ASSISTANT SECRETARY FOR VETERANS' EMPLOYMENT AND TRAINING

The conference agreement includes $181,949,000 as proposed by the House in H.R. 3755 instead of $174,225,000 as proposed by the Senate in H.R. 3755 as reported from Committee.

GENERAL PROVISIONS

The conference agreement includes a general provision proposed by the House in H.R. 3755 modified to provide that effective January 1, 1997 no Department of Labor funds shall be disbursed without the approval of the Department's Chief Financial Officer or his delegatee. The Senate bill had no similar provision.

The conference agreement does not include House language in H.R. 3755 that would have permitted employees who are 16 and 17 years of age to load materials into a cardboard baler or a compactor that is in compliance with the current safety standard promulgated by the American National Standards Institute. This matter has now been resolved in Public Law 104-174 which was signed by the President on August 6, 1996. The Senate bill had no similar provision.

The conference agreement does not include House language in H.R. 3755 that would have prohibited the enforcement of Hazardous Occupation Order No. 2 with respect to incidental and occasional driving by minors on the job, unless the Secretary finds that the operation of a motor vehicle is the primary duty of the minor's employment. The Senate bill had no similar provision.

The conference agreement does not include a general provision proposed by the Senate in H.R. 3755 as reported from Committee to exempt certain work performed by prison inmates from minimum wage and overtime requirements of the Fair Labor Standards Act under certain circumstances. This would have been a permanent change in the law. The House bill had no similar provision. The conferees believe that the provision is not necessary. The courts have uniformly held that a prisoner who is required to perform labor which serves the prison institution is not an employee of the prison or of the State and is not entitled to the minimum wage.

The conference agreement includes a general provision to allow the Secretary of Labor to waive various sections of the Job Training Partnership Act to improve intergovernmental service delivery systems. This would involve a State that has executed a memorandum of understanding with several Federal agencies, including the Department of Labor. The waivers of JTPA provisions would involve such things as definitions, planning and procurement requirements, cost categories and cost limitations, and program design requirements. This provision was not included in either the House or the Senate version of H.R. 3755 but is the same as a proviso in the fiscal year 1996 appropriations act.

TITLE II—DEPARTMENT OF HEALTH AND HUMAN SERVICES

HEALTH RESOURCES AND SERVICES ADMINISTRATION

HEALTH RESOURCES AND SERVICES

The conference agreement includes $3,405,019,000 instead of $3,082,139,000 as proposed by the House in H.R. 3755 and $3,213,096,000 as proposed by the Senate in H.R. 3755 as reported from Committee.

The conference agreement does not include the legal citation for the Pacific Basin program as proposed by the Senate. The House bill did not include the citation. The conferees have agreed to terminate the Pacific Basin program but encourage consideration of the region's needs in other Health Resources and Services Administration (HRSA) programs, as appropriate.

The conference agreement includes the legal citation for the Native Hawaiian Health Care program as proposed by the Senate. The House bill did not include the citation. The conferees have increased funding for the consolidated health centers line in part so that health care activities funding under the Native Hawaiian Health Care program can be supported under the broader health centers line if the agency feels it is appropriate.

The conference agreement includes $828,000 for facilities renovations at the Gillis W. Long Hansen's Disease Center as proposed by the Senate rather than $2,828,000 as proposed by the House.

The conference agreement includes $298,452,000 for the family planning program as proposed by the Senate rather than $192,582,000 as proposed by the House.

The conference agreement earmarks $157,000,000 for the Ryan White Title II State AIDS drug assistance programs rather than $137,000,000 as proposed by the Senate and $75,000,000 as proposed by the House. Total funding for the Ryan White programs has been increased by $238,850,000 from the fiscal year 1996 level to a total of $896,252,000. Funding increases are included for all Ryan White titles in recognition of the costs of drug purchases, particularly the new protease inhibitors, viral load testing, caseload increases and AZT therapy for pregnant women.

The conferees are aware that the new HIV drug combination therapies have not yet been approved for pregnant women and children, and that adolescents are experiencing problems in accessing these therapies. The conferees encourage the Secretary and the pharmaceutical industry to expedite clinical trials for pregnant women and children with HIV/AIDS, and to report to the Committees on these efforts by December 31, 1996, including providing access to the new drugs for adolescents.

The conferees expect that all States receiving AIDS drug assistance funding will employ cost-saving strategies to maximize assistance to HIV patients. HRSA should assure that each State seeks the best possible price for AIDS drug purchases. Such strategies might include one or more of the following: the Veterans' Health Care Act Office of Drug Pricing Program, manufacturers' voluntary rebates and discounts to States, and pharmacy discounts.

The conference agreement includes language proposed by the Senate permitting the use of funds provided to continue operating the Council on Graduate Medical Education. The House bill had no similar provision.

The conference agreement includes language proposed by the Senate allocating up to $8,000,000 of the funds provided for consolidated health centers for loan guarantees for the construction and renovation of community and migrant health centers and, if authorized, for loans made for the costs of developing managed care networks. The House bill had no similar provision.

The conference agreement includes language designating $183,609,000 of the funds provided for the Maternal and Child Health block grant for special projects of regional and national significance (SPRANS). This designation will provide $2,857,000 more for SPRANS activities than would otherwise be the case under the statutory formula. The conferees intend that this amount be used for the traumatic brain injury State demonstration projects recently authorized under title XII of the Public Health Service Act. This provision was not included in either House or Senate bill. The Senate bill

AIDS Policy Center
For Children, Youth & Families

December 2, 1996

The President
The White House
1600 Pennsylvania Avenue, NW
Washington, D.C. 20500

Dear Mr. President:

On behalf of 338 affiliate care projects serving 50,000 infected and affected children, youth and families living with HIV/AIDS, we are writing to strongly urge increased funding for Title IV of the Ryan White CARE Act in the President's FY 1998 budget request.

We understand that the budget request is under final consideration, and are certainly aware of the federal budget constraints. However, in a year of enormous focus by The White House on the growing needs of youth who are at-risk or infected with HIV/AIDS, it is imperative that Title IV of the Act, which supports youth-focused services and primary medical care, be an absolute priority for additional funding.

As The White House report on Youth & HIV/AIDS states, *"large numbers of young people are uninsured or underinsured, and the sources for funds to pay for necessary services are limited.... Title IV of the Ryan White CARE Act provides support for the development of innovative models that link systems of comprehensive primary/community-based research, medical, and social services for children, adolescents, and families"* (page 10).

In addition, this last year we witnessed an unprecedented focus by Congress to reduce perinatal HIV transmission. It is imperative that Title IV of the Act, which supports services and primary medical care for pregnant women and children aimed at reducing perinatal HIV transmission, be an absolute priority for additional funding.

Specifically, we recommend that the President's FY 1998 budget request include an additional $25 million for Title IV programs over the FY 1997 funding level of $36 million. This request reflects three priorities in FY 1998: (1) $10 million to expand social services and primary medical care to reduce perinatal HIV transmission through new therapy options; (2) $10 million to expand outreach services and primary medical care for youth infected with HIV/AIDS; (3) $5 million to support a basic program increase for existing Title IV projects.

918 Sixteenth Street, NW
Suite 201
Washington, DC 20006
Tel: (202) 785-3564
Fax: (202) 785-3579
E-mail: APCCYF@aol.com

We also strongly encourage that the funding needs of all titles of the Ryan White CARE Act be considered in the FY 1998 budget request, in addition to other federal AIDS programs that include prevention, research and housing. Attached is additional information and a funding rationale for Title IV of the Ryan White CARE Act.

Thank you for your consideration of this request.

Sincerely,

Sheri Saltzberg
President

David C. Harvey
Executive Director

AIDS
Policy Center
For Children, Youth & Families

RYAN WHITE CARE ACT TITLE IV

FY 1998 Funding Rationale Additional Primary Care Needs

Memorandum

- Title IV supports coordinated social services, primary medical care, and access to research for children, youth, women and families.
- Over 75% of Title IV projects provide direct primary medical care to children, youth, at-risk youth, and pregnant women with HIV and AIDS. Medicaid does not fully reimburse Title IV projects for the costs of primary medical care.
- Over 65% of Title IV projects are the principal source of primary medical care for children, youth, at-risk youth, and pregnant women with HIV and AIDS living in their geographic area.
- Title IV reaches 338 sites in 27 states, the District of Columbia, and Puerto Rico. Title IV is administered by the Maternal & Child Health Bureau of HRSA.
- Title IV sites serve an estimated 50,000 HIV infected and affected children, youth, at-risk youth, women, men and families. Demand for services has tripled during the past three years.

