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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

October 10, 1997

Food and Drug Administration
Rockville MD 20857

Dear Colleague:

I am enclosing information pertaining to recent and upcoming Food and Drug (FDA) activities related to HIV/AIDS. Please share this information with your colleagues and distribute it to your constituents. This mailing contains:

- ☛ Summary Minutes, Antiviral Drugs Advisory Committee, which discussed the utility of plasma HIV RNA measurement as an endpoint in clinical trials for drugs to treat HIV infection, July 14 and 15, 1997.
- ☛ Pediatric Patients; Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products; Proposed Rule, Federal Register, August 15, 1997
- ☛ FDA is announcing a public meeting on October 27, 1997 to discuss issues related to the agency's proposed rule on regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients. The meeting will be held at the Cohen Building Auditorium, 330 C Street SW, Washington, DC.
- ☛ FDA approved Famvir (famciclovir, SmithKline Beecham Pharmaceuticals) for the new indication of suppression of recurrent episodes of genital herpes in immunocompetent adults, September 17, 1997
- ☛ FDA Proposed Rule on Women in Clinical Trials, Talk Paper T97-46, September 23, 1997
- ☛ Investigational New Drug Applications; Proposed Amendment to Clinical Hold Regulations for Products Intended for Life-Threatening Diseases, Federal Register, September 24, 1997
- ☛ FDA approved Combivir, a combination of AZT (zidovudine) and 3TC (lamivudine) for treating AIDS and HIV infection, Talk Paper T97-29, September 26, 1997
- ☛ Unpasteurized Cider and Juice Alert, People with weakened immune systems, such as those with HIV, AIDS or cancer, should drink only pasteurized cider and juice.
- ☛ FDA Warns Consumers About Two Unapproved Home-Use Test Kits, HHS News, P97-33, September 26, 1997
- ☛ Liposomal daunorubicin is not recommended in patients with less than advanced HIV-related Kaposi's sarcoma, R. M. White, Medical Officer, Division of Oncology Drug Products, FDA, AIDS 1997, Vol 11 No 11, November 1997

We are updating our HIV/AIDS mailing list. If you wish to continue receiving these mailings, please complete the enclosed form and mail or FAX it back to my attention. You may contact me either by phone (1.301.827.4460) or by e-mail (Rklein@oc.fda.gov) if you have any questions or comments about these or other HIV/AIDS-related issues pertaining to the Food and Drug Administration.

Yours truly,

Richard Klein
HIV/AIDS Program Director
Office of Special Health Issues
5600 Fishers Lane, HF-12
Rockville, MD 20857

ENCLOSURES

Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES
ANTIVIRAL DRUGS ADVISORY COMMITTEE
July 14-16, 1997
Armory Place, Silver Spring, MD

Antiviral Drugs Advisory Committee

Scott M. Hammer, MD, Chair
Wm. Christopher Mathews, MD, MSPH
Pamela Diaz, MD
Judith Feinberg, MD
Wafaa El-Sadr, MD
James J. Lipsky, MD

Ermona McGoodwin, Acting Executive Secretary (7/14)

FDA SGE Consultants

John Modlin, MD (7/14-15)
Fred Valentine, MD (7/14-15)
Vernon Chinchilli, PhD (7/14-15)
Joel Verter, PhD (7/14-15)
Janet Elashoff, PhD (7/16)
Brian Wong, MD (7/16)

FDA Guests

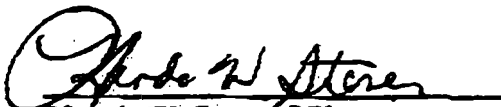
Mark Harrington (7/14-15)
Brenda Lein (7/14-15)
Virginia Kan, MD (7/16)

FDA Participants

David Feigal, MD, MPH
Donna Freeman, MD (7/14-15)
Mark Goldberger, MD, MPH (7/16)
Jeffrey Murray, MD
Michael Elashoff, PhD (7/14-15)
Paul Flyer, PhD (7/14-15)
Lauren Iacono-Connors, PhD (7/14-15)
Joyce Korvick, MD (7/16)
Thomas Hammerstrom, PhD (7/16)

These summary minutes for the July 14-16, 1997 Antiviral Drugs Advisory Committee meeting were approved on 9/15/97

I certify that I attended the July 14-16, 1997 Antiviral Drugs Advisory Committee meeting and that these minutes accurately reflect what transpired.


Rhonda W. Stover, RPh
Executive Secretary


Scott M. Hammer, MD
Chair

The July 14-16, 1997 meeting of the Antiviral Drugs Advisory Committee consisted of three open session days. On July 14 and 15, 1997, the committee discussed the utility of plasma human immunodeficiency virus (HIV) RNA measurement as an endpoint in clinical trials for drugs to treat HIV infection. On July 16, 1997, the committee discussed NDA 50-740, AmBisome® (liposomal amphotericin B, Fujisawa, USA), as empirical therapy for presumed fungal infection in febrile neutropenic patients.

MEETING PROCEEDINGS-OPEN SESSION-JULY 14, 1997

Topic: The utility of plasma human immunodeficiency virus (HIV) RNA measurement as an endpoint in clinical trials for drugs to treat HIV infection.

Approximately 350 persons were in attendance. A briefing memorandum from the FDA was the only background material sent to the committee prior to the meeting.

