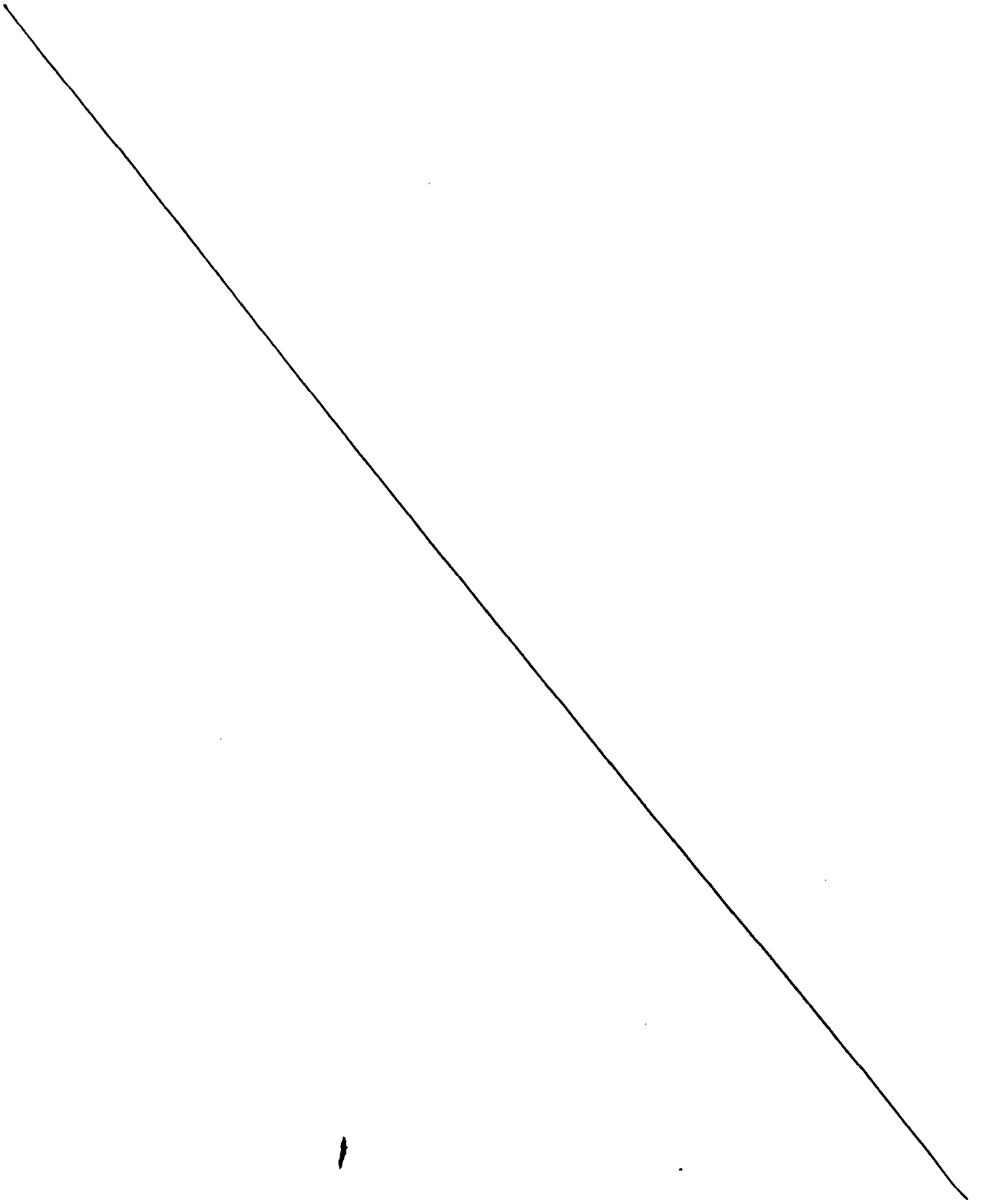
patients to the study. FDA seeks comment on the circumstances in which FDA should permit deferral. FDA also seeks comment on factors that should be considered in determining whether a



product is among those that should be studied in adults before children.

To ensure that deferral would not unnecessarily delay the submission of pediatric use information, FDA has tentatively concluded that a request for deferred submission should include a description of the planned or ongoing pediatric studies, and evidence that the studies were being or would be conducted: (1) With due diligence, and (2) at the earliest possible time. To permit FDA to monitor the conduct of postapproval studies to ensure that they were carried out with due diligence, FDA is proposing to amend § 314.81(b)(ii) of the postmarketing reports requirements to require applicants to include in their annual reports whether they have been required to conduct postmarket pediatric studies and, if so, to report the status of those studies. (Additional postmarketing reporting requirements are described under "Remedies," in section V.G of this document.) FDA seeks comment on the types of evidence FDA should examine to ensure that deferred studies are carried out in a timely fashion.

4. Sections 314.50(g)(3) and 601.27(c)--Waivers

FDA does not intend to require pediatric assessments unless the product represents a meaningful therapeutic benefit over existing treatments or is expected to be widely used in pediatric patients. FDA also does not intend to require pediatric assessments in other situations where the study(ies) necessary to carry out the assessment are impossible or highly impractical or would pose undue risks to pediatric patients. Thus,

§§ 314.50(g)(3) and 601.27(c) would require FDA to grant a waiver of the pediatric study requirement on its own initiative or at the request of the applicant if: (1) The product (a) did not represent a meaningful therapeutic benefit over existing treatments, and (b) was not likely to be used in a substantial number of pediatric patients as a whole, or was not likely to be used in a substantial number of one or more pediatric subpopulations, (2) necessary studies were impossible or highly impractical, because, for example, the number of such patients was so small or geographically dispersed, or (3) there were evidence strongly suggesting that the product would be ineffective or unsafe in some or all pediatric populations. If a waiver were granted because there was evidence that the product would be ineffective or unsafe in pediatric patients, this information would be included in the product's labeling.

An applicant could request a full waiver of all pediatric studies if one or more of the grounds for waiver applied to the pediatric population as a whole. A partial waiver permitting the applicant to avoid studies in particular pediatric age groups could be requested if one or more of the grounds for waiver applied to one or more pediatric age groups. In addition to the other grounds for waiver, the proposed rule would authorize FDA to grant a partial waiver for those age groups for which a pediatric formulation was required (see "Pediatric Formulations," in section V.E of this document), if reasonable attempts to produce a pediatric formulation had failed.

The proposed rule would require the applicant to include in the request for a waiver an adequate justification for not providing pediatric use information for one or more pediatric populations. For example, the waiver request could demonstrate that the product was indicated for a disease that does not occur in a substantial number of pediatric patients (e.g., drugs for breast or prostate cancer). The waiver request could demonstrate that the product was a member of a drug class known to be unsafe in specific pediatric age groups (e.g., chloramphenicol, an antibiotic, which has caused serious adverse events in neonates. Also, it is widely known that, except for serious or life threatening diseases where alternative therapy is needed, quinolones, anti-malarial agents, are not recommended in young children due to concerns about cartilage and bone development). Animal toxicity data or imautere metabolic pathways for newborns are examples of data that may be used to demonstrate that the product was a member of a drug class known to be unsafe in specific pediatric age groups. FDA would grant the waiver request if the agency found that there was a reasonable basis on which to conclude that any of the grounds for a waiver had been met. A full waiver would be appropriate where, for example, the product did not represent a meaningful therapeutic advance and was not likely to be used in a substantial proportion of any pediatric age group. A partial waiver would be appropriate where, for example, the product was likely to be used in substantial numbers in some pediatric age groups but not others,

where the product was likely to be unsafe or ineffective in some age groups, or where reasonable efforts to develop a pediatric formulation necessary for some age groups had failed. If a waiver were granted on the ground that it was not possible to develop a pediatric formulation, the waiver would cover only those pediatric age groups requiring a pediatric formulation.

The agency solicits comments on the proposed grounds for waiving the pediatric study requirement and whether additional grounds may exist. Such as whether cost should justify waiver of the pediatric study requirement. Additionally, FDA seeks comment on defining the term "meaningful therapeutic benefit". Comment is also requested on, what should be considered a "substantial number" of pediatric patients, i.e., how the agency should establish a level of expected use in pediatric patients below which pediatric labeling would not be required for a drug that did not represent a meaningful therapeutic advance. FDA is considering two possible methods. The first method would focus on the number of times the drug was expected to be used in pediatric patients, annually. Under this method, FDA has tentatively concluded that 100,000 or more prescriptions or uses per year in all pediatric age groups would be considered a substantial number. Products that might require studies under this test include anesthetics, anticonvulsants, asthma drugs, antidepressants, antimicrobials and antivirals, vaccines, and drugs to treat certain skin conditions. FDA has also tentatively concluded that a partial waiver for a particular pediatric age

group would be available under this method if the product were expected to be prescribed or used fewer than 15,000 times per year in that age group.