Funding Rationale

- Women and youth are the fastest growing population infected and affected with HIV in the United States and need greater access to Title IV projects.
- Additional funding for Title IV will support increased primary medical care and participation in clinical research by children, youth, and women with HIV, particularly African-Americans and Hispanics.
- $25 million in additional Title IV funds are needed to (1) prevent perinatal HIV transmission, (2) expand youth focused HIV care programs, and (3) expand existing programs.

FY 1998 Title IV Budget Request Summary

I. Prevention of Perinatal HIV Transmission	$10 million
II. Adolescent Special Initiative	$10 million
III. Basic Program Increase	$5 million
FY '98 Subtotal	$ 25 million
FY '97 Appropriation	$36 million
FY '98 Total Request	$61 million

918 Sixteenth Street, NW, Suite 201, Washington, DC 20006 • Tel. (202) 785-3564 • Fax (202) 785-3579 • E-mail APCCYF@aol.com

TOBY DONENFELD

Elizabeth -

Here are two copies of the info from the AIDS Policy Center, if you want to give a copy to Chris Jennings.

Please let me know if Bill Carr mentions anything about the report.

Thanks.

-- Toby

Debra — PHS

NIDS Policy Center —

Ryan White Title IV - funded
eg. — Case management

90% of children covered by Medicaid
Want FDA approval — can't covered. —

= Report to Congress
— FDA authority
— Keystone Project.

Deadline — when consent & studied in kids concurrently.

Better Pharmaceuticals Act. — Patent Extension -

Senator Specter — put in conference
language request for report.

FDA - historically has been passive
— issued request for data on kids — by Dec 31 1998
— greatly ~~expanded~~ simplified
What they needed to get
pediatric approval
— drug companies — asked
for 3 months extension.
— impact of changes — clearly
Inadequate.

Other groups

sometimes said — don't want to test → risk of adverse rxn

— also product liability concern

In '94 FDA said it has the authority to require testing -

— Orphan Drug studies —

— patent extension — that system doesn't work with one that's on the market or a difference use -

Parents are dosing kids, sometimes without physician supervision.

---

starts

Tobe drug companies on board - will you have to address liability issues

a) liability

b) costs

AZT ~~name~~ trials were rigid, costly -

American Academy of Pediatrics

child welfare league

Red AIDS

Agency decision — way to encourage it

- NMAC

- National Organizations responding to AIDS Coalition
- co-chair

— Also chair Minority —

sherry — have Sites - have met criteria for conducting clinical trials —

AIDS Drug Assistance Program work group

ADAP → major players in Title II of Ryan White — a lot of help from Pharmaceutical Co's.

Public Liason

THE WHITE HOUSE
WASHINGTON

Elizabeth –
The Pediatric AIDS Foundation sent this to me. Pluse tell me what you think. I have also sent it to Greg Simon & Toby D on the VP's staff.

Thanks & Happy New Year!

Paulie
x65374

12/96
From Pediatric AIDS Foundation

PROPOSED ACTION PLAN

- During the week of December 16, the President would issue an Executive Order and accompanying statement, directing the FDA to take immediate regulatory action to ensure that all drugs be proven safe and effective for use by children prior to their approval by the FDA.

- The Executive Order would:

  - ***Describe the dire need for pediatric data.*** The Order would explain that 80% of all drugs currently on the market have not been proven safe and effective for use by children. The Order would explain the ramifications of this situation, namely that (1) children are being denied life-saving therapies because physicians are afraid to prescribe potentially toxic drugs that have not been approved for use by children, and (2) children may be exposed to an increased risk of adverse reactions or decreased effectiveness of the drugs prescribed because pediatricians do not have appropriate dosage data.

  - ***Explain that FDA has the statutory authority to require pediatric data prior to its approval of a new drug.*** The Order would explain that pursuant to the approval and labeling requirements of the Food, Drug, and Cosmetic Act, the FDA has the authority to require pediatric data.

  - ***Direct the FDA to promulgate regulations requiring, as a condition of approval for all new drugs for which children are foreseeable users, that pharmaceutical manufacturers submit pediatric safety data, and, as appropriate, pediatric efficacy data.***[1] The Order would direct the FDA to promulgate new regulations in accordance with the "notice and comment" procedures of the Administrative Procedure Act.

  - ***Direct the FDA to issue the proposed regulations as soon as possible.*** The Order would direct the FDA to publish, within 90 days, new proposed regulations for public comment.

---

[1] In most instances, efficacy data for use by children can be extrapolated from adult efficacy data.

- The statement accompanying the Executive Order would:
  - ***Describe the urgent need for pediatric data.***
  - ***Declare that drugs should be safe and effective for all foreseeable users, not just adults.***
  - ***Speak about the need to ensure that children share in and benefit from therapeutic progress.***
  - ***Dedicate this action to Elizabeth Glaser, and her work to improve child health.*** (Note: December 3rd was the 2nd anniversary of Elizabeth's death from AIDS-related complications.)
- Prior to issuance of the Executive Order, David Kessler and Bill Schultz (as well as PAF representatives) would be consulted about the wording of the Order to ensure that is on clear legal footing.
- Children, pediatricians, scientists, and advocates would be present when the President signs the Order. Attendees could include:
  - Representatives from the Pediatric AIDS Foundation
  - Children with life-threatening illnesses, such as AIDS and cancer
  - Parents of children with life-threatening illnesses who have been denied needed therapies because of the lack of pediatric data
  - Pediatricians and scientists who have advocated for the need for pediatric data
- Pediatric AIDS Foundation and other child advocacy organizations would issue press releases lauding the President's efforts to protect the health and safety of American children.

12/96
Pediatric AIDS Foundation

PEDIATRIC STUDIES IN PHARMACEUTICALS URGENTLY NEEDED

THE PROBLEM

Approximately 80% of all pharmaceuticals now on the market have not been tested for safety and effectiveness in children.

- Pediatricians, pharmacists, and parents are generally forced to guess about the safety and dosing of such drugs for children, even when the drug is the only known therapy for a serious disease.

- FDA has tried to encourage drug companies to conduct pediatric studies, but generally without success.

- FDA maintains that it has no means by which to compel pediatric research.

The problem seems to be getting worse.

- None of the new AIDS therapies has pediatric data, even though there is every theoretical reason to believe that the drugs would be as effective in children as in adults. Despite drug company promises to FDA that they would start research in children after the drug is approved for adults, such trials have not begun, delaying pediatric use by years.

- A survey of pediatric AIDS patients has shown that very few of these children are taking the new therapies, despite access to good medical care. Surveys of similarly situated adults would show that many are getting such drugs.

Distinct pediatric data are needed. Children are not just "little adults;" they often metabolize drugs very differently from adults and dosages are dependent on both metabolism and size.

- There are classic cases of drugs that are safe in adults being toxic--even lethal--for children.

Drug companies do not gather pediatric data for a number of possible reasons.

- Children are a very small market for most drugs. Research on children will not provide the enormous returns that research on adults will.

- Drug companies sometimes believe that children are difficult to recruit for trials (although when such trials are actually begun such problems are rare).

- Drug companies sometimes believe that a side effect or bad reaction by a child in research may slow FDA approval of the therapy for adults. (Companies also may fear that if they do pediatric trials and their competitors do not, such an adverse reaction may put them at a competitive disadvantage with similar companies who do not do such research.)

THE PROPOSAL

FIRST, FDA should require that all <u>new</u> drug applications (for drugs for which children are foreseeable users) contain pediatric safety and dosing data as a condition for approval.

- Such a requirement is supported by the law.
- The Food, Drug, and Cosmetic Act requires that drugs be "safe and effective," not "safe and effective for adults only."
- The legislative history of the Act is filled with clear Congressional intent to protect children.

Such a requirement for pediatric data will not slow approval of drugs.

- Pediatric safety and dosing studies can be done *at the same time* as adult studies on effectiveness. Since safety and dosing are relatively brief when compared to effectiveness studies, they can be completed long before effectiveness trials are completed and ready for submission to the FDA.
- Under revised regulations (December 1994), drug companies are *not required to conduct the more time-consuming effectiveness trials in children.* FDA will generally allow companies to extrapolate adult effectiveness trials to show effectiveness in children, so long as safety and dosing studies are done.
- Safety and dosing studies are generally relatively brief (3-12 months) and relatively small (30-60 patients) and are, therefore, relatively inexpensive.

SECOND, FDA should require manufacturers of already-approved drugs (that are determined to be significantly needed by children) to conduct pediatric trials over a reasonable period of phase-in or have the drug withdrawn as mislabeled.