Call to Order

The meeting was called to order by Dr. Scott Hammer, Chair, at 8:30 a.m. The committee members, guests, and the FDA participants at the table introduced themselves.

Conflict of Interest

The conflict of interest statement was read by Ermona McGoodwin, Acting Executive Secretary. General matters waivers were granted to all committee participants with interests in companies or organizations that could be affected by the committee's discussion of the meeting topic.

Introduction

Dr. David Feigal, Director, Office of Drug Evaluation IV, FDA, reviewed the history of surrogate markers and the accelerated approval of HIV medications. The purpose of this cooperative meeting was to examine the effects of HIV medications on viral load and treatment response issues.

Presentations-HIV RNA Assays

Lauren Iacono-Connors, PhD (FDA), gave an overview of HIV-RNA measurements. Don Brambilla, PhD (New England Research Institute), discussed the assay characteristics of the Chiron ES bDNA, Organon Teknika NASBA, and Roche Amplicor HIV Monitor assays. Winston Cavert, MD (University of Minnesota), presented data on the comparative tissue compartment activity for plasma RNA and lymphoid tissue RNA.

Presentations-Review of Pediatric Data

Lynne Mofenson, MD, (NICHD), presented the natural history of HIV infection in pediatric patients. Paul Palumbo, MD (University of Medicine and Dentistry of New Jersey), discussed the virology data from the ACTG study 152. The virology data from the ACTG study 300 was given by George Johnson, MD (Medical University of South Carolina).

Open Public Hearing

The following 7 open public hearing speakers presented data, information, and views to the Committee on the meeting topic and other HIV treatment issues. The speakers were requested to make presentations of approximately 5 minutes and to disclose their financial associations.

- Victor DeGruttola, PhD, Harvard School of Public Health
- David Scondras, Search for Cure, Boston, MA
- Alan Norburn, AIDS Treatment Project, London, England
- Francois Houyez, European AIDS Treatment Group (EATG), Paris, France
- Bill Bahlman, ACT-UP, New York
- Iris Long, PhD, ACT-UP, Mount Sinai ACTG-CAP
- Ronald Baker, San Francisco AIDS Foundation, (BETA)

Presentations-Clinical Confirmation of HIV-RNA Changes

After a review of the current antiretroviral guidelines by Sherilyn Stanley, MD, (NIAID), the presentations on clinical confirmation of HIV-RNA changes were introduced by Jeffrey Murray, MD (FDA). Dr. Murray gave the rationale for the agency's decision to explore plasma HIV-RNA as a clinical endpoint in HIV trials. Plasma HIV-RNA as a clinical endpoint would be less complex than current endpoints, more reflective of current medical practice, and allow treatment switches before clinical failure. However, the agency must be confident that HIV-RNA reduction is associated with a decreased clinical progression rate as well as other related issues.

Ian Marschner, PhD, (Harvard School of Public Health/ACTG) presented a cross-protocol analysis of 7 ACTG studies (116A, 116B/117, 175, 197, 229, 241, 259) involving a variety of treatment regimens. After an introduction by Lynn Smiley, MD (GlaxoWellcome), Ralph DeMasi, PhD, (GlaxoWellcome) discussed data from 6 controlled trials (CAESAR, NUCA3001, NUCA3002, NUCB3001, NUCB3002, AVANTI-01) of ZDV+3TC (67%) versus control treatments (33%).

Christy Chuang-Stein, PhD, (Pharmacia and UpJohn), presented combined data from studies 0017 (DLV+ddI versus ddI) and 0021 (DLV+ZDV versus ZDV). Data from the intent to treat population of trial NV14256 (ddC, saquinavir, and ddC+saquinavir) was

given by Lesley Struthers (Hoffman La Roche) and Mike Shear (Hoffman La Roche). Margo Heath Chiozzi, MD (Abbott Laboratories), reviewed data from study M94-247 of ritonavir treated patients.

Michael Elashoff, PhD (FDA), gave a summary of the 5 presentations. Overall, the data that comprised many studies, regimens, and methods of analysis, supported an association between RNA changes and clinical event rates. A reduction of 0.5 log, the smallest decrease studied across trials, was associated with clinical benefit and greater decreases resulted in lower clinical event-rates. Dr. Elashoff stated that there was an association between longer suppression and lower clinical event rates. However, the effect of long-term durability remains to be characterized since durable responses past 24 weeks were rare in these trials.

The committee was given the opportunity to ask questions of the presenters and the FDA representatives. The agency's formal discussion points were posed to the committee on the second day of the meeting-July 15, 1997, after additional presentations and discussion.

The meeting was adjourned at 4:30 p.m. to reconvene at 8:00 a.m. on July 15, 1997.

MEETING PROCEEDINGS-OPEN SESSION-JULY 15, 1997

Topic: The utility of plasma human immunodeficiency virus (HIV) RNA measurement as an endpoint in clinical trials for drugs to treat HIV infection.

Approximately 300 persons were in attendance. A briefing memorandum from the FDA was the only background material sent to the committee prior to the meeting.

Call to Order

The meeting was called to order by Dr. Scott Hammer, Chair, at 8:00 a.m. The committee members, guests, and the FDA participants at the table introduced themselves.

Conflict of Interest

The conflict of interest statement was read by Rhonda Stover, RPh, Executive Secretary. General matters waivers were granted to all committee participants with interests in companies or organizations that could be affected by the committee's discussion of the meeting topic.