The second possible method for establishing the level of expected use would focus on the number of pediatric patients affected by the disease or condition for which the product is intended. Physician mention data from the IMS National Disease and Therapeutic Index[1], shows pediatric use of certain products generally falling within two ranges (i.e., those products either exceeding 100,000 physician mentions for pediatric use per year or those falling below 15,000 physician mentions for pediatric use per year. Thus, under this method, FDA has tentatively concluded that 100,000 pediatric patients affected by the disease or condition for which a product was indicated would be considered a "substantial number" of pediatric patients. A partial waiver for a particular pediatric age group would be available under this method if fewer that 15,000 patients in that age group were affected by the disease or condition. FDA seeks

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[1]IMS, National Disease and Therapeutic Index, IMS America; Plymouth Meeting, PA.

physician mention data from the IMS National Disease and Therapeutic Index.[2] All priority NME's were assumed to be therapeutically important, and assigned to the first category, unless the drug's pediatric page specifically noted a low potential for pediatric use or the IMS data indicated no pediatric use. For nonpriority NME's, FDA assumed that wide

[2] IMS, National Disease and Therapeutic Index, IMS America; Plymouth Meeting, PA. FDA's analysis does not include data from 1996 because the IMS data are not yet available.

pediatric use would have been expected for only those products that exceeded 100,000 physician mentions for pediatric use during 1995. Assessments of therapeutic importance for biologicals were developed retrospectively by CBER.

As shown, 60 of the 142 approvals (42 percent) over this 5-year period fell into the first two categories; that is, 47 drugs were classified as therapeutically important with at least some potential pediatric use and 13 less therapeutically important drugs were designated as offering a potential for wide pediatric use based on physician mentions. The 82 drugs (58 percent) grouped under the third category would presumably not have met the therapeutic importance and pediatric use criteria of the proposed rule.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 200, 312, 314, and 601

[Docket No. 97N-0165]

RIN 0910-AB20

Regulations Requiring Manufacturers to Assess the Safety and Effectiveness of New Drugs and Biological Products in Pediatric Patients

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing new regulations requiring pediatric studies of certain new drug and biological products. Many new drugs and biological products represent treatments that are, at least at times, the best available treatment for children, but most of them have not been adequately tested in the pediatric subpopulation. As a result, product labeling frequently fails to provide directions for safe and effective use in pediatric patients. The proposed rule would attempt to partially address this lack of pediatric use information by requiring that manufacturers of a limited class of new drugs and new biological products provide sufficient data and information to support directions for pediatric use for the claimed indications, before or soon after approval. Manufacturers of a limited class of marketed drugs and biologics would also in compelling circumstances have to provide such data. This proposed rule is part of a comprehensive effort to increase the number of new drugs and biological products with clinically

significant use in children that carry adequate labeling for use in that subpopulation.

DATES: Written comments and recommendations by (insert date 90 days after date of publication in the FEDERAL REGISTER). Written comments on the information collection provisions should be submitted by (insert date 30 days after date of publication in the FEDERAL REGISTER). For further information of the agency's implementation plan, see section VII of this document.

ADDRESSES: Submit written comments and recommendations to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857. Submit written comments on the information collection provision to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725 17th St. NW., rm. 10235, Washington, DC 20503, Attn: Desk Officer for FDA.

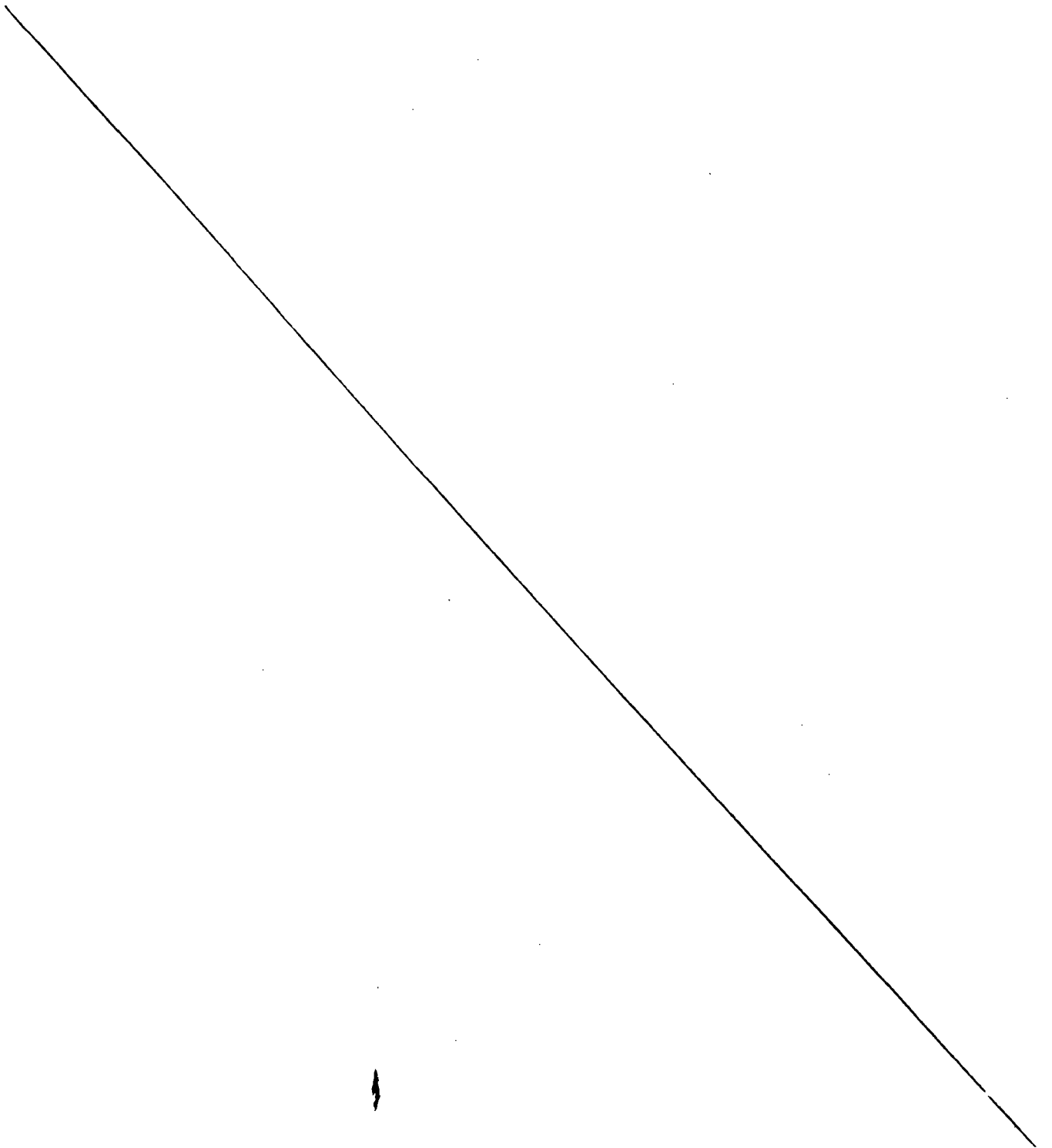
FOR FURTHER INFORMATION CONTACT:

Paula Botstein,
Center for Drug Evaluation and Research (HFD-103),
Food and Drug Administration,
5600 Fishers Lane,
Rockville, MD 20857,
301-827-3144, and
Ann M. Witt,
Office of Policy (HF-22),
Food and Drug Administration,
5600 Fishers Lane,
Rockville, MD 20857,
301-827-5321.

SUPPLEMENTARY INFORMATION:

I. Introduction

Children are subject to many of the same diseases as adults, and are, by necessity, often treated with the same drugs and



biological products as adults. According to the American Academy of Pediatrics, however, only a small fraction of all drugs and biological products marketed in the United States have had clinical trials performed in pediatric patients and a majority of marketed drugs are not labeled for use in pediatric patients or for use in specific pediatric age groups (Ref. 1). A recent FDA survey similarly concluded that most products that are indicated for diseases occurring in both adults and children have very little information about pediatric use in their labeling (Ref. 2). For some products, including vaccines and antibiotics, pediatric use information is generally adequate. Many drugs used in the treatment of both common childhood illnesses and more serious conditions, however, carry little information about use in pediatric patients. Less than half the drugs approved for treatment of human immunodeficiency virus (HIV) infection or accompanying opportunistic infections carry any pediatric safety or effectiveness information, and, of those that do, the data are often incomplete and limited to certain pediatric age groups. Pediatric labeling is also inadequate for such drug classes as steroids, drugs to treat gastrointestinal problems, prescription pain medications, antihypertensives, antidepressants, antirheumatic drugs, and drugs to treat ulcerative colitis.

Safety and effectiveness information for some pediatric age groups is particularly sparse. For example, there is almost no information on use in patients under 2 years of age for most drug classes (Ref. 2).