- An immediate enforcement of a requirement of pediatric studies would be unfair and unworkable for already approved drugs.
- Such pediatric data are, nonetheless, needed, both because some doctors prescribe such drugs for children (even without data) and because some doctors do not prescribe such drugs (because of the lack of data).
- Since effectiveness trials are generally not required for children, these trials can be relatively small and relatively brief, and, therefore, relatively inexpensive.

EXPECTED RESPONSE

Some drug companies will protest that the requirement of pediatric data will cost them money.

- But note that the requirements for safety and dosing data can be met by doing relatively brief, small, and inexpensive studies.

- And note that drug companies will be forced to argue against a pediatric data requirement *without an alternative proposal* for gathering such data and *with a very bad past history* of ignoring the issue.

Some drug companies and Members of Congress may propose to create quasi-patent incentives for doing pediatric studies rather than requirements.

- Such legislation was discussed in both the 103rd and 104th Congress, but with no action.

- But note that such incentives are not efficient (only the biggest drugs will be tested) and are expensive (because market exclusivity delays the advent of cheaper generic drugs).

Pediatric groups (ranging from generalities (such as the American Academy of Pediatrics) to specialists such as the Pediatric AIDS Foundation) will actively support the new requirements.

Press interest will be high.

Prepared by the Georgetown Federal Legislation Clinic on behalf of the Pediatric AIDS Foundation (h:\therapies)

THE WALL STREET JOURNAL. FRIDAY, NOVEMBER 15, 1996 B1

In the Line for AIDS Drugs, Children Are Last

By LAURIE MCGINLEY
Staff Reporter of THE WALL STREET JOURNAL

The revolutionary drug therapies helping many adult AIDS patients are unavailable to most infected children.

None of the three protease inhibitors prescribed for adults – Roche Holding Ltd.'s Invirase, Abbott Laboratories' Norvir and Merck & Co.'s Crixivan – has been

MEDICINE

tested widely in children. Lacking pediatric data, the Food and Drug Administration hasn't cleared the drugs for use in children. While doctors can legally prescribe a drug for a child without such clearance if it has been approved for use by adults, many won't do so in the case of the protease inhibitors because of a paucity of information. They worry that incorrect use of the drugs could be harmful or make it difficult for a child to use a better, yet-to-be-developed medication.

"I'm frustrated," says Ann Petru, director of the pediatric AIDS program at Children's Hospital Oakland in California. "I don't have any dosing information. I have no idea what is a safe dose or a toxic one."

One of her patients is nine-year-old Samuel Fox of Newark, Calif. While Samuel appears healthy – playing soccer, scrapping with his older brother – tests show that the amount of virus in his blood is six times higher than it was in March. His mother, Marilyn, wants Samuel, who is adopted, to start taking a protease inhibitor. "It just scares the hell out of me that I'm going to lose him," she says. But Dr. Petru wants more information about the drugs before she considers putting him on one of the new drugs.

Of the three protease inhibitors, Roche Holding's Invirase was approved for adults last December; Abbott Laboratories' Norvir and Merck's Crixivan were cleared early this year. Studies in adults showed that the protease inhibitors, when combined with existing AIDS drugs, were the most potent anti-AIDS weapons yet devised.

Teenagers with AIDS are routinely treated with the new drugs, but only the sickest of the younger children or those in small-scale clinical trials are getting them. Newborns aren't getting the drugs at all. Heightening the frustration of pediatricians and parents is the fact that some of these trials suggest that the protease inhibitors may be of great benefit to infected children. Just last week, for example, the National Cancer Institute reported that, in a small study of children aged six months to 14 years, Abbott's drug is safe and appears to have "a significant antiviral effect."

"There is such a feeling of optimism and hope among adults, but it hasn't yet been translated into hope for children," says Michael Kaiser, a New Orleans doctor who works with people with AIDS.

How did this happen?

The fact is that the protease inhibitors are part of a larger picture: Only about 20% of all drugs approved for use in the U.S. have been tested in children and have had labeling information about their pediatric use approved by the FDA, says Susan DeLaurentis, co-founder and chief executive officer of the Pediatric AIDS Foundation, which is based in Santa Monica, Calif. Of the nine AIDS drugs that have been approved for adults over the last decade, only three have also been approved for pediatric use: AZT, ddI and 3TC.

In the case of the protease inhibitors, critics contend that drug companies have been slow to develop pediatric data because children make up only a small proportion of infected individuals. Since 1981, more than 7,200 children aged 12 and under have been diagnosed with AIDS in the U.S. compared with more than 548,000 adults, according to the Centers for Disease Control and Prevention. "The attitude of the drug companies is that it's not economically feasible or profitable because there is a limited number of infected children," asserts Dianne Donovan, a resident of Queensbury, N.Y., who adopted two children who are HIV-positive.

Abbott, in particular, comes in for tough criticism. Because Norvir was initially developed as a liquid, making it readily ingestible by infants and small children, it "was the one that could have been pushed into pediatric studies at a much earlier stage," says Philip Pizzo, a leading AIDS researcher who is physician in chief and chairman of the department of

Please Turn to Page B9, Column 1

Mostly Out of Reach

BRAND NAME	MANUFACTURER	APPROVAL DATE
Retrovir	Glaxo Wellcome	Adults, 1987; infants and children, 1989
Videx	Bristol-Myers Squibb	Adults and children, Oct. 1991
Hivid	Roche Holding	Adults only, June 1992
Zerit	Bristol-Myers Squibb	Adults only, June 1994
Epivir	Glaxo Wellcome	Adults, children and infants, Nov. 1995
Invirase*	Roche Holding	Adults only, Dec. 1995
Norvir*	Abbott Laboratories	Adults only, March 1996
Crixivan*	Merck & Co.	Adults only, March 1996
Viramune	Boehringer Ingelheim	Adults only, June 1996

*Protease inhibitors

Sources: Pediatric AIDS Foundation; Food and Drug Administration

In Line for Medicines Used to Treat AIDS, Children Come Last

Continued From Page B1

medicine at Children's Hospital in Boston. "But the company simply didn't push hard to put pediatric studies in place."

Abbott officials vehemently deny that they acted too slowly or that the small size of the pediatric market has influenced their priorities. They say they have followed the prudent course of testing the drug extensively on adults first. "We go through a careful process where adults, who can give their consent, can participate; and once we have the information from adults, we can take it to the children," says John Leonard, the head of Abbott's antiviral venture. Abbott has begun having preliminary talks with the FDA about adding recommended doses for children on Norvir's label, and the company hopes it will get the go-ahead before long.

Merck and Roche are further behind. Merck officials say they are moving as quickly as they can to develop a liquid that young children can take, but have encountered frustrating obstacles involving taste and the way the drug is absorbed in the body. Roche is working on a powder-like pediatric version of Invirase that can be sprinkled into a child's milk or formula bottle. All three protease makers say they are proceeding quickly by historical standards; in any case, various studies involving larger numbers of children are likely to begin later this year or early next year.

- Two other drug companies that are working on new protease inhibitors, Agouron Pharmaceuticals Inc. and Glaxo Wellcome PLC, plan to seek FDA approval for use by children at the same time they seek approval for use by adults. On another front, researchers at the University of Massachusetts Medical Center have gotten encouraging results in tests involving infants given a new mixture of drugs not including any protease inhibitor.
- FDA Commissioner David Kessler, who already has eased the rules on pediatric drug approvals once, says more needs to be done to prod companies to develop pediatric data. The Pediatric AIDS Foundation backs legislation that would give companies an extra period of market exclusivity if they develop the needed information on the use of their pediatric drugs.
- As for Samuel Fox, he has begun speaking out about kids' access to the drugs. "He wants to do something," his mother says. "He's angry right now. We're all angry."

Says Samuel: "I want to live to be an adult."

EXECUTIVE OFFICE OF THE PRESIDENT

31-Dec-1996 11:44am

TO: jennings_c
TO: drye_e

FROM: Nickandtim

SUBJECT: Pediatric drug approval

Dear Chris and Elizabeth:

Happy new year from cold and snowy London. If more places had central h eat, it would be truly pleasant; as it is, it's often just picturesque (although the fireplace in our apartment is being well used).

I am writing to give you heads up about the Pediatric AIDS Foundation's (PAF) ongoing work to try to get pharmaceutical companies to do more research on drugs for children (both children with HIV and children with other illnesses and conditions). I know you both know about PAF's efforts during the legislative year to enact the Kassebaum bill to provide market-exclusivity incentives for such research; so close to unanimous consent and suspension, but so far.

At the same time, I have been exploring possible administrative solution s to the problem of insufficient pediatric data. I have met several times with David Kessler, Bill Schultz, and their lawyers to make the case that current law requires pediatric data. I think you will find them supportive.