Introduction

Paul Flyer, PhD (FDA), stated that the previous day's presentations indicated that there is a strong relationship between the treatment induced changes in HIV RNA and clinical outcome. He discussed the use of HIV RNA as a surrogate marker and its proposed use as a clinical endpoint. The FDA proposes adding a new treatment indication, the suppression of HIV RNA, to serve as the confirmatory trial for a drug approved under accelerated approval. Dr. Flyer stated that the focus of this meeting day would be trial design issues in evaluating HIV RNA response.

Presentations-Viral Changes in Response to Antiretroviral Treatment

The four presentations utilized study data to address issues that included time to virologic response and durability of virologic response. Jeff Chodakewitz, MD (Merck Laboratories), presented data from indinavir protocols 028, 033, and 035. Barry Quart, PharmD (Agouron Pharmaceuticals), discussed Viracept study 511. The results of nevirapine trial BI 1046 were given by David Hall, PhD (Boehringer Ingelheim Pharmaceuticals). The final industry presentation consisted of ZDV+3TC data from 6 controlled trials (CAESAR, NUCA3001, NUCA3002, NUCB3001, NUCB3002, AVANTI-01) and was given by Lynn Smiley, MD (GlaxoWellcome) and Ralph DeMasi, PhD, (GlaxoWellcome).

Michael Elashoff, PhD, (FDA) discussed the design of an RNA-based clinical trial and summarized the four presentations. Dr. Elashoff stated that a primary study endpoint of

time to loss of response could include RNA as well as CD4 and other clinical endpoints. The initial phase of the RNA-based clinical trial could be used for accelerated approval on the basis of percent response and the long-term followup would address the durability of the drugs. Furthermore, the RNA-based clinical trial should allow patients to switch if they do not experience an initial or sustained response and to exit the study, if appropriate.

Dr. Elashoff commented on the utility of the data from the four presentations in defining treatment response for an RNA-based clinical trial. In these studies, a response was considered to be achieving the assay limit, although a less stringent response definition and a flexible loss of response definition may be needed in some trials. The time of response may be as long as 16 to 24 weeks and the time of loss of response may exceed 48 weeks after response.

Open Public Hearing

The following 7 open public hearing speakers presented data, information, and views to the Committee on the meeting topic and other HIV treatment issues. The speakers were requested to make presentations of approximately 5 minutes and to disclose their financial associations.

- Ben Cheng, Project Inform
- Jules Levin, National AIDS Treatment Advocacy Project (NATAP)
- Spencer Cox, Treatment Action Group, New York, New York
- Bill Bahlman, ACT-UP, New York
- John S. James, AIDS Treatment News
- Mike Donnelly, ACT-UP, Golden Gate
- Beverly Dale, Roche Molecular Systems

Charge to the Committee

Dr. David Feigal, Director, Office of Drug Evaluation IV, FDA, discussed HIV trial design issues. He commented on the emergence of individualizing HIV therapy and the need for decision rules versus only following surrogate markers. Dr. Feigal informed the committee that the agency hopes to change product labeling from a label which only states that an agent is approved to treat HIV infection to a label that would describe the performance characteristics of a product.

Committee Discussion

The committee posed questions to the presenters and discussed all the issues that arose from the presentations. The committee was asked by the agency to **comment** (no formal vote) on the following discussion points:

1. Does the available information support our conclusion that a durable reduction in plasma HIV-RNA is evidence of clinical benefit?

Yes, the committee agreed that the data presented suggested correlation between a durable reduction in plasma HIV-RNA and clinical benefit. Several committee members stated that a durable reduction in plasma HIV-RNA predicts (versus is evidence of) clinical benefit.

2. For the purpose of evaluating drug efficacy;
 - A. What is the most appropriate definition of a clinically meaningful virological response?
 - B. Should the definition differ for subpopulations such as:
Children
Antiretroviral experienced patients or
Baseline disease status
 - C. Given this definition what would constitute a loss of that response?
 - D. How long should responders be followed to assess a durable virologic response?

The committee decided to answer this question grouped as 2A and 2B and 2C and 2D.

2A and 2B

The majority of the committee stated that the definition would vary based on the treatment population. The definitions of a clinically meaningful response ranged from the minimum of a 0.5 log reduction from baseline to a maximum of below quantifiable levels. It was also stated that the definition may have to be a composite inclusive of time to response, CD4 counts, and resistance issues.

2C and 2D

The definition of a loss of response was dependent on the definition of a clinically meaningful virological response. Therefore, the committee's views ranged from an increase to within 0.5 log of baseline to any quantifiable amounts of HIV-RNA. The agency's proposed time to failure was also cited as a reasonable endpoint. The committee agreed that patients should be followed for at least 48 weeks. Additionally, it was suggested that patients be followed 48-52 weeks past the last enrolled patient as the minimum and for as long as possible as the maximum.

3.
 - A. What events should prompt altering randomized therapy during a clinical trial?
 - B. Are there circumstances in which this would differ from the virologic endpoint?

The committee stated that there are clinical and immunologic factors that differ from the virologic endpoint that could prompt altering randomized therapy during a clinical trial. Progressive CD4 decline, toxicity, and changes in standard clinical practice were cited as some of these factors. Several committee members cautioned that the therapy switch

criteria be conservative to allow time for the patient to achieve maximal benefit on the randomized regimen.