Many of the drugs and biological products most widely used in pediatric patients carry disclaimers stating that safety and effectiveness in pediatric patients have not been established (Refs. 2 and 3). Based on 1994 data from IMS America, Ltd., a research firm that provides data on prescription drug usage, FDA compiled a list of the 10 drugs that were most widely prescribed for pediatric patients, on an outpatient basis, despite inadequate pediatric labeling. In each case, the label lacked any use information for the age group prescribed to, or the information was inadequate. The drugs were: Albuterol inhalation solution for nebulization for treatment of asthma (prescribed 1,626,000 times to pediatric patients under 12); Phenergan for treatment of allergic reactions (prescribed 663,000 times to pediatric patients under 2); ampicillin injections for treatment of infection (prescribed 639,000 times to pediatric patients under 12); Auralgan otic solution for treatment of ear pain (prescribed 600,000 times to pediatric patients under 16); Lotrisone cream for treatment of topical infections (prescribed 325,000 times to pediatric patients under 12); Prozac for treatment of depression and obsessive compulsive disorder (prescribed 349,000 times to pediatric patients under 16, including 3,000 times to infants under 1); Intal for treatment of asthma (solution prescribed 109,000 to pediatric patients under 2; aerosol prescribed 399,000 times to pediatric patients under 5); Zoloft for treatment of depression (prescribed 248,000 to pediatric patients under 16); Ritalin for treatment of attention

deficit disorders and narcolepsy (prescribed 226,000 times to pediatric patients under 6); Alupent for treatment of asthma (184,000 times to pediatric patients under 6). These 10 drugs were thus prescribed over 5 million times in 1 year for pediatric patients in age groups for which the label carried a disclaimer or lacked adequate use information (Ref. 2).

The absence of pediatric labeling information may sometimes require the physician caring for children to choose between prescribing drugs without well-founded dosing and safety information or utilizing other, potentially less effective, therapy.

Inadequate pediatric labeling thus exposes children to the risk of unexpected adverse reactions or lack of optimal treatment. Even after a drug has been used in pediatric patients for some time, and there has been substantial clinical experience with the drug, directions for safe and effective use in pediatric patients are not provided on the label.

Children were once viewed as a population entirely distinct from adults, in whom safety and effectiveness of new drugs had to be established entirely independently. It has become increasingly clear, however, that children may be considered a demographic subpopulation with many similarities to the adult population. In most cases, drugs and biological products behave similarly in demographic subgroups, including age and gender subgroups, even though there may be variations because of differences in, for example, pharmacokinetics. As FDA has

already stated in a FEDERAL REGISTER document, where the disease and the drug's effects are similar in adults and children, adequate and well-controlled trials may not be needed in children to establish pediatric use information (59 FR 64240, December 13, 1994) (hereinafter referred to as the 1994 rule).

Although use of a drug in children is no longer considered a new indication (with the exception of specific "pediatric indications"), the development of additional information in pediatric patients is needed to provide appropriate dosing recommendations. Correct pediatric dosing cannot necessarily be extrapolated from adult dosing information using an equivalence based either on weight milligrams per kilogram (mg/kg) or body surface area (mg/square meter (m^2)). Potentially significant differences in pharmacokinetics may alter a drug's effect in pediatric patients. The effects of growth and maturation of various organs, maturation of the immune system, alterations in metabolism throughout infancy and childhood, changes in body proportions, and other developmental changes may result in significant differences in the doses needed by pediatric patients and adults. For example, studies have shown that fentanyl, a potent opioid, widely used in anesthetic management of infants and small children but not labeled for use in pediatric patients under 2 years of age, demonstrates differences in clearance between the neonatal period and 2 or more months of age due to improving hepatic blood flow and hepatic microsomal maturation (Ref. 4). Comparable doses in adults and neonates (calculated on

a microgram (μg)/kg basis) produce twofold to threefold higher plasma concentrations in neonates (Ref. 5). Pharmacokinetic differences of this kind demonstrate the importance of studying the pharmacokinetics of a drug in pediatric patients of different ages before they are widely exposed to it. Inadequate dosing information may expose pediatric patients to dangerously high doses or to ineffective treatment. The absence of pediatric testing may thus result in less than optimal treatment for many pediatric patients.

Pediatric patients receiving inadequately tested and labeled drugs are also exposed to the risk of unexpected adverse reactions. One of the earliest cases in which serious adverse events were observed in neonates following administration of a drug that had not been adequately studied in pediatric patients was the development of "gray baby syndrome" from chloramphenicol, an antibiotic (Ref. 6). After an initial report of 5 deaths and a subsequent report of 18 deaths in neonates, it was learned that the immature livers of these infants were unable to clear chloramphenicol from the body, allowing toxic doses of the drug to accumulate. Other cases in which inadequately studied drugs have resulted in serious adverse effects in pediatric patients include teeth staining from tetracycline, kernicterus from sulfa drugs, withdrawal symptoms following prolonged administration of fentanyl in infants and small children, seizures and cardiac arrest caused by bupivacaine toxicity, development of colonic strictures in pediatric cystic fibrosis patients after exposure

to high-dose pancreatic enzymes, and hazardous interactions between erythromycin and midazolam (Refs. 7, 8, 9, 10, 11, 12, 13, 14, 15, and 16). Many such adverse reactions could be avoided if pediatric studies were conducted before drugs were widely used in pediatric patients.

Failure to conduct pediatric testing may, in unusual cases, deprive pediatric patients of significant therapeutic advances. Failure to develop a pediatric formulation of a drug, where younger pediatric populations cannot take the adult formulation, may also deny pediatric patients access to important therapeutic advances, or require pediatric patients to take the drug in homemade, poorly bioavailable formulations.

II. FDA Initiatives to Improve Pediatric Use Information

FDA has taken a number of steps in recent years to address inadequate pediatric drug testing and inadequate pediatric use information in drug labeling. Perhaps the most significant step was the issuance of the 1994 rule requiring drug manufacturers to survey existing data and determine whether those data are sufficient to support additional pediatric use information in the drug's labeling (59 FR 64240). Under the 1994 rule, if a manufacturer determines that existing data permit modification of the label's pediatric use information, the manufacturer must submit a supplemental new drug application (NDA) to FDA seeking approval of the labeling change. The rule explicitly recognizes that controlled clinical studies to support pediatric use information need not have been carried out in pediatric patients

where the course of the disease and the effects of the drug are sufficiently similar in children and adults to permit extrapolation from the adult effectiveness data to pediatric patients. In these cases, controlled clinical studies in adults together with pharmacokinetic and adverse reaction data in pediatric patients may be sufficient to establish pediatric safety and effectiveness.

Although the preamble to the 1994 rule recognizes FDA's authority to require drug manufacturers to conduct pediatric studies on a case-by-case basis, the rule does not impose a general requirement that manufacturers carry out studies if existing information is not sufficient to support pediatric use information. Instead, where there is insufficient information to support a pediatric indication or pediatric use statement, the rule requires the manufacturer to include in the drug's labeling the statement: "Safety and effectiveness in pediatric patients have not been established." Because the rule focuses on gathering existing information about pediatric use, rather than carrying out new studies, supplements filed in response to the rule will be for marketed drugs. The rule does not apply to products first entering the marketplace, except to the extent that pediatric studies conducted on such products before approval can take advantage of the rule's explicit authorization to rely on pharmacokinetic data rather than adequate and well-controlled studies in pediatric patients, and that labeling statements about pediatric use must conform to the rule's labeling requirements.

FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation (CBER) and Research have implemented a "Pediatric Plan" designed to focus attention on and encourage voluntary development of pediatric data both during the drug development process and after marketing. At specified points during the investigation of a new drug or biological product, FDA staff discuss with the sponsor the data needed to support pediatric labeling and encourage them to conduct needed studies. CDER and CBER have also begun to implement a program in which, after review of an NDA, biologics license application (BLA), or supplemental application, the FDA reviewer fills out a "pediatric page." The pediatric page does not itself impose any requirements, but describes the adequacy of product labeling for pediatric patients and plans for further pediatric studies. If pediatric labeling is found to be inadequate, the pediatric page states whether additional pediatric studies are needed. If pediatric studies are needed, the pediatric page states whether the applicant has agreed to conduct the necessary studies and, if necessary, to develop a pediatric formulation. FDA is also developing a draft guidance document on pediatric pharmacokinetics.

In addition, FDA has taken steps to improve pediatric use information for marketed drugs under the pediatric plan. CDER has identified the 10 drugs most used in pediatric populations for which there is no pediatric use information or for which the pediatric use information is inadequate given the pattern of use

in pediatric patients. The manufacturers of these drugs have been notified of the widespread use of their drugs in the pediatric population and asked to respond to the 1994 rule. CBER is currently identifying the biological products most frequently used in pediatric patients without labeling information. FDA has developed guidance to manufacturers on the content and format for pediatric use supplements under the 1994 rule and is tracking pediatric use supplements and commitments.