PAF has now privately proposed that the President issue an Executive Ord er, directing the FDA to take immediate regulatory action to ensure that all drugs be proven safe and effective for use by children prior to their approval by the FDA.

The long and the short of it is that PAF has taken the case directly to Mrs. Clinton and, through Joel Johnson of Daschle's staff, to Rahm Emmanuel. They have both been supportive as well.

Since you would deal with this more directly than they, I thought I shou ld let you know. There has recently been very good coverage of the problem (WSJ, Time, AP), and I think the press would like this. Industry people probably will not; they will probably ask for the market exclusivity compensation instead.

I've attached a brief outline of the argument. Let me know if you want or need anything more.

Thanks.

Tim Westmoreland
e-mail at: Nickandtim@aol.com
H: 011-44-171-235-8932
W: 011-44-171-725-1601

Background

Eighty percent of the drugs currently on the market in the US have no pediatric data.

The problem has been particularly obvious in HIV/AIDS. None of the new protease inhibitor drugs has been tested on children, and children are not being given the new drugs despite the success in adults.

Separate safety testing is needed for children.

Children metabolize drugs differently than adults and drugs that may be safe for adults may not be in children. Dosages will also differ.

Since December 1994, separate effectiveness testing for children is NOT generally required by FDA. Adult effectiveness data may be extrapolated to children.

The Food, Drug, and Cosmetic Act (FDCA) does not allow the Commissioner to approve a drug for commercial use unless it is "safe and effective."

The law does not say "safe and effective for adults only."

The plain language of the law and the legislative history of the statute make it clear that Congress intended to cover children.

Both major amendments to the FDCA have come in the wake of pediatric disasters. It is not conceivable that Congress responded to these disasters with legislation that did not include protections for children.

The legislative history is replete with statements of Congressional intent to assist children.

The FDCA also requires that labeling be neither false nor misleading and that it bear adequate directions and warnings.. Current FDA-allowed labeling regarding children is inadequate because it does not recognize that desperate parents and doctors will (and do) use drugs in children.

Action requested:

The President would issue an Executive Order and accompanying statement, directing the FDA to take immediate regulatory action to ensure that all drugs be proven safe and effective for use by children prior to their approval by the FDA.

The Executive Order would:

Describe the dire need for pediatric data. The Order would explain that 80% of drugs currently on the market have not been proven safe and effective for use by children. The Order would explain the ramifications of this situation, namely that (1) children are being denied life-saving therapies

because physicians are afraid to prescribe potentially toxic drugs that have not been approved for use by children, and (2) children may be exposed to an increased risk of adverse reactions or decreased effectiveness of the drugs prescribed because pediatricians do not have appropriate dosage data

Explain that FDA has the statutory authority to require pediatric data prior to its approval of a new drug. The Order would explain that pursuant to the approval and labeling requirements of the Food, Drug, and Cosmetic Act, the FDA has the authority to require pediatric data.

Direct the FDA to promulgate regulations requiring, as a condition of approval for all new drugs for which children are foreseeable users, that pharmaceutical manufacturers submit pediatric safety data, and, as appropriate, pediatric efficacy data. The Order would direct the FDA to promulgate new regulations in accordance with the "notice and comment" procedures of the Administrative Procedure Act.

Direct the FDA to issue the proposed regulations as soon as possible. The Order would direct the FDA to publish, within 90 days, new proposed regulations for public comment.

The statement accompanying the Executive Order would:

Describe the urgent need for pediatric data.

Speak about the need to ensure that children share in and benefit from therapeutic progress.

Dedicate this action to Elizabeth Glaser, and her work to improve child health. (Note: December was the second anniversary of Elizabeth's death from AIDS-related complications.)

Prior to issuance of the Executive Order, David Kessler and Bill Schultz (as well as PAF representatives) would be consulted about the wording of the Order to ensure that is on clear legal footing.

E X E C U T I V E O F F I C E O F T H E P R E S I D E N T

31-Dec-1996 11:51am

TO: Nickandtim

FROM: Christopher C. Jennings
Domestic Policy Council

CC: drye_e

SUBJECT: RE: Pediatric drug approval

Thanks for the heads up. I really appreciate it.

I will look into this. I need to talk with Greg Simon of the VPs office on an unrelated matter soon and will raise this one as well.

My first reaction is that it is a very good idea. However, I will be surprised if the industry does not extract some patent extension/market exclusivity or other benefits before this debate is all over.

Hope all is well with you. Keep me posted on your journey and general developments.

My best for a Happy New Year!!!

cj

HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

P94-21
FOR IMMEDIATE RELEASE
Dec. 13, 1994

Food and Drug Administration
Don McLearn (301) 443-1130
Home (301) 926-6909

FDA ANNOUNCES NEW RULES FOR CHILDREN'S MEDICINES

The Food and Drug Administration today announced new steps to provide health care professionals with the information necessary to prescribe medications more safely for children.

The new measures announced today are designed to eliminate unnecessary risks faced by children and adolescents aged 16 and under when treated with drugs primarily tested in adults. The vast majority of prescription drugs currently on the market lack information about appropriate use in children.

A key element is amending a 1979 regulation that required full clinical trials in the pediatric population as a basis for labeling for use in children. That rule is being amended to allow companies, in some situations, to extrapolate from adult studies and use that information -- along with other information about use of the drug in children -- to provide labeling information on the appropriate use in children.

"Taking care of our children is our top priority," said HHS Secretary Donna E. Shalala. "These measures promise the kind of quality medical care our children deserve."

FDA Commissioner David A. Kessler, M.D., a pediatrician, proposed this rule change in a speech to the American

-MORE-

Academy of Pediatrics in October 1992. In addition to the final rule change announced today, FDA's Center for Drug Evaluation and Research is taking steps to increase the number of pediatric studies included in submissions for new prescription medicines.

"We have a duty to our children," said Kessler. "We can get the information we need to treat our children safely and effectively if we think creatively and are willing to commit resources to the challenge."

The new rule, being announced in the Federal Register today, revises the "Pediatric Use" subsection of prescription drugs labeling and makes it easier, in some situations, for manufacturers to include pediatric information on the label of their prescription products.

One of the rule's key provisions sets forth the conditions under which the agency permits pediatric use statements based on adequate and well-controlled studies in adults together with other information, such as pharmacokinetic and safety data, that supports pediatric use.

The rule makes clear that such pediatric use statements can be made only if the course of the disease and the drug's effects are sufficiently similar in the pediatric and adult populations to permit extrapolation from the adult data to pediatric patients.

Under the new rule, manufacturers also must reexamine existing information to determine whether the pediatric labeling of their marketed products can be modified on the basis of adult studies and

Pediatric Corner

Center IDs Top 10 Drugs Used Off-Label in Out-Patient Setting

By L. Miriam Pina, M.D.

After the Final Pediatric Rule was published in December 1994, the Pediatric Use Survey Working Group of the Pediatric Subcommittee was formed. The group's first charge was to identify the drugs most widely used in pediatrics on an out-patient basis for which there was inadequate use information.

Results of the survey disclosed that most drugs that are indicated for diseases occurring in both adults and children have very little information about pediatric use in the labeling. Some age groups have less information available to them than others. The population of less than 2 years of age, for instance, has virtually no pediatric use information on drug products in several class categories. In general, drugs used to treat diseases like asthma, and seasonal and perennial rhinitis, so common in children, present very little information about pediatric drug use. For other therapeutic areas, such as infectious diseases, the pediatric information is, in contrast, quite good.

The working group analyzed survey data from IMS America, Ltd., to provide estimates for pediatric use for 1994. The IMS database is an ongoing pharmaceutical marketing research survey describing drugs mentioned during patient contacts by a nationwide panel of office-based physicians randomly selected from the American Medical Association and the American Osteopathic Association (more than 2,940 physicians representing 27 specialties).

Data collected from the panel are projected nationally by multiplying the raw number of mentions in each stratum, defined by region and specialty, by a corresponding projection factor.

The table displays the drugs that were most widely used off-label in the pediatric population in 1994, according to the IMS database. The drugs are presented in order of frequency of mentions per year and reflect neither the severity of the diseases being treated nor the adverse events reported. Also, for drugs used to treat chronic conditions, the number of mentions may not correlate well with the number of patients being treated. In the chronic use of the Schedule II drug Ritalin, for example, the physician is required to prescribe it with no refills under close surveillance (the prescribing requirements vary from state to state). Thus, in this case, the number of appearances will be overestimated when compared with other drugs used chronically. Nonetheless, in every case, the physician had to make a decision to use the drug with inappropriate pediatric use information.