The meeting was adjourned at 2:55 p.m. to reconvene at 8:30 a.m., July 16, 1997, to discuss NDA 50-740, AmBisome® (liposomal amphotericin B, Fujisawa, USA), as empirical therapy for presumed fungal infection in febrile neutropenic patients.

federal register

Friday
August 15, 1997

Part V

Department of Health and Human Services

Food and Drug Administration

**21 CFR Parts 201, 312, 314, and 601
Pediatric Patients; Regulations Requiring
Manufacturers To Assess the Safety and
Effectiveness of New Drugs and
Biological Products; Proposed Rule**

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 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 November 13, 1997. Written comments on the information collection provisions should be submitted by September 15, 1997. For further information of the agency's implementation plan, see section VII of **SUPPLEMENTARY INFORMATION** in 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 times to pediatric patients under 2; aerosol prescribed 399,000 times to pediatric patients under 5); Zoloft for treatment of depression (prescribed 248,000 times 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 (m²)). 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. CDER 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 other 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 supplements containing pediatric use studies for which FDA granted a request to defer submission until after approval.

Finally, FDA has issued a policy statement describing the types of evidence necessary to support supplements. In that policy, FDA provides guidance to manufacturers on the circumstances in which FDA may approve a supplement in which confirmation of the results of an adequate and well-controlled trial is provided by information other than a second adequate and well-controlled trial precisely replicating the first trial, or by studies without the extensive documentation ordinarily required.

The agency believes that financial and other incentives to manufacturers, although largely beyond FDA's current authority, could further increase the number of drugs and biologics with adequate pediatric labeling.

IV. Public Hearing

Because of the importance of ensuring the safety and effectiveness of the medications administered to children and the need to address the absence of pediatric labeling in the most effective manner possible, FDA intends to hold a public hearing at which recognized experts in the field, members of the pharmaceutical industry, and other interested parties will have an opportunity to discuss the issues raised by this proposal.

V. Description of the Proposed Rule

The proposed rule is designed to ensure that new drugs and biological products that are likely to be commonly used in children or that represent a meaningful therapeutic benefit over existing treatments for children contain adequate pediatric labeling for the approved indications at the time of, or soon after, approval. The rule would therefore require a manufacturer of a drug classified as a "new chemical entity" or a new (never-before-approved) biological product to submit, before approval, safety and effectiveness information on relevant pediatric age groups for the claimed indications. The

submission of information could be deferred until after approval if, for example, pediatric studies should not begin until information on adults was collected, or where the collection and filing of pediatric data would delay the availability of a product that provides a significant therapeutic advantage to adults. The requirement would be waived for some or all pediatric age groups, if: (1) The product did not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and was unlikely to be used in a substantial number of pediatric patients, (2) studies on the product were impossible or highly impractical because, for example, the population was too small or geographically dispersed, (3) the product were likely to be unsafe or ineffective in pediatric patients, or (4) reasonable efforts to develop a pediatric formulation (if one were needed) had failed.

The rule is also intended to assist in improving pediatric use information for already marketed drugs and biological products where there is a compelling need for more information. The rule would therefore codify FDA's authority, discussed in the 1994 rule, to require, in compelling circumstances, that manufacturers of already marketed drugs and biological products conduct studies to support pediatric use labeling for the claimed indications.

The proposed rule also contains provisions designed to encourage discussions of the need for pediatric studies early in the drug development process, as well as postmarketing reporting requirements designed to assist FDA in determining whether pediatric studies are needed for particular products and whether required studies are being carried out with due diligence.

FDA notes that the Federal Food, Drug, and Cosmetic Act (the act) authorizes FDA, under certain circumstances, to grant periods of exclusive marketing to manufacturers who obtain approval of labeling supplements adding pediatric use information to a drug's label. First, a manufacturer is entitled to 3 years of exclusive marketing under section 505(c)(3)(D)(iii) and (j)(4)(D)(iv) of the act (21 U.S.C. 355(c)(3)(D)(iii) and (j)(4)(D)(iv)) for obtaining approval of pediatric use labeling based on clinical studies, other than bioavailability studies. Second, a manufacturer may be entitled to 7 years of exclusive marketing under the Orphan Drug Amendments for obtaining approval of an application for use of a drug to treat a disease or condition affecting a

pediatric population of less than 200,000.

A. Scope

The proposed rule would cover only original applications for those drugs classified as "new chemical entities," including antibiotics, and new biological drug products that have never been approved for any indication. A "new chemical entity," defined in 21 CFR 314.108(a), is a drug that contains no previously approved active moiety. (An "active moiety," also defined in § 314.108(a), is the molecule or ion, excluding certain appendages, that is responsible for the physiological or pharmacological action of the drug.) New chemical entities and new biological products are generally the most innovative and therapeutically significant of the new drug products approved by FDA.

In an effort to limit the scope of the rule to those products for which pediatric labeling is most urgently needed and to minimize the burden on manufacturers and on agency resources available to review new product applications, FDA has tentatively concluded that the pediatric study requirement would not apply to subsequent applications for the drug or biological product, e.g. to supplements for new indications or dosage forms. FDA recognizes that, in some cases, a change to an approved product, particularly a new indication, may have clinically significant use in children. FDA seeks comment on whether the requirement should apply more broadly, e.g., to applications for minor chemical variations of approved products, new indications, new dosage forms or new routes of administration, and, if so, how the rule could be applied in a manner that does not impose undue burdens on manufacturers or agency resources.