III. Results of Actions to Date and Need for Additional Steps

Although the actions taken by FDA to date have produced some gains in pediatric labeling, they have not yet substantially increased the number of drugs and biological products for which there is adequate pediatric use information. The percentage of new products entering the marketplace that contain adequate pediatric safety and effectiveness information has not shown consistent improvement in the last decade. An informal survey conducted by the American Academy of Pediatrics in 1990 found that of all new molecular entities (NME's) approved between 1984 and 1990, 20 percent had information on pediatric use. Not all NME's have usefulness in pediatric patients, however. For example, for NME's approved in the years 1991-1996, 53 percent were regarded by FDA as having potential usefulness in pediatric patients. Presumably, if only the NME's with usefulness in pediatric patients had been considered in the survey, the percentage with pediatric labeling would have been somewhat higher, and as high as 42 percent.

FDA compared the number of NME's approved in 1991 and 1996 with potential usefulness in pediatric patients and looked at the adequacy of pediatric labeling for those drugs. Fifty-six percent (9/16) of the NME's approved in 1991 with potential usefulness in pediatric patients had some pediatric labeling at the time of approval. In 1996, only 37 percent (15/40) of the NME's with potential usefulness in pediatric patients had some pediatric labeling at the time of approval. (For both 1991 and 1996, those drugs counted as having pediatric labeling may not have been labeled for all age groups in which the drug was useful.) The manufacturers of an additional 17 drugs promised to conduct pediatric studies after approval. It is uncertain how many of these promises will result in pediatric labeling. Of the seven NME's approved in 1991 for which postapproval pediatric studies were promised, only one now has pediatric labeling.

These data indicate that voluntary efforts have, thus far, not substantially increased the number of products entering the marketplace with adequate pediatric labeling. Therefore, FDA has tentatively concluded that additional steps are necessary to ensure the safety and effectiveness of drug and biological products for pediatric patients. This proposed rule includes provisions that would require the manufacturers of certain new and marketed drugs and biological products to evaluate the safety and effectiveness of their products in pediatric patients, where existing information is not sufficient to support pediatric use labeling but the product is likely to be commonly used in

pediatric patients, the product is a new drug or biological product which would provide a meaningful therapeutic benefit to pediatric patients over existing treatments, or the product is a marketed drug or biological product which is indicated for a very significant or life threatening illness.

Although this proposal would address the lack of pediatric labeling through the imposition of regulatory requirements, the agency solicits comment on whether there are alternative ways to assure that manufacturers reliably conduct pre- or postapproval studies in pediatric patients.

At the same time as it is issuing this proposed rule, FDA has initiated other actions that it hopes will encourage the development of adequate pediatric use information. FDA plans to develop guidance on clinical trial designs for assessing pediatric safety and effectiveness. The agency has also discussed with the pharmaceutical industry a policy on user fees for pediatric studies designed to encourage the submission of these studies. Such a policy could be implemented through legislation at the time of reauthorization of the Prescription Drug User Fee Act of 1992. FDA has proposed that user fees be waived for supplements to add pediatric use labeling, unless the supplements contain adequate and well-controlled clinical trials. Thus, supplements that rely on pharmacokinetic data to extrapolate from existing adult studies would not be subject to user fees. FDA might also be prepared to waive the user fee for

IND annual report, the "end of phase 2" meeting, and the pre-NDA meeting are codified in part 312, FDA's regulations governing IND's.

FDA has already proposed to amend the IND annual report requirement to include discussion of pediatric studies (60 FR 46794, September 8, 1995). FDA is proposing to amend the remaining regulations to specify that these meetings and reports should include discussion of the assessment of pediatric safety and effectiveness. To assist manufacturers in planning for studies that may be required under this proposed rule, FDA is also proposing to inform manufacturers at the "end of phase 2" meeting of the agency's best judgment, at that time, of the pediatric studies that will be required for the product and when the studies should be submitted.

In addition to the discussions of pediatric testing codified in this proposed rule, FDA will also assist manufacturers by providing early consultations on chemistry and formulation issues raised by requirements under this rule.

2. Sections 314.50(g)(1) and 601.27--Required Studies

Under proposed §§ 314.50(g) and 601.27(a), an original application for a drug classified as a new chemical entity or an application for a new biological product would be required to contain data adequate to assess the safety and effectiveness of the drug product for all pediatric age groups for the claimed indications, unless FDA granted a deferral or full or partial waiver of the requirement. Assessments required under this

section for a product that represented a meaningful therapeutic benefit over existing treatments would have to be carried out using appropriate formulations for the age group(s) for which the assessment is required (see "Pediatric Formulations," in section V.E of this document), unless reasonable efforts to produce a pediatric formulation had failed (see "Waivers," in section V.B.4 of this document).

The proposed rule does not mandate particular types of studies. The sponsor should consult with FDA on the types of data that will be considered adequate to assess pediatric safety and effectiveness. As described in the 1994 final rule, gathering adequate data to establish pediatric safety and effectiveness may not require controlled clinical trials in pediatric patients. Where the course of the disease and the product's effects are similar in adults and children, FDA may conclude that pediatric safety and effectiveness can be based on adult effectiveness data together with pharmacokinetic and safety data in pediatric patients. The proposed rule also does not necessarily require separate studies in pediatric patients. In appropriate cases, adequate data may be gathered by including pediatric patients as well as adults in the original studies conducted on the product.

3. Sections 314.50(g)(2), 314.81(b)(2)(vii), and 601.27(b)--Deferred Submission and Postmarketing Reports

In some cases, pediatric testing should not begin until certain safety and/or effectiveness information in adults has

not require a manufacturer to study its product for unapproved ("off-label") indications, even if the product were widely used in pediatric patients for those indications. Although the proposed rule would not apply to unapproved pediatric indications, nothing in the rule would diminish the physician's power to prescribe drugs and biological products for such unapproved indications.

B. Not-Yet-Marketed Drug and Biological Products

1. Sections 312.23(a)(3)(v), 312.33(a)(8), and 312.47(b)(1)(i) and (b)(2) (21 CFR 312.23(a)(3)(v), 312.33(a)(8), and 312.47(b)(1)(i) and (b)(2))--Early Discussion of Plans for Pediatric Studies

In the development of a new drug or biological product, decisions about appropriate populations to study and the design of such studies must often be made well before the submission of an NDA or BLA. FDA has identified several critical points in the drug development process, before submission of an NDA or BLA, during which the sponsor and FDA should focus on the sponsor's plans to assess pediatric safety and effectiveness. These time points include: Any pre-investigational new drug application (IND) meeting or "end of phase 1" meeting for a drug designated under subpart E of part 312 (21 CFR part 312), the IND submission, the IND annual report, any "end of phase 2" meeting, the presentation of the IND to an FDA drug advisory committee, and any pre-NDA or pre-BLA meeting. Of these, the pre-IND meeting, the "end of phase 1" meeting, the IND submission, the

Prescription Drugs and Children

Clinton Announces Action to Force New Studies, Different Labeling

By Peter Baker
Washington Post Staff Writer

More than a half-century after requiring that new medications be proven safe and effective for adults, the federal government for the first time plans to force drug manufacturers to conduct separate studies on how their products will affect children.

Under new rules announced by President Clinton at the White House yesterday, pharmaceutical companies beginning next year would be obligated to test the safety of their prescription drugs for children, determine the proper dosages and then label them accordingly.

"The executive action that I take today simply is designed to ensure that parents and pediatricians have the safety information they need," Clinton said. Without such tests, he said, "the pediatricians' other alternative is to guess—with potentially grave consequences."

Currently just 20 percent of drugs marketed in the United States are labeled for use by children, often forcing pediatricians to make judgments about prescribing medications based on incomplete information or to simply refrain rather than risk causing more harm than good. The decisions on how much and how often to give drugs to infants, toddlers and adolescents are far more complicated than simply cutting adult dosages in half, according to physicians.

Each year, more than 5 million children under age 6 are given commonly used drugs such as Prozac, Ritalin and others that treat asthma, allergies and ear infections even though they have not been adequately tested, according to the administration. About half of the drugs used to treat adults with the AIDS virus have not been tested for children.

"Children are not little adults," said Joseph R. Zanga, vice president of the American Academy of Pediatrics. "At every age and stage of their development, they respond to things, drugs included, in different ways than adults."

In having Clinton announce the rule rather than the Food and Drug Administration, the White House continued its strategy of promoting relatively modest initiatives that, while important in the everyday lives of some Americans, traditionally have not merited presidential attention.

It also fit into the Clinton approach to restructuring the health care system one piece at a time, a strategy adopted after the failure of the comprehensive overhaul crafted by first lady Hillary Rodham Clinton, who was on hand for yesterday's event. The most recent and prominent example of that was the $24 billion expansion of health coverage for indigent children included in the balanced budget plan signed into law by Clinton last week.

Joined by Vice President Gore and Health and Human Services Secretary Donna E. Shalala, the Clintons unveiled the pediatric drug rule at a White House ceremony that featured Regan Ralph, a Washington lawyer whose son was treated for asthma with drugs not labeled specifically for children.