Members of the Pediatric Use Survey Working Group are: **L. Miriam Pina, M.D.**, chairperson, Division of Pulmonary Drug Products, **Kimberly Struble**, Division of Anti-Viral Drug Products; **Linda Hu**, Division of Over the Counter Drug Products; **Jones Bull, M.D.**, Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products; **Cazimiro Martin**, Division of Over the Counter Drug Products; **Frank Rosa**, recently retired from the Division of Pharmacovigilance and Epidemiology; and **Charles Maynard**, Division of Pharmacovigilance and Epidemiology. The December *Pike* lists representatives from each of the Center's review divisions who can assist you with Pediatric Rule issues. The working group plans on publishing in-patient data in a future issue.

L. Miriam Pina, M.D., is a visiting scientist in the Division of Pulmonary Drug Products.

Product	Indication(s)	Label Statement	Off-Label Prescribing Frequency	Prescriber's Specialty (percentage)
Albuterol inhalation solution for nebulization (albuterol sulfate, 0.083 mg/ml)	Prevention and relief of bronchospasm.	Safety and effectiveness (S&E) have not been established in children below 12 years of age.	1,626,000 to children <12 years old.	Pediatricians (62%) Family practitioners and allergists (20%)
Phenergan (promethazine HCl)	Relief of diverse allergic reactions.	Should not be used in children below 2 years of age.	663,000 to children <2 years old.	Pediatricians (82%)
Ampicillin sodium for intravenous or intramuscular injections.	Infections due to susceptible organisms.	S&E have not been established in infants and children under the age of 12.	639,000 to children <12 years old.	Pediatricians (88%) Most common indication: perinatal infections

Product	Indication(s)	Label Statement	Off-Label Prescribing Frequency	Prescriber's Specialty (percentage)
Auralgan otic solution	Prompt relief of pain of acute otitis media and to facilitate the removal of excessive or impacted cerumen.	No instructions for pediatric use at any age.	600,000 to children <16 years old.	Pediatricians (62%) Family practitioners (23%)
Lotrisone cream (clotrimazol 1%, betamethasone dipropionate 0.05%)	Topical treatment of particular dermal, fungal infections.	S&E in children below the age of 12 have not been established.	325,000 to children <12 years old.	Pediatricians (51%) Family practitioners (24%)
Prozac (fluoxetin HCl.) pulvules and liquid	Depression and obsessive compulsive disorders.	S&E in children have not been established.	349,000 to children <16 years old. Note: was mentioned to 3,000 infants <1 year of age were in 1994.	Psychiatrists (81%) Most common indication: depressive disorders
Intal (cromolyn sodium).	Prophylactic agent in the management of bronchial asthma.	For inhalation (nebulization) solution, S&E below the age of 2 have not been established. For inhalation aerosol solution (MDI). S&E have not been established below the age of 5.	Intal inhalation solution was prescribed 109,000 times to infants <2 years of age. Intal inhalation aerosol (MDI), 399,000 times to children < 5 years.	Pediatricians (71%)
Zoloft (sertraline HCl)	Depression.	S&E have not been established in children.	248,000 for children <16 years.	Psychiatrists (72%)
Ritalin tablets and sustained-release tablets (methylphenidate HCl) *(Schedule II drug)*	Treatment of attention deficit disorders and narcolepsy.	S&E have not been established in children <6 years of age.	226,000 to children <6 years old.	Pediatricians (47%) Psychiatrists (26%)
Alupent Syrup (metaproterenol sulfate).	Bronchodilator for bronchial asthma and for reversible bronchospasms.	Clinical trial experience in children under the age of 6 is limited.	184,000 to children <6 years old.	Pediatricians (59%) Family practitioners (23%)
Beclomethasone dipropionate nasal sprays (includes Beconase AQ and Vancenase AQ nasal sprays).	Relief of symptoms of seasonal and perennial rhinitis and for the prevention of recurrence of nasal polyps following surgical removal.	S&E in children below the age of 6 have not been established.	174,000 to children <6 years old.	Pediatricians (46%)

December 15, 1994
Paula Botstein M.D.

CDER Pediatric Plan [the PeP]

The CDER Pediatric Plan aims at focusing sponsors, and FDA, on thinking about all drugs in the pediatric population during two time periods: throughout a drug's development up to approval, and during marketing. The goal is adequately supported instructions in drug labeling for health practitioners to prescribe medicines for the pediatric population.

1. **Publish new pediatric labeling regulation.**
FDA will publish a new **pediatric labeling regulation** to increase adequately supported pediatric information in physician labeling of marketed drugs. Sponsors' existing obligations to provide instructions for physicians on using drugs in the pediatric population and FDA's existing authority to require pediatric studies are highlighted in discussion in the FR notice. Published 12/13/94.

2. **Focus attention on pediatric patients throughout drug development.**
CDER will early and repeatedly **throughout clinical drug development** cause commercial sponsors and FDA staff to focus on use of drugs in the pediatric population. The goal is to determine, for each drug, if studies are needed in the pediatric population, which studies are needed, when they are needed, and get them done.

For an IND with a commercial sponsor, the key opportunities for focusing on a drug's use in the pediatric population are:

1]. Pre-IND meeting and pre-IND submission
2]. Initial IND submission
3]. IND annual report
4]. End of phase 2 meeting to discuss a drug's full development plan and to outline further data needed for approval
5]. Presentation of IND to an FDA drug advisory committee
6]. Pre-NDA meeting to discuss the content and format of the NDA
7]. The NDA submission and FDA's 45 day filing meeting
8]. Presentation of NDA to an FDA drug advisory committee

At each of these opportunities, as appropriate for a drug, the sponsor will be required to submit either a brief written pediatric plan [**sponsor's pediatric plan**] or other appropriate document, e.g. Sponsor's End of Phase 2 Pediatric Plan. FDA staff will develop methods to insure discussion of the pediatric population at meetings about a drug's development. FDA will, as needed, revise or create regulations and **guidances** to sponsors and to FDA staff.

3. **Extend Offices of Drug Evaluation Pediatric Page.**
CDER will extend the current Offices of Drug Evaluation **pediatric page** to all NDAs: for all action letters. A pediatric page summarizing the state of pediatric studies is now completed only for each NME [new molecular entity] by a reviewing division when it proposes approval to an Office of Drug Evaluation.

Target time: second quarter of 1995.

4. **May refuse to file NDAs.**
CDER may **refuse to file NDAs** which lack appropriate **analyses** of safety and effectiveness data which a sponsor already has in the pediatric population. FDA may now refuse to file NDAs which lack appropriate analyses of safety and effectiveness data by age [or gender], and analyses by age includes the pediatric population. CDER will clarify its refuse-to-file policy, guidances, and regulations, as necessary, to specify that FDA may refuse to file NDAs for drugs with recognized potential widespread use of the product in children if the NDAs 1]. lack a sponsor pediatric plan **and** 2]. lack necessary pediatric data.

5. **Get studies done.**
CDER will work with and advise the **Pediatric Pharmacology Research Units** funded by the NICHD. The PPRUs are a new resource able to conduct clinical and pharmacokinetic studies of drugs in the pediatric population.

6. Require **NDA Pediatric Safety Evaluation.**
FDA has proposed a rule which would, among other things, require an **Overall Safety Evaluation** in each periodic report to an approved NDA; this section will require critical analysis of safety information in **pediatric treatment**, along with other analyses of safety information. Published in Federal Register, 10/27/94.

7. **NDA Periodic Pediatric Use Report.**
CDER will explore the best mechanism for insuring that **periodic reports** to an NDA explicitly include **pediatric use** of the drug. As FDA communicates in the preamble to the new pediatric labeling regulation, a sponsor is already required to summarize new information about effectiveness, or safety, of a drug and to describe actions planned because of the new information.
Periodic reports need to include information such as the extent the drug is used in the pediatric population, the indications for which it is used, an analysis of available effectiveness data, and changes proposed in labeling because of this pediatric information. Also needed is an assessment of further pediatric data needed to assure safe and effective use of the product in the pediatric population and the sponsor's plan for obtaining it.

Target time: fourth quarter of 1995, when final rule is promulgated. NOPR--see above--just published in Federal Register, 10/27/94.

8. **Track Phase 4 Commitments.**
CDER will intensively track **phase 4** pediatric clinical studies. Before approval of a drug, a sponsor may make commitments to conduct clinical studies in the pediatric population during phase 4 [after marketing approval] . CDER will track commitments made, submission of protocols, performance of studies, submission of results to NDAs, and the percentage of commitments that result in the addition of pediatric prescribing information to drug labeling.