The proposed rule would require an assessment of safety and effectiveness in one subpopulation (pediatric patients) only for the indications already claimed by the manufacturer. It would 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 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, or at the earliest appropriate opportunity, 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 been collected. FDA believes that in certain cases it may be appropriate to defer submission of pediatric studies. For example, in such cases, an NDA or biological product license could be ready for approval for adult use before pediatric studies were completed. Also, where a product was needed to treat a serious or life-threatening disease for which there were not satisfactory alternative therapies or where the product represented a meaningful therapeutic benefit over existing therapies, it would be contrary to the public health to delay approval until pediatric studies were submitted.

Proposed §§ 314.50(g)(2) and 601.27(b) would permit FDA to defer the submission of some or all of the

required pediatric data until after approval of the product for adult use, on its own initiative or at the request of the applicant. If the applicant requested deferral, the request would be required to contain an adequate justification for delaying pediatric studies. If FDA concluded that there were adequate justification for deferring the submission of pediatric use studies, the agency could approve the product for use in adults subject to a requirement that the applicant submit the required pediatric studies within a specified time after approval. FDA would consult with the sponsor in determining a deadline for the deferred submission, but would ordinarily require the submission not more than 2 years after the date of the initial approval. The deadline for submission of studies would take account of likely or actual difficulties encountered in recruiting pediatric 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, or (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 immature 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 Index¹, 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 than 15,000 patients in that age group were affected by the disease or condition. FDA seeks comment on these methods of assessing expected pediatric exposure and on the specific numerical thresholds suggested.

5. Section 314.50(d)(7)—Pediatric Use Section of Application

Under proposed § 314.50(d)(7), applicants would be required to include in their applications a section summarizing and analyzing the data supporting pediatric use information for the claimed indications. The proposed new section of the application would contain an integrated summary of the clinical pharmacology studies, controlled clinical studies, uncontrolled clinical studies, or other data or information that are relevant to the safety and effectiveness, and benefits and risks of the drug in pediatric populations. Because full descriptions of all such studies must already be provided under § 314.50 (d)(3) and (d)(5), the new pediatric use section would be required to contain only brief summaries of the studies together with a reference to the full description of each provided elsewhere in the application.

C. Marketed Drug and Biological Products

1. Section 201.23—Required Studies

As discussed in the preamble to the 1994 rule, FDA has the authority, under certain circumstances, to require the manufacturers of marketed drugs that are used in pediatric patients to submit pediatric studies assessing safety and effectiveness for the already approved

indications (59 FR 64240 at 64243). Proposed § 201.23 would authorize FDA to require a manufacturer of a marketed drug or biological drug product to submit an application containing data evaluating the safety and effectiveness of the product in pediatric populations, in compelling circumstances. FDA has tentatively concluded that it should impose such a requirement only where the agency made one of two findings that: (1) The product was widely used in pediatric populations and the absence of adequate labeling could pose significant risks to pediatric patients; or (2) the product was indicated for a very significant or life threatening illness, but additional dosing or safety information was needed to permit its safe and effective use in pediatric patients.

Before requiring a study under § 201.23, the appropriate center, CDER or CBER, would consult with the manufacturer on the type of studies needed and on the length of time necessary to complete them and would notify the manufacturer, by letter, of the center's tentative conclusion that such a study was needed and provide the manufacturer an opportunity to provide a written response and to have a meeting with the center. At the center's discretion, such a meeting could be an advisory committee meeting. If, after reviewing any written response and conducting any requested meeting, CDER or CBER determined that additional pediatric use information were necessary, the center director would issue an order requiring the manufacturer to submit a supplemental application containing pediatric safety and effectiveness data within a specified time. The manufacturer would be able to request reconsideration by the Commissioner for Food and Drugs (the Commissioner) of the order under the provisions at 21 CFR 10.33.

Proposed § 201.23(c) would require FDA to grant full or partial waivers of study requirements on their own initiative or at request of the applicant for reasons analogous to those which would entitle not-yet-marketed drug and biologic products to waivers.

FDA seeks comment on whether it should codify its authority to require the manufacturers of marketed drugs to conduct pediatric studies, and, if so, the circumstances under which the agency should exercise that authority. The agency also solicits comment on the proposed grounds for waiving the pediatric study requirement for already marketed drug and biological products and whether additional ground may exist, such as whether cost should justify waiver of the pediatric study requirement. Comment is also sought on

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

defining the term "very significant illness".

D. Studies in Different Pediatric Age Groups

Because the pharmacokinetics and pharmacodynamics of a drug or biological product may be different in different pediatric age groups or stages of development, it could be necessary to conduct studies in more than one pediatric age group. The following age categories for the pediatric population are commonly distinguished: (1) Neonates; (2) infants; (3) children, and (4) adolescents. In the 1994 rule, FDA defined neonates as birth up to 1 month, infants as 1 month to 2 years, children as 2 years to 12 years, and adolescents as 12 years to 16 years (59 FR 64242). The need for studies in more than one age group would depend on whether the drug or biological product was likely to be used in each age group (see "Waivers," in sections V.B.4 and V.C.1 of this document) and whether safety and effectiveness in one age group could be extrapolated to other age groups. The metabolism and elimination of the drug and the stage of development of the child may be important in determining which age groups should be tested. There would generally need to be sufficient data, including pharmacokinetic data to establish dosing and safety for each group. (Pharmacokinetic data are generally collected from pediatric patients receiving the drug or biologic as treatment rather than from healthy children.) In cases where the product was expected to have similar pharmacokinetics in more than one age group, pharmacokinetic data from one age group could be sufficient to support labeling for other age groups. Such extrapolation would not be routine.