> *"I consider it a national scandal that 80 percent of the drugs have not been fully tested for kids."*
>
> —Sen. Mike DeWine (R-Ohio)

Her son, 21-month-old Sam Hanoura, stole the show by wandering around stage and ultimately plopping down in the chair between the president and first lady. "Drugs can be good, but it's scary not knowing exactly what's going to happen," his mother said afterward.

The same sentiment prompted Sens. Mike DeWine (R-Ohio) and Christopher J. Dodd (D-Conn.) to introduce legislation last spring providing incentives to drug makers to conduct pediatric tests. "I consider it a national scandal that 80 percent of the drugs have not been fully tested for kids," DeWine said in a telephone interview.

Clinton aides said they decided to impose the regulation after a voluntary system launched in 1994 failed to win much industry cooperation. "We have not had good success in increasing the number of new drugs that are tested in kids," said FDA Deputy Commissioner William B. Schultz. The estimated $20 million cost to industry, he said, would be "relatively modest" out of hundreds of millions of dollars already spent on drug development.

The proposed regulation would take effect in six months and focus first on 10 commonly used drugs already on the market.

Industry leaders yesterday said they shared Clinton's goal, but disputed the notion that they have not made progress on their own. Alan F. Holmer, president of the Pharmaceutical Research Manufacturers of America, said the "vast majority" of the 10 drugs singled cited have been approved for children's labels or have been tested and have label revisions pending.

"We question whether a government mandate is needed because of all the progress that has been made and is being made," Holmer said, "but we pledge to work with the president on a collaborative and constructive basis."

Staff writer John Schwartz contributed to this report.

The Washington Post
THURSDAY, AUGUST 14, 1997

BC-CLINTON-DRUGS

Clinton seeks pediatric testing for new drugs

By Laurence McQuillan

WASHINGTON (Reuter) - President Clinton Wednesday proposed regulations that would force drug companies to conduct pediatric studies and recommend child dosage for new prescription medicines likely to be given to children.

Under the presidential plan, the Food and Drug Administration will propose a new regulation that would require drug-makers to conduct studies to determine the correct dosage amounts of medications used by youngsters.

Currently physicians frequently are forced to estimate the proper dosage of medications for children, including antibiotics and asthma drugs, because drug companies routinely do not determine a recommended dosage.

``The rule I announce today will put an end to this guesswork,'' Clinton said at a White House ceremony attended by first lady Hillary Rodham Clinton, Vice President Al Gore and Health and Human Services Secretary Donna Shalala.

``It will require all manufacturers of medicines needed by children to study the drug's effects on children,'' he said. ''The results will then be displayed on drug labels to help pediatricians and other health care professionals make good decisions about how to treat their young patients.''

Clinton was introduced by Regan Ralph, whose 21-month-old son, Sam, had his first asthma attack when he was four months old. The youngster roved around the stage as his mother spoke, and was finally entertained by Clinton and Mrs. Clinton as the crowd laughed.

According to the American Academy of Pediatrics, 80 percent of all drugs sold in the United States have not been labeled for use by infants, children and adolescents. Of the medications widely used by young people, only 42 percent of them have been tested on children.

The pharmaceutical industry reacted cautiously to the announcement, which if implemented is expected to cost it between $13 million and $21 million a year in testing.

Alan Holmer, president of the Pharmaceutical Research and Manufacturers of America, said the idea of providing ``better medicine for children'' was ``a goal we all share.''

``In view of all the ongoing testing and studying of medicines in children, we question whether a government mandate is needed,'' Holmer said.

White House officials, however, countered that one of the reasons Clinton took his action was that the percentage of drug tests involving children declined by one-third between 1991 and 1996.

``The drug industry has indicated ... that they look forward to working with us on a collaborative effort,'' said Chris Jennings, a White House official who coordinates health policy.

``I think that they are not overly thrilled about the concept of it being required or mandated,'' he said, but added that he did not believe the industry would try to block the administration's effort.

Although the proposed regulation is aimed primarily at new drugs, the testing requirement also would apply to medicine now on the market if there is a ``compelling need for more information'' involving health safety.

Once the FDA formally issues the language of the proposed regulation, various experts from the industry and health care experts will have 90 days to offer comments.

The agency will then review the comments and issue its final regulation, most likely next year.

REUTER

**** filed by:RB--(--) on 08/13/97 at 15:50EDT ****
**** printed by:WHPR(SCOH) on 08/14/97 at 13:24EDT ****

PM-Children-Drugs, 3rd Ld-Writethru, a0564,650
Drugs would be labeled if safe for children
Eds: LEADS with 8 grafs with Clinton order; picks up 4th graf, About 80
By LAURAN NEERGAARD= Associated Press Writer=

WASHINGTON (AP) President Clinton today ordered the nation's drug-makers to test whether the medicines they sell to adults are safe and effective for children and to put the dosages on the label.

At a White House ceremony, Clinton proposed to the Food and Drug Administration a set of rules that would require manufacturers to promptly provide relevant information for children on the labels of new drugs.

He said it is unacceptable that so many medicines that prove useful for sick children have not been approved for them, and that pediatricians often are left to estimate appropriate dosages for children, ``with potentially grave consequences.''

``The rule I announce today will put an end to this guesswork,'' Clinton said.

First lady Hillary Rodham Clinton, a longtime advocate for children, recalled the struggles of the late AIDS activist Elizabeth Glaser to obtain AIDS medication for her daughter, Ariel.

``Elizabeth's struggle ... made clear a heartbreaking problem,'' Mrs. Clinton said. Now, she said, ``No child or parent would have to endure this kind of agonizing uncertainty.''

Donna Shalala, the secretary of Health and Human Services, said Clinton's actions today ``place our most exciting scientific discoveries within the grasp of every American child.''

About 80 percent of the nation's prescription drugs are not labeled for children's use because they never were tested in children. Desperate pediatricians often must guess a safe dose when they have to use adult drugs such as asthma or AIDS medications on their smallest patients.

The drug industry has largely ignored previous efforts by the Food and Drug Administration, dating back to 1994, designed to spur more children's prescription information.

Manufacturers now are testing 146 drugs specifically for children, many of which have been sold for adults for years.

``In view of all the ongoing testing and studying of medicines in children, we question whether a government mandate is needed,'' said Alan Holmer of the Pharmaceutical Industry Manufacturers Association. But he pledged to work with the FDA ``to advance the goal of better medicine for children.''

Under the proposed rules, when a company seeks FDA permission to test an experimental drug in adults, the agency would decide whether it has potential for children, said officials who spoke on condition of anonymity. If so, the company would be ordered to provide a plan for determining the safe child dose.

The FDA would not delay approving a drug for adults, stressed one administration official. Pediatric labeling could be added soon after sales to adults begin, as long as the move is timely, the official said.

The proposed rules do not require massive, expensive clinical trials in children. Instead, a drug that previous studies indicated would be safe in adults would be tested solely to determine the proper dose for children.

Companies would be expected to take from three to six months to discover the dose that delivers a therapeutic level of the medicine into a child's bloodstream.

``People assume any drug that is prescribed for their children has been tested, and that's not the case,'' said Susan DeLaurentis of the Pediatric AIDS Foundation. ``This will now be a requirement.''

The proposed rules also would require existing adult drugs that are widely prescribed for children such as bronchodilators for asthma patients or the antidepressant Prozac to have the pediatric dose added to the label. But a deadline on that was not immediately set.

Of 183 drugs approved in the last five years, only 44 were quickly labeled to include child prescription information. The FDA targeted 64 more drugs that offered promise for children, but only two ultimately were labeled for children, the AIDS foundation said.

**** filed by:APE-(--) on 08/13/97 at 15:06EDT ****
**** printed by:WHPR(SCOH) on 08/14/97 at 13:14EDT ****

THE SECRETARY OF HEALTH AND HUMAN SERVICES
WASHINGTON, D.C. 20201

JUN 11 1997

The Honorable James M. Jeffords
Chairman, Committee on Labor
and Human Resources
United States Senate
Washington, D.C. 20510

Dear Senator Jeffords:

For the past several months the Administration has been working with the Senate Labor and Human Resources Committee on legislation to improve the performance and accountability of the Food and Drug Administration (FDA or the Agency), while preserving and enhancing the Agency's ability to protect and promote the public health. I appreciate the efforts that you, Senator Kennedy, and the other members of the Committee have made in this regard and believe that considerable progress has been made toward these goals.

The Food and Drug Administration Modernization and Accountability Act of 1997, S. 830, includes approximately 20 provisions that represent significant consensus reforms. Among the provisions that we all agree on are those that set forth the Agency's mission, codify reforms to the regulation of biotechnology products, provide expedited authority for the adoption of third party performance standards for device review and for the classification of devices, and streamline submission requirements for manufacturing changes and marketing applications for drugs and biologics.

I must emphasize that these provisions represent very significant reform, on which all parties have worked hard to reach consensus, and which I hope will not be jeopardized by insistence on other provisions on which we have not reached agreement.