9. **Survey Pediatric Drug Use.**
CDER will obtain data on **drugs used** in the pediatric population. CDER intends to develop and fund more sources of survey data on use of marketed drugs in the pediatric population. Drugs in categories used frequently in the pediatric population, drugs of particular therapeutic importance or necessity, and drugs with potential safety hazards will be initially targeted to assure that they have adequate prescribing information in the labeling.

10. **Work with Pediatric, Pharmacy and other Communities.**
CDER will intensify work with pediatric and pharmacy **communities.** These include the NICHD, American Academy of Pediatrics Committee on Drugs, AAP Committee on Infectious Diseases, Pediatric Pharmacy

Administrative Group, ASCPT, National AIDS Task Force, and numerous others.
FDA will work also with its drug advisory committees, and with industry organizations.

END of PLAN

Intra-agency Efforts.
We are pleased that CBER will join CDER in many elements of this Pediatric Plan. CDER will work with **CBER, and CDRH,** on initiatives in the CDER Pediatric Plan that may be useful for biologics and devices for the pediatric population.

Acknowledgments
Many people have contributed thought, discussion and language to the CDER Pediatric Plan.

PEDIATRICS

American Academy of Pediatrics

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VOLUME 98
NUMBER 1

ARTICLES

SECTION REPORT

COMMENTARIES

EXPERIENCE AND REASON

Committee Statements—For Contents See Pages A10 and A13

Is the "Therapeutic Orphan" About to Be Adopted?

In this issue of *Pediatrics*, the Committee on Drugs (COD) has examined the continued problem of the "unapproved" use of "approved" medications in pediatrics.[1] This commentary will expand on the issues that have restricted drug research in children and describe current initiatives to facilitate and encourage such research to achieve the necessary drug labeling to reduce unapproved uses of medications in children.

BACKGROUND

Physicians who treat infants and children frequently prescribe medications that have never been approved by the Food and Drug Administration (FDA) for pediatric patients; unfortunately, many drugs are released without labels for pediatric use and often with pediatric disclaimers. The need for specific pediatric studies to document safety and efficacy before widespread exposure of children to a new drug has been well documented.[2] Generally recognized examples of catastrophes arising from the lack of such studies include tetracycline-induced dental dysplasia and neonatal deaths attributed to chloramphenicol-induced "gray baby" syndrome.[3,4] From an ethical and moral perspective, children of all ages deserve the same proof as adults that the medications they use are safe and efficacious. However, most new medications and the vast majority of older medications have not been labeled as safe and efficacious for pediatric use, because the research that meets FDA standards for establishing their safety and efficacy in children has not been carried out.[5]

Clinical trial data submitted to the FDA as part of a New Drug Application (NDA) form the basis for FDA approval and labeling of the drug. Phase I and II premarketing clinical trials are typically limited to adult subjects (usually men) 20 to 40 years of age, followed by phase III investigations in a larger adult population, which may include the elderly. Children are not included in the majority of premarketing clinical studies. Even when a pediatric application of a new (or old) medication is investigated, it frequently is carried out in a limited pediatric age range, thus leaving out the majority of children. Typically, phase III is the earliest point in the clinical drug development process that the FDA requests that pediatric studies be performed.

Until recently, the FDA has not assumed a proactive stance to ask nor did it have the regulatory authority to force manufacturers to perform pediatric studies. Most new drugs have been labeled with disclaimers for pediatric use.[6] As a result, the labeling for many important newly approved drugs and the majority of old drugs contains pediatric disclaimers (Table). Significant segments of the patient population are left without the benefit of appropriate age-specific research to document a drug's safety, efficacy, or metabolic and kinetic profiles. With the absence of FDA-approved prescribing information, the selection and dosing of these drugs is left to the discretion of the individual physician. For the vast majority of indications, even in young pediatric patients, the benefits of using many of these medications "off-label" outweigh the risks of not using them.[7]

Drugs commonly used to treat mental or physical pain in children, (morphine, meperidine, fentanyl, midazolam, bupivacaine, and ketorolac) illustrate the problem. Morphine and meperidine are commonly prescribed opioids for postoperative analgesia. The package insert of one manufacturer of patient-controlled analgesia (PCA) opioid formulations states that for morphine, "the intravenous route via the . . . PCA infuser is not recommended for use in individuals younger than 12 years" (Baxter morphine sulfate injection, United States Pharmacopoeia [USP] package insert for PCA formulation, July 1994) The same manufacturer states that meperidine "administered by the intravenous route via a compatible infusion device is not recommended for use in individuals younger than 19 years" (Baxter meperidine hydrochloride injection, USP package insert for PCA formulation, July 1994). Fentanyl, because of its minimal adverse cardiovascular effects, is perhaps the opioid of choice in critically ill premature and term neonates. However, the fentanyl label states that "safety and efficacy in children under two years has not been established" (Janssen fentanyl citrate [Sublimaze] injection package insert, September 1992).

The importance of developing age-specific drug kinetic data is well recognized from many therapeutic misadventures, some of which ended in patient death ("gray baby" syndrome with chloramphenicol).[3,4] Despite these misadventures, potent drugs used in sick children are not adequately studied. An excellent example is fentanyl, as described above, despite the knowledge that the pharmacokinetics of fentanyl is significantly altered by age-specific activity of enzymatic metabolism and neonatal hepatic blood flow.[8–10]

Children also have been left out of the picture with other frequently prescribed medications, such as medications to treat asthma, seizures, psychiatric disorders, and gastrointestinal motility problems, sedatives, and others (Table).[2,11] One of these commonly prescribed medications not labeled for pediatric use, cisapride (Janssen cisapride [Propulsid] package insert, January 1995), has recently been described as causing potentially life-threatening bradycardia and prolonged QT interval in a 2-month-old infant.[12] Adenosine is now the drug of choice to treat pediatric supraventricular tachycardia (S. Mithani, personal communication, Bureau of Human Prescription Drugs Health Protection Branch, Canada, 1996), but "no controlled studies have been conducted in pediatric patients"

Received for publication Mar 7, 1996; accepted Apr 4, 1996
Reprint requests to (C.J.C.) Department of Anesthesia, Children's Memorial Hospital, Northwestern University Medical School, 2300 Children's Plaza, Chicago, IL 60614.

TABLE. Drugs with Widespread use in Children and Their Pediatric Disclaimers*

Generic Name	Manufacturer's Name	Pediatric Disclaimer
Adenosine	Adenocard	No controlled studies have been conducted in pediatric patients (Fujisawa, package insert, May 1994)
Albuterol	Ventolin	Safety and effectiveness have not been established in children <12 y of age for Ventolin inhalation solution and Ventolin nebules inhalation solution; in children <4 y for Ventolin inhalation aerosol and Ventolin Rotacaps for inhalation; and children <2 y for Ventolin syrup (Glaxo, package insert, March 1995)
Bupivacaine hydrochloride	Sensorcaine	Not recommended in children <12 y due to limited experience in controlled clinical trials (Astra, package insert, February 1995)
Cisapride	Propulsid	Safety and effectiveness in children have not been established (Janssen, package insert, January 1995)
Meperidine hydrochloride injection (PCA)	Demerol (PCA)	Not recommended for use in individuals younger than 19 y (Baxter, package insert, July 1994)
Dobutamine	Dobutrex solution	Safety and effectiveness in children have not been established (Lilly, package insert, November 1993)
Dopamine	Dopamine hydrochloride injection	Safety and effectiveness in children have not been established (American Regent, package insert, August 1992)
Fentanyl citrate	Sublimaze	Safety and efficacy of Sublimaze in children under 2 y has not been established (Janssen, package insert, September 1992)
Flumazenil	Romazicon	Not recommended for use in children, as no clinical studies have been performed to determine risks, benefits, and dosages to be used (Hoffmann-La Roche, package insert, October 1994)
Fluoxetine hydrochloride	Prozac	Safety and effectiveness in children have not been established (Lilly, package insert, March 1995)
Gabapentin	Neurontin	Safety and effectiveness in children below the age of 12 y have not been established (Parke-Davis, package insert, December 1994)
Ketorolac tromethamine	Toradol	Safety and efficacy in children (<16 y) have not been established; therefore, use of Toradol in children is not recommended (Syntex, package insert, March 1995)
Mexiletine hydrochloride	Mexitil	Safety and effectiveness in children have not been established (Boehringer Ingelheim, package insert, October 1993)
Morphine (PCA)	Morphine sulfate injection (PCA)	Not recommended for use in individuals <12 y (Baxter, package insert, April 1994)
Midazolam hydrochloride	Versed	Safety and effectiveness of Versed in children below the age of 18 y have not been established (Roche, package insert, June 1994)
Nicardipine hydrochloride	Cardene	Safety and efficacy in children <18 y have not been established (Syntex, package insert, September 1993)
Terbutaline sulfate	Brethine	Brethine is not recommended for patients under the age of 12 y because of insufficient clinical data to establish safety and effectiveness (Ciba-Geigy, package insert, August 1992)

* This table is not meant to be an all inclusive list, nor is any drug or manufacturer meant to be singled out. Data were abstracted from package inserts. Some manufacturers may have since submitted new labeling to the Food and Drug Administration.