FDA recognizes that studies in neonates and young infants present special problems. On one hand, failure to adequately test drugs in this age group has led to both under treatment and, conversely, some of the most serious therapeutic mishaps known to have occurred among pediatric patients. On the other hand, studies in this age group may be significantly more difficult to carry out in the period before or soon after approval than studies in older age groups. However, FDA recognizes that for some conditions, early study would be advantageous. FDA would therefore expect to apply the study requirement to patients in this age group with caution and would, whenever appropriate, permit such studies to occur after the product has been successfully studied in older children. The agency seeks comment on

the issues raised by requiring studies in this age group.

E. Pediatric Formulations

In some cases, testing of a product in pediatric patients could require the development of a pediatric formulation. Many children below a certain age are unable to swallow pills and may require a liquid, chewable or injectable form of the product. The need to develop a pediatric formulation does not necessarily mean that the product would not have been used in children in its adult dosage form. In many cases, physicians prescribing tablets to young children direct the parent to grind up the tablet and sprinkle the powder into the child's food. In other cases, pharmacists may compound tablets into pediatric formulations of their own choosing. These methods of administering adult dosage forms to children may be unsatisfactory, however, because the bioavailability of any particular product in this form is untested and dosing may be highly variable. A standardized pediatric formulation ensures bioavailability and consistency of dosing, and permits meaningful testing of safety and effectiveness.

FDA has tentatively concluded that it would be reasonable to expect a manufacturer of a product to produce a pediatric formulation, if one were necessary, only in those cases where a new drug or new biological product provided a meaningful therapeutic benefit over existing treatments, and where the study requirement had not been waived in the age group requiring the pediatric formulation. Proposed §§ 201.23, 314.50(g)(1) and 601.27(a) contain this requirement. The type of formulation needed would vary depending on the age group in which the product were to be used and the disease being treated. Young children unaccustomed to taking drugs may need liquid or chewable formulations, while children with serious and chronic diseases may need only smaller tablets.

The difficulty and cost of producing a pediatric formulation may vary greatly depending upon such factors as solubility of the compound and taste. FDA would waive the requirement for pediatric studies (see "Waivers," in section V.B.4 of this document) in age groups requiring a pediatric formulation, if the manufacturer provided evidence that reasonable attempts to produce a pediatric formulation had failed.

FDA solicits comment on whether it is appropriate to require a manufacturer to develop a pediatric formulation and, if so, the circumstances in which it

would be appropriate to impose such a requirement. For example, should the cost of developing a pediatric formulation justify a waiver of the pediatric study requirement? Should the number of patients affected by the disease or condition in the relevant age group be considered in determining whether to require the development of a pediatric formulation for that age group? Is it appropriate to ask the manufacturer of a not-yet-approved product to allocate resources to developing pediatric formulation(s)? Where cost is a significant issue, would it be appropriate to defer development of a pediatric formulation until after approval of the product? What should be considered "reasonable attempts" to develop a pediatric formulation?

As noted above, FDA was unable to quantify the potential benefits of this rule due to the unavailability of relevant data and studies. Nevertheless, the agency will attempt to assess the benefits of the final rule and solicits comment on the appropriate design and methodology of such measurement. In particular, FDA seeks information and data that would help the agency to: (1) Quantify the societal costs of the adverse drug events experienced by pediatric populations and (2) assess the proportion of these adverse drug events that would be eliminated by the new information that would result from the rule. In addition, FDA seeks information and data that would help the agency to: (1) Quantify the societal costs of the underused or inadequate drug therapies prescribed to pediatric populations and to (2) assess the proportion of these costs that would be eliminated by the new information that would result from the rule.

F. Ethical Issues

Ethical concerns may have contributed to reluctance to conduct studies in pediatric patients. To address these concerns, both the American Academy of Pediatrics (Ref. 1) and the Department of Health and Human Services, 45 CFR part 46, subpart D, have developed guidelines or regulations for the ethical conduct of clinical studies in pediatric patients. Because pediatric patients represent a vulnerable population, special protections are needed to protect their rights and to shield them from undue risk. As the American Academy of Pediatrics has observed, however, administration of untested drugs "may place more children at risk than if the drugs were administered as part of well-designed, controlled clinical trials" (Ref. 1 at p. 286). The ethical guidelines currently in place are designed to

protect children's rights and protect them from undue risk. Sponsors should adhere to these guidelines for pediatric studies conducted under this rule. The agency seeks comment on ethical issues that may be raised by this proposal.

G. Remedies

FDA has tentatively concluded that the most practical remedy for failure to submit a required study is an injunctive action brought under the "misbranding" or "new drug" provisions of the act. Denying or withdrawing approval of an otherwise safe and effective drug or biological product is not a satisfactory remedy, because removal of a product from the marketplace could deprive other patients of the benefits of a useful medical product. FDA does not intend to deny or withdraw approval of a product for failure to conduct pediatric studies, except possibly in rare circumstances.