Unfortunately, the Chairman's substitute to S. 830, also includes a number of provisions which as drafted do not reflect consensus and about which I have very significant concerns. Also, the current version is not "balanced" in that it does not take advantage of significant opportunities to strengthen current law so FDA can more effectively protect the public health. The most significant of the non-consensus provisions, summarized on the enclosed list, would undermine the public health protections that the American people now enjoy, by: 1) lowering the review standard for marketing approval; 2) allowing distribution of experimental therapies without adequate safeguards to assure patient safety or completion of research on efficacy; 3) allowing health claims for foods and economic claims for drugs and biologic products without adequate scientific proof; 4) requiring third party review even for devices that require clinical data; and 5) burdening the Agency with extensive new regulatory requirements that will detract resources from critical Agency functions without commensurate enhancement of the pubic health. Another significant nonconsensus item is the set of adjustment provisions in sections 703 and 704, which together require significant increases in FDA's appropriations levels over FY 1998 through 2002 (almost $100 million above the FY 1998 Budget with

levels rising thereafter). We recognize that the ability of the FDA to commit to specific performance goals under PDUFA depends on the resources it will have available. We would support a user fee proposal that is consistent with our FY 1998 Budget proposal, but we are concerned that the proposal to collect user fees in this legislation imposes additional pressure on the fixed level of discretionary resources agreed to under the Bipartisan Budget Agreement.

We note the inclusion of the provision on pediatric labeling in the most recent version of the Committee mark. We believe it should be revised to assure a more appropriate system for testing drugs for pediatric use before they are prescribed for children.

I want to commend you and members of the Committee on both sides of the aisle on the progress we have made together to develop a package of sensible, consensus reform provisions that are ready for consideration with reauthorization of the Prescription Drug User Fee Act (PDUFA). We are interested and prepared to continue working with the Committee to reach consensus on additional issues -- and have proposed acceptable alternative approaches to many of the objectionable provisions. My concern is the time for reauthorization of PDUFA is running perilously short. As I indicated in my recent letter to you, I am concerned that the inclusion of non-consensus issues in the Committee's bill will result in a protracted and contentious debate. This would not serve our mutual goal of timely reauthorization of PDUFA and passage of constructive, consensus bipartisan FDA reform.

A copy of this letter is also being sent to the ranking Minority member, Senator Kennedy, and the other members of the Senate Labor and Human Resources Committee.

Sincerely,

Donna E. Shalala

Enclosure

S. 830 (Chairman's Substitute)

A. Major Concerns

1. Cumulative Regulatory Burdens/No Provisions to Promote Public Health

- many new regulatory burdens are being imposed on FDA (list enclosed) and little that can be advanced as promoting public health

2. Third Party Review of Devices (Sec. 204)

- expansion of FDA's existing pilot project for review of medical devices (includes devices that require clinical data) by organizations accredited by FDA

3. Approval Standard for Drugs/Biologics/Devices (Secs. 404/409/609/610/611/619)

- effectiveness standard for drugs and biologics needs further clarification; for supplements (applications for new uses) lowers standard such that they might not ever require a single investigation
- limits FDA authority to evaluate clinical outcomes for devices
- lowers approval standard for radiopharmaceuticals, including PET drugs

4. Health Claims For Foods (Sec. 617)

- health claims not approved by the FDA but consisting of information published by authoritative government scientific bodies (e.g., NAS or NCI) would be permitted for use by companies in the labeling of food products, even if it is very preliminary

5. Expanded Access to Investigational Therapies (Sec. 102)

- would allow drug and device companies to sell an investigational product for any serious disease or condition without FDA approval and without appropriate protections for clinical investigations

6. **Device Modifications (Sec. 601)**

- would allow companies to make manufacturing changes that affect a device's safety and effectiveness without FDA agreement

7. **Health Economic Claims (Sec. 612)**

- would allow industry to discuss health economic claims given to managed care organizations under a lower evidentiary standard and without FDA review, even if the claim compared the safety or efficacy of two drugs

8. **Pediatric Labeling**

- would provide an incentive of six months of market exclusivity to encourage pharmaceutical companies to conduct necessary clinical trials for FDA approval of their products for children
- doesn't assure that necessary labeling for children will be included.
- might undercut FDA's ability to use other means such as regulations

B. **Other Significant Concerns**

1. Expanded Humanitarian Use of Devices (Sec. 103)
2. Device Collaborative Determinations/Review (Secs. 301/302)
3. Limitations on Initial Classification Determinations (Sec. 407)
4. Evaluation of Automatic Class III Designation (Sec. 604)
5. PMS (Sec. 606)

C. **Currently In The Bill - No Language Provided Yet**

1. Off-Label Use of Drugs (floor amendment expected)
2. Drug Compounding (amendment expected)

FAX

To: Jennifer Klein

Fax:

From: David Haney

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

Number of Pages Including Cover Page 4

If this amount of pages does not transmit please call.

BE SURE TO MARK YOUR CALENDAR
APC ANNUAL POLICY CONFERENCE
MAY 18-20, 1997 ~ BETHESDA, MD.!!!
Please call our office for more information about the conference!

AIDS Policy Center
For Children, Youth & Families

July 3, 1997

The President
The White House
1600 Pennsylvania Avenue
Washington, DC 20500

Dear Mr. President:

We understand that the administration may consider an additional FY 1998 budget request for the Ryan White CARE Act AIDS Drug Assistance Program. On behalf of our 350 affiliate care projects serving 50,000 infected and affected children, youth, women and families living with HIV/AIDS throughout the United States, we are writing to strongly urge you to support increased funding for Title IV of the Ryan White CARE Act and to consider the funding needs of the AIDS Drug Assistance Program strictly in the context of comprehensive HIV care.

We understand that within the next few weeks, the FY 1998 Labor/HHS appropriation bill will be under final consideration. We are certainly aware of funding cuts necessary to ensure a balanced budget. However, we strongly recommend that the administration consider the urgent needs of children, youth, women and families living with HIV and AIDS who now constitute the fastest growing group of new AIDS cases.

In addition, a balanced approach must be taken by the administration to addressing the comprehensive HIV care needs of persons living with HIV and AIDS served under each title of the Ryan White CARE Act as well as providing access to the new AIDS drugs. As you know, the new AIDS drugs have shown great promise and given hope to thousands of people living with HIV and AIDS when used in the context of comprehensive HIV care.

However, testing the new drugs in children and pregnant women living with HIV and AIDS has been slow and as a result, none of the new therapies are approved for use in pregnant women and only 2 of the new drugs are approved for children under the age of 13. Youth have additional special needs in accessing comprehensive HIV care and drug therapies. Children, youth, women and families living with HIV and AIDS need improved access to primary care and other social services provided through Title IV if they have any hope of accessing the new AIDS drugs and experiencing success with the difficult drug regimen.

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Washington, DC 20006
Tel: (202) 785-3564
Fax: (202) 785-3579
E-mail: APCCYF@aol.com

Thank you for your leadership on HIV and AIDS issues and for your consideration of this request. For further information, we attach a Title IV funding rationale.

Sincerely,

Mildred Williamson
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 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 Latinos.

- $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 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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FAX COVER MEMORANDUM

DATE: _____

NUMBER OF PAGES, INCLUDING THIS SHEET: _____

TO: Jen Ekin

FAX NUMBER: 456-2878

FROM: Tim

COMMENT: Sent to Chris yesterday; when I called him today he said he had a disaster on his hands & could I call you.

With pleasure.

Tim

111 F Street NW Room 340 Washington DC 20001-2095
202-662-9595 Fax # 202-662-9682
fedlegis@law.georgetown.edu

ASAP

To Chris Jennings
From Tim Westmoreland
Re: Suggestions on Draft Document
August 10, 1997

Thank you (and Sarah) for getting me the draft. Overall, I think it is clear, well argued, and to the point.

I have a few, brief comments and suggestions.

1) p. 13, first full paragraph:

The draft solicits comments on "alternative" ways to get this data. Please consider using the word "additional" instead, so as not to suggest that this one can be thrown out but rather to request comments on complementary additional proposals.

2) p. 15, first full paragraph:

Similar comment. Please consider inserting the word "also" between "could" and "further."

3) Unnumbered, but between 23 and 25, first full paragraph.

The second sentence is not a sentence but a sentence fragment. It also is unnecessary here to affirmatively seek comment on whether cost should be a consideration in this requirement. You and I know that the manufacturers are going to raise cost as an issue. FDA does not need to seek this comment. To do so, makes the whole proposal look too tentative.

Moreover, there's already an exception in the proposed reg for "impractical" studies. If anyone dares to say this is too expensive during the ceremony, you can point to that as including any extreme costs.

4) p. 28, last paragraph

Similar comment. FDA should not deliberately seek comment on whether to codify its authority. These comments will fly in from the manufacturers, and this is the wrong tone. Same for the last line about soliciting comments on cost considerations. Too tentative.

5) p. 32, last paragraph and on to top of 33

Similar comment on asking for comments on whether cost should be a justification for a waiver, whether manufacturers should allocate resources to a pediatric formulation, and whether cost could be a factor in delaying the pediatric formulation. Trust me; you'll get these comments without soliciting them and having them solicited makes the reg sound too uncertain about itself.