(Fujisawa adenosine [Adenocard] intravenous package insert, May 1994). Even older vasoactive medications such as dopamine (American Regent, dopamine hydrochloride injection, August 1992) and dobutamine (Lilly dobutamine hydrochloride solution [Dobutrex] injection, November 1993) have pediatric disclaimers.

It is a cause of deep concern that so many medications lack the developmental metabolic, pharmacokinetic, and pharmacodynamic data needed for their safe and effective use in children. Children should not be denied the benefit of these or any medications simply because of their age. The importance of developing such information cannot be overemphasized. The use of medications inadequately studied in children has contributed to a variety of adverse outcomes, including seizures and cardiac arrest caused by bupivacaine toxicity, pro-

longed narcotic effects caused by altered hepatic blood flow, intermediate-acting muscle relaxants becoming long-acting in neonates, benzodiazepine withdrawal, and interactions with antibiotics and other sedatives.[7,8–10,13–19] These are but a few examples of why pediatric pharmacologic research is important. However, the funds needed to conduct such studies are difficult to obtain, particularly for older drugs, which are no longer patented.[7,20] Most manufacturers are not interested in financing the studies necessary to develop appropriate pediatric labeling for off-patent drugs, because they have no financial incentive to do so. Therefore, the pediatric patient is often a "therapeutic orphan."[21] If the necessary studies are to be carried out, they likely will require funding from sources other than industry.

A recent example of the importance of pediatric studies is the new inhaled anesthetic agent desflurane. In preclinical studies and clinical adult trials, desflurane seemed ideal for pediatric application because of its gas partition coefficient and lack of metabolic degradation. However, the pharmaceutical company-supported and FDA-approved pediatric studies conducted before approval in adults found an unexpected and unacceptably high incidence of airway-related complications, particularly laryngospasm.[22] This observation resulted in pediatric-specific labeling clearly stating that desflurane may be associated with airway-related complications. Serious injury may have resulted had the appropriate studies not been carried out in the hands of experienced pediatric clinical investigators. In this situation, the pharmaceutical company, the FDA, and the academic and medical community together fulfilled their obligations to investigate this new drug in children. Serious adverse effects in children and potential litigious losses would probably have resulted had the drug been released without proper pediatric labeling. The drug is presently recognized to be safe for use in children after induction and control of the airway.

Several factors contribute to the lack of appropriate pediatric studies: relatively small market share, fear of legal liability, potential long-term adverse effects, the reluctance of parents to give permission to allow their children to be research subjects, and the lack of adequate research funding from government, industry, and health care providers.[20] Although legal liability is often an expressed concern, the actual number of such lawsuits arising from pediatric clinical trials is negligible.[20,23] Another factor that has impeded pediatric clinical trials in the past is that the FDA relied on the manufacturer to advise the FDA whether a drug had a pediatric indication rather than independently assessing potential pediatric use.

Shirkey, who originally coined the term "therapeutic orphan,"[21] pointed out that the lack of financial support by government and industry for pediatric drug investigation is particularly ironic, because most of the major laws that support the FDA's role in regulating drugs have been passed in response to drug-induced adverse effects occurring in the pediatric population (ethylene glycol poisoning in 1938 and thalidomide in 1962).[24–26] Is it true that more than two decades after Shirkey's editorial, the pediatric patient continues to be a therapeutic orphan?

INITIATIVES TO SOLVE THE PROBLEM

The COD of the American Academy of Pediatrics (AAP) prepared a report for the FDA in 1979 that documented the absence of pediatric labeling for several hundred drugs used in pediatric patients. In 1982 the AAP COD published an additional report for the FDA, "General Considerations for the Clinical Evaluation of Drugs in Infants and Children." In 1984 a list of 103 parenteral drugs administered to neonates, but without neonatal labeling, was prepared by the AAP COD; this was followed in 1985 by a list of the top 10 drugs widely used in neonates for which there were published data (ranked according to use and availability of data) but that were not labeled for pediatric use. Despite good intentions, few of these drugs subsequently have had their labels revised for use by infants and children.

The Orphan Drug Act of 1982 was primarily designed to provide financial incentives to encourage the development of drugs with applications to small patient populations so that drugs with proven applicability might be developed and released to a limited market (<200 000 patients per year).[20] However, the Orphan Drug Act was not targeted specifically at pediatric patients. Although children with rare diseases have benefited from the Orphan Drug Act, the act has not stimulated or facilitated studies to obtain pediatric labeling for drugs widely used in adults. This failure is evidenced in part by the marked delay in FDA approval of zidovudine for children, because the appropriate pediatric studies were not carried out concurrently with clinical trials in adults.

In 1984, the Drug Price Competition and Patent Term Restoration Act modified the process for approval of abbreviated NDAs, allowing more rapid approval based on bioequivalency studies and extending patent rights to encourage studies of new indications for approved drugs. However, this act has not facilitated labeling of drugs for children.

Despite the concerns for children voiced by the industry through the Pharmaceutical Manufacturers Association,[27] a survey of drug labeling in the 1990 *Physicians' Desk Reference*® revealed that for 91% of 491 medications for which disclaimers or precautions against their use in children were cited, the disclaimers or precautions were based on a lack of adequate data. Approximately 80% of new chemical entity drugs approved between 1984 and 1989 were not labeled for use in children. This proportion has not changed; 92 (71%) of 130 new drugs approved from 1991 to 1995 did not have pediatric labeling at the time of approval. (At the time of this writing, complete data for 1995 were not available.) However, at the request of the FDA, the manufacturers of 43 (33%) of these new drugs committed to or are conducting pediatric studies. The manufacturers of 49 (38%) of the new drugs told the FDA that these drugs would have no pediatric indications, although at least 21 will likely have some pediatric use, and another is currently one of the most commonly pre-

scribed drugs for the treatment of gastroesophageal reflux in children of all ages (G. Troendle, personal communication, 1996; Janssen cisapride [Propulsid] tablets package insert, January 1995).

DEVELOPING SOLUTIONS

In 1988 a meeting of the AAP COD, with representatives of the FDA and the pharmaceutical industry, was held for the purpose of discussing the issues and problems associated with pediatric drug investigation. At the time, the role proposed for the FDA was to encourage drug companies to sponsor pediatric research, "if applicable," by making pediatric studies a priority: (1) if a new drug had a unique pediatric application; or (2) if a drug would be used in adults but would also have an important pediatric application for the same indication. If there would be little therapeutic gain, but a drug may be "applicable" to pediatric patients, then "after approval" studies would be encouraged. The concept of a "pediatric studies page" for NDAs for new molecular entities was introduced. Also, the need for incentives to the industry to sponsor pediatric studies was discussed by representatives of the FDA familiar with the problems related to drug development for children. However, it was recognized that the FDA did not have any legal means of compelling drug companies to perform pediatric research, even if the drug had a recognized, important pediatric application.

In April 1990 the Forum on Drug Development of the Institute of Medicine, National Academy of Sciences, sponsored a workshop, "Drug Development and the Pediatric Population."[28] This meeting was convened to examine the issues that create barriers to drug testing in children. Input was enlisted from the FDA, the industry, the AAP, the National Institutes of Health (NIH), and many pediatric pharmacologists and toxicologists. The problems cited were numerous and somewhat specific to each group of individuals, depending on its perspective.[28] A plea was made to the research community to develop more innovative and cost-effective research protocols with better statistical designs, to avoid arbitrary age restrictions, and to develop a greater sense of community between parties interested in pediatric research. FDA representatives indicated that regulatory changes were being explored to improve pediatric labeling, such as: (1) including peer-reviewed, published information on the pediatric use of drugs in drug labeling in addition to the information from FDA-approved clinical trials; (2) establishing a policy of identifying the need for pediatric studies in every NDA for new molecular entities; and (3) removing the FDA requirement for additional randomized and double-blind efficacy studies when the disease is the same in children as in adults and when information required for infants and children is primarily for dose and adverse effects rather than efficacy. The need for practical endpoints for long-term follow-up studies was also described. It was pointed out that support for long-term follow-up would likely need to come from government rather than industry.