If a manufacturer failed, in the time allowed, to submit adequate studies to evaluate pediatric safety and effectiveness, under proposed §§ 201.23(d) or 314.50(g), FDA could consider the product misbranded under section 502 of the act (21 U.S.C. 352) or an unapproved new drug under section 505(a) of the act (see "Legal Authority," in section VI of this document). When a product is misbranded or an unapproved new drug, sections 302, 303 and 304 of the act (21 U.S.C. 332, 333, and 334) authorize injunction, prosecution or seizure. For violations of this rule, should it become final, FDA would ordinarily expect to file an enforcement action for an injunction, asking a Federal court to require the company to submit an assessment of pediatric safety and effectiveness for the product. Violation of the injunction would result in a contempt proceeding or such other penalties as the court ordered, e.g., fines.

To assist FDA in determining whether pediatric assessments are needed or are being carried out with due diligence, FDA is proposing to amend § 314.81 (other postmarketing reports) to require that annual reports filed by the manufacturer contain information on labeling changes that have been initiated in response to new pediatric data, analysis of clinical data that have been gathered on pediatric use, assessment of data needed to ensure appropriate labeling for the pediatric population, and information on the status of ongoing pediatric studies. Where possible, the annual report would also contain an estimate of patient exposure to the drug product, with special reference to the pediatric population.

FDA seeks comment on appropriate remedies for failure to conduct a required pediatric study and the circumstances, if any, in which the agency should deny or withdraw approval of a drug product.

VI. Legal Authority

Therapeutic tragedies in pediatric patients have prompted some of the most important federal legislation to ensure that drugs are safe and effective. For example, the act was enacted in 1938 in the wake of a tragedy in which many pediatric patients died after taking an untested medicine called Elixir of Sulfanilamide. The legislative history of this enactment demonstrates that Congress intended to ensure that children, as well as adults, received adequately tested and appropriately labeled drugs. (See, e.g., 78 Congressional Record 567-573 (1934) (statement of Sen. Copeland).)

Every mother is anxious that the food and medicine given her baby shall be above suspicion. The welfare of every man, woman, and child is involved in the quality and preparation of the foods and drugs sold in America * * *. [T]he purpose of this legislation * * * is to protect the public, to protect the mothers and the children * * * 81 Congressional Record 7312 (1937) (remarks of Rep. Coffee)

The agency has stated, in the context of both pediatric studies and studies in women, that an application for marketing approval should contain data on a reasonable sample of the patients likely to be given a drug or biological product once it is marketed (59 FR 64240 at 64243; 58 FR 39406 at 39409, July 22, 1993). The agency has further stated that in some cases it could require studies in pediatric patients and in women for both not-yet-approved products and marketed products (Id.).

The primary rationale for such a requirement is the same for women and pediatric patients. In most cases, drugs and biological products behave similarly in demographic subgroups, including age and gender subgroups, even though there may be variations among the subgroups, based on, for example, differences in pharmacokinetics. Thus, where a drug or biological product is indicated for a disease suffered equally by men, women, and children, and is not contraindicated in women or pediatric patients, the product will be widely prescribed for all three subgroups even if it were studied only in, or labeled only for, men. As described above, there is extensive evidence that many drugs labeled only for adult use are in fact widely used in pediatric patients for the same indications.

FDA notes that this proposal addresses only use of drug products for their approved indications in a significant subpopulation. The proposed rule does not address "off-label" or unapproved uses of approved drugs and biological products, in which an approved product is used for diseases or conditions other than those in the label. This rule would apply only where a product was expected to have clinically significant use in pediatric populations for the indications already claimed by the manufacturer.

In addition to the provisions cited below as authority for the proposed rule, the agency relies on section 701(a) of the act (21 U.S.C. 371(a)), which authorizes FDA to issue regulations for the efficient enforcement of the act.

A. New Drug and Biological Products

Biological drug products are subject both to section 351 of the Public Health Service Act (the PHS Act) and to the provisions of the act and implementing regulations applicable to drugs, except that manufacturers of biological products covered by approved BLA's are not required to submit NDA's under section 505 of the act. References to "drugs" in the following sections include biological drugs.

1. Sections 502(a), 502(f), 505(d)(7), and 201(n) of the Act

A drug is misbranded under section 502(a) of the act if its labeling is "false or misleading in any particular." Similarly, a new drug application must contain labeling that is not false or misleading (section 505(d)(7) of the act). Section 201(n) of the act (21 U.S.C. 321(n)) defines labeling as misleading if it "fails to reveal facts material * * * with respect to consequences which may result" not only from use of the product as labeled, but "from the use of the [product] * * * under such conditions of use as are customary or usual." Information on dosing and adverse effects are facts "material" to the consequences that may result from customary use in pediatric patients. A drug product is misbranded under section 502(f) of the act, if its label fails to provide adequate directions for each intended use. 21 CFR 201.5 states that adequate directions must be provided for each use recommended in the labeling and each use "for which the drug is commonly used." Thus, FDA may require a product to carry labeling that provides safety and effectiveness information on use in subpopulations in which the product is customarily or commonly used.

There is extensive evidence that drugs for diseases that affect both adults and pediatric patients are routinely used in pediatric patients despite the absence of pediatric labeling, and even in the face of disclaimers stating that safety and effectiveness have not been established in children. FDA may therefore consider pediatric use to be "customary or usual" or "commonly used" where the drug is indicated for a disease or condition that affects both adults and children, and the drug is not contraindicated in pediatric patients. In many cases, the use in pediatric patients of a drug labeled only for adults will increase over time, as physicians become aware of the drug's potential usefulness in children and familiar with the drug's uses and effects. Thus, FDA may conclude that a drug that was appropriately labeled for adult use at the time of approval is, at some later date, no longer appropriately labeled.