Finally, I have a general concern about the phrasing of "pediatric use" versus "use by pediatric patients," but I'll try to discuss that with Bill Schultz. It sounds picky, but the manufacturers have continued to argue that children are a "use" and I argue they are a "user." It can make a difference in some of the construction of the statutory authority for FDA. I'll talk to FDA.

Thanks again for this whole effort.

TMW

Fact Sheet
Proposed Regulation on Pediatric Labeling

August 11, 1997

"This is an important time for America's children. They're growing up in a world that is changing rapidly. They need our help more than any generation before them. As Hillary says, children are not rugged individualists; they depend upon us -- their parents and others in the community who love them -- to give them love and guidance and discipline, to provide for them, and to defend them. That's as it should be. Their future and ours depends upon how well we do our job."

-- President Bill Clinton, Radio Address, June 1, 1996

Today, President Bill Clinton announced the Administration's intent to provide physicians with more information on using new drugs in children and, consequently, improve the health care American children receive. The proposed regulation would require pediatric-use data for any medicine which may offer improved treatment for children over existing therapies. The regulation also requires pediatric data on approved therapies that are used commonly in kids but lack labeling guidance for health care providers.

The proposed plan was published today in the Federal Register and includes the following key points:

- Many new drugs and biological products represent treatments that are, at least at times, the best available treatment for children, but many of them have not been adequately tested in pediatric populations. This regulation would require these sorts of new drugs to submit pediatric data prior to approval.

- For drugs that are already marketed, this regulation also would codify FDA's authority to require, in compelling circumstances, that manufacturers conduct studies to support pediatric-use labeling for the approved indications.

- The proposed rule would allow post-approval submission of pediatric data if FDA had safety concerns about testing the drug on children prior to approval.

- Likewise, the requirement could be waived if (1) FDA found that the product was likely to be unsafe or ineffective in pediatric patients; (2) that pediatric studies were impossible or highly impractical; or (3) that reasonable efforts to develop a pediatric formulation had failed.

- Because this rule has just been proposed, the Administration invites written

comments on the proposal from the public and industry, which may be submitted to the Dockets Management Branch, HFA-305, Food and Drug Administration, 12410 Parklawn Drive, Room 1-23, Rockville, MD 20857, until Nov. XX, 1997.

Improving American Children's Health Care

In 1963, Dr. Harry Shirkey coined the phrase "therapeutic orphans" to describe children. Shirkey was alluding to the plight of children for whom many drugs have not been studied. Pharmaceutical firms have had little incentive to study drugs for use in children because the population--and therefore the financial return--is likely to be small. Moreover, testing drugs in children can be more complicated than in adults.

In 1992, the Food and Drug Administration issued a regulation to encourage drug manufacturers to submit pediatric data voluntarily for review. However, many new drugs are still being approved without information on how they should be used in children.

Today's proposal would require data that can then be put on a drug's label to help pediatricians and other health care providers make treatment decisions based on scientific information aimed at their patient population.

When drug labels do not include pediatric information, health care providers are forced to guess at the appropriate dose or forego possibly the best treatment available. Likewise, without pediatric data, these health care providers have no information on potential side effects that might occur specifically in this patient population.

More information on this proposed rule is available at http://www.fda.gov/cder/regguide.htm.

Executive Office of the President
August 11, 1997

Draft Press Release

FDA PROPOSES TO REQUIRE PEDIATRIC DATA
PRIOR TO DRUG AND BIOLOGIC PRODUCT APPROVALS

FDA has proposed a rule to provide physicians with more information on using new drugs in children. Published in today's Federal Register, the proposed rule would require pediatric-use data for any medicine which may offer improved treatment for children over existing therapies.

For drugs that are already marketed, this regulation also would codify FDA's authority to require, in compelling circumstances, that manufacturers conduct studies to support pediatric-use labeling for the approved indications.

Despite FDA efforts in recent years, many prescription drugs commonly prescribed for children have labeling that states the safety and effectiveness in children has not been established. Without adequate information, physicians may be reluctant to prescribe certain drugs for their pediatric patients, or they may prescribe them inappropriately. As a result, children may be exposed to an increased risk of adverse reactions or decreased effectiveness of the drugs, or they may be denied access to valuable therapeutic agents.

Today's proposal would require data that could then be put on a drug's label to help pediatricians and other health care providers make treatment decisions based on scientific information aimed at their patient population.

"Kids deserve the same access to newly developed drugs that their parents get," said Donna E. Shalala, secretary of Health and Human Services. "With this proposal, we will have the power to ensure pediatricians and other health care providers who treat children have the best scientific information available on which to base their medical decisions."

"When drug labels do not include pediatric information, health care providers are forced to play a guessing game and may not properly dose their patients," said Michael A. Friedman, M.D., FDA lead deputy commissioner. "Not only does this mean sick kids sometimes don't get better, but they also have the potential to get worse as a result of unexpected adverse events."

The proposed rule would allow post-approval submission of pediatric data if FDA had safety concerns about testing the drug on children prior to approval.

Likewise, the requirement could be waived if:

- FDA found that the product was likely to be unsafe or ineffective in pediatric patients
- that pediatric studies were impossible or highly impractical
- that reasonable efforts to develop a pediatric formulation had failed.

FDA invites written comments on the proposal from the public and industry, which may be submitted to the Dockets Management Branch, HFA-305, Food and Drug Administration, 12410 Parklawn Drive, Room 1-23, Rockville, MD 20857. The closing date for comments is Date, 1997. All comments received will be reviewed and considered by the agency in developing the final rule.

###

PEDIATRIC LABELING FOR DRUGS

BACKGROUND

Children suffer from most of the same diseases as adults, and by necessity, are treated with many of the same drugs as adults. Manufacturers of drugs are not currently required to study and label their products for use in children, even where they can anticipate that the products will be prescribed for children. Although pediatric studies are conducted for some drug classes and by some manufacturers, the majority of drugs and biological products that pediatricians use have not been tested by their manufacturers in pediatric populations. As a result, product labeling frequently fails to provide directions for safe and effective use in children. The absence of pediatric labeling information poses a serious risk of inappropriate dosing and unexpected adverse effects in children. It also may result in failure to provide children with optimal treatment in cases where physicians are reluctant to prescribe potentially toxic drugs to children before the drugs have undergone pediatric testing.

Despite these risks, pediatricians often have no choice and the use of drugs that have not been adequately labeled is widespread. An FDA survey of drugs prescribed during 1994 identified the ten drugs prescribed most frequently to children without adequate labeling. Together, these ten drugs were prescribed to children more than 5,000,000 times in one year (see Tab 1). The pediatric physician community has therefore urged FDA to take steps to ensure that drug labels provide information on the safe and effective use of the drugs in children.

In recent years, FDA has undertaken several initiatives to encourage the voluntary addition of pediatric use information to drug labels. FDA implemented a "Pediatric Plan" designed to focus attention on, and encourage, voluntary development of pediatric data during drug development. As part of the Plan, FDA staff meets with manufacturers at several stages of drug development and encourages them to conduct pediatric studies of their drugs. FDA has also identified the top ten 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 labels on the basis of substantially less data than required before. The rule also required manufacturers to survey existing data to determine whether there was sufficient information to support pediatric use information on the drug's label.

These voluntary efforts to increase the amount of pediatric use information on labelling have not resulted in significant gains. The response to the 1994 rule has not been encouraging. Moreover, efforts to date have not increased the number of new drugs entering the marketplace with adequate pediatric labeling. As shown in the chart below, a comparison of new molecular entities (NME's) approved in 1991 through 1996 shows no improvement in the percentage approved with adequate pediatric labeling. While approximately 56% of the drugs approved in 1991 with potential use in children had some pediatric labeling, 37% of those approved in 1996 with potential use in children had pediatric labeling. The data also suggest that commitments by manufacturers to conduct pediatric studies after approval frequently do not result in pediatric labeling.

FDA estimates that pediatric studies are needed for approximately 10-15 products per year that would not otherwise have been studied in children. This figure includes an estimated 10-13 new drugs and biological products and two already marketed products.

Status of pediatric labeling/studies for NME's approved in 1991-1996	1991	1992	1993	1994	1995	1996	Total
Total number of NME's approved	30	25	25	22	28	53	183
Those with potential use in children (pediatric studies needed)	16	14	14	15	14	40	113
Label included some pediatric use information or pediatric studies complete at time of approval (as a percent of NME's needing pediatric studies)	9 (56%)	4 (29%)	5[1] (36%)	6[1] (40%)	5 (36%)	15 (37%)	44 (39%)
Post-approval pediatric studies promised or requested	7	10	10[2]	10[2,3]	10[2]	17	64
Pediatric labeling added after approval	1	0	1	0	0	0	2

REGULATORY STRATEGY

The absence of adequate pediatric labeling continues to pose a significant public health issue. New approaches to the problem are needed. Financial incentives may be successful in generating pediatric labeling for some drugs, but there is no assurance that such incentives will work since they would leave it up to the manufacturer's discretion to conduct the studies. In addition, FDA's experience shows that a significant minority of manufacturers conduct needed pediatric testing without financial incentives. Providing exclusive marketing rights to companies that would have conducted pediatric studies without incentives may impose

[1] In one case, pediatric use information provided for one of two approved indications.