Representatives from the industry stated that the greatest obstacle to industry-supported drug research was the potential for litigation and ethical problems encountered when carrying out research in children. This concern seems incongruent with the fact that few such lawsuits have occurred, and ethical guidelines for drug research in children have existed since 1977 and have been revised recently.[23,29] The financial discrepancy between monetary return and the investment in pediatric research required to support pediatric studies was described. The need to develop legislation to provide economic incentives for investigating in pediatric clinical trials was noted.

The workshop highlighted eight recommendations to be addressed by all concerned parties in a cooperative effort to promote and develop adequate pediatric labeling: (1) inclusion of available pediatric data in drug labeling, even if this provides only limited pediatric information; (2) the need for a new awareness within FDA of the importance of pediatric studies; (3) a de-emphasis of the need for long-term follow-up studies unless specifically indicated; (4) recognition of the cost and time required to carry out pediatric studies; (5) the need by industry, academia, and publishers of journals to provide better incentives to conduct and publish pediatric research; (6) the need for the pediatric community to identify drugs important to the care of pediatric patients that need further data in children (7) the need for the NIH to stimulate pediatric research by providing core funding for a recommended clinical trials network; and (8) the need for the pharmaceutical industry to consider pediatric studies at all levels of drug development. There was a consensus that the implementation of these recommendations could be achieved only by the combined effort of the industry, the federal government (FDA and NIH), the medical community, and the general public.

SOLUTIONS

It is gratifying and encouraging that several key recommendations from the 1990 Institute of Medicine workshop subsequently have been implemented. The FDA recently promulgated regulatory changes that allow available pediatric data to be included in labeling, even though the data may not meet FDA criteria for approval on the basis of safety and efficacy. If the disease for which the drug is indicated is substantially the same in children as adults, efficacy in children may be extrapolated from adult studies. However, dose-finding and pharmacokinetic studies to obtain information on appropriate doses and safety in children will be required.[30] A pediatric studies page in the NDA has been implemented by the FDA and is being expanded to include drugs that already have approved indications if they are being evaluated for new indications or dose formulations. The pediatric studies page requires the FDA and sponsoring company to identify whether pediatric studies are being conducted or planned and, if not, to explain why. Manufacturers will be required to reexamine existing information on marketed drugs to determine whether the labeling can be modified to include pediatric information on the basis of adult studies and available pediatric data. If so, they will

be required to submit applications for supplemental labeling within 2 years. In addition, the FDA has the authority under the new regulations to request specific pediatric use information when deemed necessary. Within the FDA, a special Pediatric Subcommittee of the Medical Policy Coordinating Committee of the Center for Drug Evaluation and Research, with representatives from each division, has been formed to track the implementation of the new regulations and to facilitate the inclusion of pediatric testing in the drug development process.

The USP also has begun to include the latest pediatric uses and drug doses in the USP Dispensing Information based on available literature and consultation with subspecialty experts. This provides a ready reference source for the practitioner, although it does not address the lack of pediatric clinical trials with which official labeling can be supported. Nonetheless, inclusion of pediatric information will help address the reluctance of insurance carriers and other third-party payers to pay for the use of medications that are not labeled for children. Because the USP Dispensing Information is one of the compendia used to document accepted medication uses, this effort by the USP may help slow a reimbursement denial trend, which threatens the care of children.

The National Institute of Child Health and Human Development recently funded a network of pediatric pharmacology research units expressly to carry out pediatric pharmacologic research that will support pediatric labeling. The FDA is working closely with the pediatric pharmacology research unit network to conduct pediatric studies on selected therapies that otherwise would not be studied.[31]

In 1994 legislation was sponsored by Senator Nancy Kassebaum,[32] with a companion House bill sponsored by Representative Kreidler,[33] which proposed extending the period of exclusivity of a drug if the sponsoring company conducted pediatric studies that supported labeling for children. Unfortunately, this legislation was not reported out of committee. If such a bill eventually becomes law, it will provide an economic incentive to conduct pediatric studies by enhancing the opportunity for companies to recover their investment in pediatric studies for drugs that are necessary for the treatment of childhood illnesses but have limited market potential in children.

The COD of the AAP continues to work closely with the FDA to foster the study and labeling of drugs for pediatric use. The committee recently submitted a list of six drugs to the FDA that are considered priorities for studies in children (fentanyl, bupivacaine, midazolam, cimetidine, albuterol, and metronidazole).

It is past time that all drugs with potential pediatric applications should be investigated in infants and children with appropriately designed industry-supported and FDA-approved studies. The unapproved or off-label use of drugs is not an acceptable alternative to documentation of the safety and efficacy of drugs used by the pediatric population. The pediatric academic and private practice communities must become more vocal in demanding support for pediatric studies and for greater cooperation between industry, government, and academia to conduct the necessary studies when new drugs that have potential to be of help in caring for children are introduced. There is a need to make the general public more aware of these issues to encourage voluntary participation in and the financial support necessary for studies in children. Children have the same medical, legal, and ethical rights as all other segments of the patient population to have clinically important drugs available to treat disease effectively and safely. Recent efforts by the AAP, FDA, USP, NIH, and Congress suggest that perhaps the drug development and approval process is changing in a positive direction for children. The recently announced FDA changes in regulations and the establishment of the Pediatric Subcommittee of the Medical Policy Coordinating Committee of the Center for Drug Evaluation and Research to track the implementation of new regulations regarding pediatric drug testing will specifically address the importance of pediatric studies within each of the FDA's 12 divisions. This should go a long way to increasing and improving pediatric pharmacologic research of new drugs and, it is hoped, in cooperation with the pediatric pharmacology research units funded by the NIH, should also address pediatric labeling problems for old drugs.[34] Perhaps it is also time for large purchasers of drugs, such as health care systems and managed-care organizations, to apply economic pressure by basing those purchases in part on the presence of pediatric labeling. Perhaps now, with the cooperation of the industry, USP, NIH, FDA, AAP, parents, children, and health care providers, children no longer will be therapeutic orphans.

CHARLES J. COTÉ, MD
Department of Anesthesia
Children's Memorial Hospital
Northwestern University Medical School
Chicago, IL 60614

RALPH E. KAUFFMAN, MD
Departments of Pediatrics and Pharmacology
Children's Mercy Hospital
Kansas City, MO 64108

GLORIA J. TROENDLE, MD
Division of Metabolic and Endocrine Drug Products
Food and Drug Administration
Rockville, MD 20857

GEORGE H. LAMBERT, MD
Department of Pediatrics
Clinical Research Center
University of Medicine and Dentistry of New Jersey
Piscataway, NJ 08855

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Tuberculosis Skin Testing: New Schools of Thought

In the past 10 years, I have cared for more than 500 children and adolescents with tuberculosis. Only one of them—an asymptomatic 5-year-old with mild hilar adenopathy—was discovered via a school skin-testing program, although since 1990, the Houston Independent School District has required all new entrants to have a tuberculin skin test. During the last 5 years, the number of children in Houston with tuberculosis has increased. School-based skin testing has neither found many active cases nor prevented their occurrence.

At first glance, requiring all schoolchildren to have a tuberculin skin test seems to be a reasonable response to the desire to promote prevention of a potentially serious and still prevalent disease. This approach has been championed by many well-meaning pediatricians—including myself in the past—with the best of intentions. Some school boards have been convinced that skin testing of all children is an essential element of tuberculosis control. The well-publicized resurgence of tuberculosis in the United States during the past decade has created both appropriate concern and unnecessary anxiety about the risk of tuberculosis in children.

However, within the past few years, the American Academy of Pediatrics (AAP),[1,2] the Centers for Disease Control and Prevention (CDC),[3] and the American Thoracic Society[4] have stated unequivocally that mandatory school-based tuberculin skin testing of all children is undesirable, an "ineffective method of detecting or preventing cases of childhood TB and should be discontinued."[3] The study by Driver et al[5] in this issue of *Pediatrics* further supports this viewpoint, but for different reasons.

Are there potential benefits of school skin test programs? It is clear they are an extremely inefficient and expensive means to find cases of tuberculosis. Driver et al[5] report that recent programs discovered tuberculosis in 0.02% or less of children tested. Previous investigations of childhood tuberculosis have shown that skin test screening finds few if any cases.[6–8] Most children with tuberculosis are found in one of two ways. In Houston, in about half of the children with tuberculosis, symptomatic illnesses develop, which are diagnosed after the children seek medical attention. In the other half, tuberculosis is discovered when they receive tuberculin skin tests, chest radiographs, and physical examinations after exposure to an adult or adolescent with suspected or proven pulmonary tuberculosis. This activity, performed by the local public health department, is called a contact investigation, and it has been the cornerstone of finding children with recent tubercu-

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Reprint requests to (J.R.S.) Associate Professor of Pediatrics, Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030.

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.