[2] In one case, pediatric data requested for second of two approved indications.

[3] In one case, pediatric data requested for additional age groups.

unnecessary costs on prescription drug consumers, and on governmental and third party payers in the form of more expensive drugs.

The adequacy of pediatric labeling can be substantially improved by imposing a limited pediatric study requirement applicable only to the drugs and biological products needed most urgently by children. Pediatric studies would be required for certain innovative new drugs and never-before approved biological products if they (1) provide a meaningful therapeutic advance to children over existing treatments, or (2) are likely to be widely used in pediatric patients. The requirement could be deferred until after approval if, or example, it was appropriate to delay pediatric studies until sufficient data were collected in adults, or if imposition of the requirement would delay the availability of an important new therapy. Where deferral was permitted, a deadline for submission of the studies could be established. The study requirement could be waived altogether if among other things, the product was likely to be unsafe or ineffective in pediatric patients, pediatric studies were impossible or highly impractical, or reasonable efforts to develop a pediatric formulation had failed.

The pediatric study requirement would also, in compelling circumstances, apply to manufacturers of already marketed drugs and biological products to support pediatric use labeling for already approved indications. Appropriate circumstances would be (1) where the marketed product is widely used in children and the absence of pediatric labeling presents significant risks to children, and (2) where the product offers a meaningful therapeutic benefit over existing therapies, but additional dosing or safety information is needed to permit safe and effective use in children.

In the event that a manufacturer failed to carry out a required pediatric study, the drug would not be disapproved or withdrawn, because such an action would deprive adult patients of important therapies. Instead, an order from a Federal court requiring the manufacturer to conduct or fund the needed studies would be sought.

GEORGETOWN UNIVERSITY LAW CENTER

Federal Legislation Clinic

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FAX COVER MEMORANDUM

DATE: 8/12/97

NUMBER OF PAGES, INCLUDING THIS SHEET: 4

TO: Jen Klein

FAX NUMBER: 456-2878

FROM: Tim Westmoreland

COMMENT:

111 F Street NW Room 340 Washington DC 20001-2095
202-662-9595 Fax # 202-662-9682
fedlegis@law.georgetown.edu

Current Debates and Arguments

The manufacturers will criticize the proposed FDA regulation, arguing that they should not be required to do pediatric trials because they are (1) routinely expensive, (2) not appropriate for all drugs, (3) difficult to recruit subjects for, (4) a liability problem, and (5) unethical. Each of these arguments can be answered or outright refuted.

(1) Argument: Routinely expensive
Most manufacturers argue that the reason that pediatric studies are not conducted is because of expense. They estimate the costs to be $1 to $5 million per trial. They also point to the need for re-formulation of tablets and pills to a liquid formulation.

Response: The major cost of performing drug approval trials has been removed from pediatric studies. Since 1994, neither of the large studies (Phase 2 and Phase 3) is required. All that is required is a Phase 1 safety and pharmacokinetics trial, which is estimated to cost between $250,000 to $500,000, far less than the tens or hundreds of millions needed to bring a new drug to market.

Re-formulation is sometimes a problem, but it is not the reason studies are not conducted. Many drugs are already in liquid or aerosol and still have no pediatric data. Also, if re-formulation were the issue, there should be a full range of drugs tested on older children who can swallow pills and tablets--and there isn't.

Finally, I would note that the proposed FDA regulation has a general exception in cases in which pediatric trials are impractical or and a specific exception in cases in which re-formulations cannot be accomplished.

2) Argument: Not appropriate for all drugs.

Response: Agreed. But the proposed regulations recognize that. The requirement would be for drugs that represent a significant therapeutic advance for children or for drugs expected to be taken by more than 100,000 children a year. No one is trying to get pediatric studies for

prostate cancer drugs, but there is no excuse for the lack of pediatric data for virtually all asthma drugs.

(3) Argument: Difficult to recruit subjects for.

Response: Not proven. In the instances in which private or NIH-funded trials have been initiated for children, the trials have usually been fully subscribed. (Note that when the PAF offered to recruit the researchers and the subjects for an AIDS drug trial if only the company would allow it to start, the request was rejected.)

Moreover, the proposed regulations provide an exception if the trials were impractical to conduct. Failure to recruit after diligent attempts to do so would seem a reasonable ground for such an exception.

(4) Argument: Liability problem.

Response: Not true. Even in areas as potentially dangerous as vaccines (in which a healthy child is submitted to research risk), clinical trials have not been a subject of liability. During the vaccine compensation debates, the manufacturers themselves agreed that clinical trial liability was not a problem. Recently, when I have asked drug company lobbyists who make this argument to check with their lawyers and describe a real case, I have gotten no responses (and, to their credit, these lobbyists have stopped making the argument).

(5) Argument: Unethical.

Response: Both the American Academy of Pediatrics and HHS have developed ethics guidelines for research using children. The Academy went so far as to say that, administration of untested drugs "may place more children at risk than if the drugs were administered as part of well-designed, controlled clinical trials." The proposed FDA regulations would require manufacturers to adhere to ethics guidelines and provide an explicit exception to the requirement of studies if such studies would be unethical to conduct. (From the standpoint of pediatric AIDS it is nearly impossible to argue that a drug as potentially successful as, for example, protease

inhibitors should be withheld from children with an otherwise fatal illness because of possible research risk in carefully designed trials; children get sicker faster with AIDS than do adults; their greatest risk is of dying from AIDS.)

For immediate release
August 13, 1997

CONTACT: Cheryl Cook

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

In its press release dated August 12, 1997, PhRMA argues against the FDA's proposed regulations to require that drugs be tested for safety and dosing for children's use. In that press release, a number of serious errors, omissions, and misleading statements are made. This is an effort to correct the record.

Argument in Press Release:
Manufacturers are voluntarily testing drugs for children. "We question whether a government mandate is needed."

Response: The industry is not testing most drugs for children.

80% of the drugs already on the market have not been tested for children.

In 1991, only 56% of new drugs approved with potential usefulness in children were actually tested for children. In 1996, only 37% of new drugs approved with potential usefulness in children were actually tested for children.

During the period between 1991 and 1995, it is estimated that 60 drugs were approved that would be affected by the proposed regulation. Of those 60, 37 (61%) had no pediatric labeling.

Argument in Press Release:
The industry is primarily concerned about protecting the safety of children and avoiding risks of research.

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

Drugs that are untested in children are widely used already. Five million prescriptions a year are written for the top ten unstudied drugs alone.

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

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

Argument in Press Release: There are practical difficulties in testing drugs for children and in developing formulations appropriate for them.

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

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

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

Argument in Press Release: Adult drugs should not be delayed.

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

Conclusion

The current practice in most of the pharmaceutical industry is not to test drugs on children except in special circumstances. The Pediatric AIDS Foundation believes that presumption should be reversed: Drugs should be tested on children unless there is a reason not to. The proposed FDA regulation to be announced by the President today would accomplish that goal.

THE WHITE HOUSE

May 28, 1998

Ms. Susan DeLaurentis
Pediatric Aids Foundation
1311 Colorado Avenue
Santa Monica, California 90404

Dear Susan:

Thank you for your note and copy of your letter to Dr. Friedman. I understand you are working with Jen Klein on the drug testing issue and that she will follow up with you.

I am sorry you and your husband will not be able to join us for the Georgetown Reunion, but understand how important it is for you to attend Francesca's performance. We will just have to party without you!

With warm regards, I remain

Sincerely yours,

Hillary

Hillary Rodham Clinton

cc: Jen Klein

vcc: J. Klein

ope for Children with AIDS

Pediatric AIDS Foundation

August 25, 1997

Hillary Rodham Clinton
c/o Pam Cicetti
Second Floor, West Wing
1600 Pennsylvania Ave.
Washington, DC 20500

Dear Hillary,

Thank you for making sure that the pediatric drug regulation became a reality. We have dreamed of this day for many years, but it never would have happened without your help and support.

I know how pleased Elizabeth would have been to see this milestone, not only for HIV infected children, but for all children.

I am proud to have been a part of the new pediatric drug regulation. There is no doubt that the work of your dedicated staff, especially Jennifer Klein, was also instrumental.

It is clear that your work on behalf of America's children will have a dramatic impact on generations to come. When the history of the Clinton Administration is written, it will undoubtedly reflect this tireless commitment.

Congratulations and my most heartfelt thanks.

With love,

Susan

Susan DeLaurentis
Co-founder

Hope your Vineyard vacation was great!

CO-FOUNDERS: Susan DeLaurentis/Elizabeth Glaser/Susie Zeegen
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