2. Sections 201(p), 301(a), and 505(a) of the Act

Under section 301 (a) and (d) of the act (21 U.S.C. 331 (a) and (d)) and section 505(a) of the act, a drug product is subject to enforcement action if it is a "new drug" for which no NDA has been approved. A product is a new drug under section 201(p) of the act if it is not recognized to be safe and effective under the conditions "prescribed, recommended, or suggested" in the drug's labeling. There is widespread evidence that, despite the absence of pediatric labeling, drugs are routinely used in pediatric patients for the labeled indications. FDA may therefore consider pediatric use to be "suggested" in a drug's labeling where the drug is indicated for a disease or condition that affects both adults and pediatric patients, unless the drug is specifically contraindicated for pediatric patients. As described above, because pediatric use of new drugs often increases over time, FDA may conclude that labeling that is appropriate at the time of approval is later no longer appropriate.

3. Section 502(j) of the Act

Section 502(j) of the act defines as misbranded those drugs that are dangerous to health when used in the manner prescribed, recommended, or suggested in their labeling. FDA may consider pediatric use to be "suggested" in a drug's labeling where the drug is indicated for a disease or condition that affects both adults and pediatric patients, unless the drug is specifically contraindicated for pediatric patients. As described earlier in this notice, the absence of pediatric testing and labeling poses risks to children including the

risk of unanticipated adverse reactions, and under- and over-dosing.

4. Section 505 (i) and (k) of the Act

Section 505(i) of the act that authorizes the issuance of regulations governing the use of investigational drugs, and the proviso in 505(k) of the act, which requires regulations issued under 505(i) to have "due regard * * * for the interests of patients," together authorize FDA to impose conditions on the investigation of new drugs, including conditions related to the ethics of a proposed investigation and to the interests of patients. Fairness in distribution of the burdens and benefits of research is one of the ethical principles underlying federal regulations on investigational drugs. (See, e.g., 44 FR 23192 at 23194, April 18, 1979 ("Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research").) Because exclusion of pediatric patients from clinical trials may deny them an equitable share of the benefits of research, section 505 (i) and (k) authorize FDA to require their inclusion in clinical trials.

5. Section 351 of the Public Health Service Act

Section 351 of the PHS Act (42 U.S.C. 262) provides authority to regulate the labeling and shipment of biological products. Under section 351(d), 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. The "potency" of a biological product includes its effectiveness (21 CFR 600.3(s)).

B. Marketed Drug Products

1. Section 502(f) of the Act and 21 CFR 201.5

A drug product is misbranded under section 502(f) of the act, if its label fails to provide adequate directions for each intended use. 21 CFR 201.5 states that adequate directions must be provided for each use recommended in the labeling and each use "for which the drug is commonly used." Where there is evidence that a drug product is widely used in pediatric patients, failure to provide adequate directions for the use could misbrand the product.

2. Sections 502(a) and 201(n) of the Act

A drug is misbranded under section 502(a) of the act if its labeling is false or misleading. Section 201(n) of the act defines labeling as misleading if it fails to reveal facts that are material in light of the consequences of the customary or

usual use of the product. Where a drug is widely used in pediatric patients, FDA may consider pediatric use to be "customary." Failure to provide adequate information on dosing and adverse effects in the pediatric population could render the product misbranded, even where the manufacturer does not promote the product for that subpopulation.

3. Section 502(j) of the Act

Section 502(j) of the act defines as misbranded those drugs that are dangerous to health when used in the manner prescribed, recommended, or suggested in their labeling. FDA may consider pediatric use to be "suggested" in a drug's labeling where the drug is indicated for a disease or condition that affects both adults and pediatric patients, unless the drug is specifically contraindicated for pediatric patients. As described earlier in this notice, the absence of pediatric testing and labeling poses risks to children including the risk of unanticipated adverse reactions, and under- and over-dosing.

4. Section 505(k) of the Act

Section 505(k) of the act authorizes FDA to order the holder of an approved NDA to submit reports of data necessary to determine whether there are grounds to withdraw approval of the NDA. FDA has in the past issued regulations under section 505(k) of the act (formerly section 505(j) of the act) requiring postapproval studies of certain drugs (see, e.g., 21 CFR 310.303 ("Continuation of long-term studies, records, and reports on certain drugs for which new drug applications have been approved") (1972); 21 CFR 310.304 ("Drugs that are subjects of approved new drug applications and that require special studies, records, and reports") (1972); and 21 CFR 310.500 ("Digoxin products for oral use; conditions for marketing") (1974)). Section 505(k) of the act also authorizes the agency to require other postmarketing reports on drug products.

5. Section 351 of the Public Health Service Act

Section 351(d) of the PHS Act authorizes FDA to ensure the "continued safety, purity, and potency" of biological products. Section 351(b) of the PHS Act prohibits false labeling of a biological product.

VII. Implementation Plan

All applications for drug and biological products covered by the final rule would be required to contain an assessment of pediatric safety and effectiveness for the claimed

indications, unless the applicant has obtained a waiver or deferral of this requirement from FDA.

FDA proposes that the final rule become effective 90 days after the date of its publication in the Federal Register. For new drug and biologic product applications submitted before the effective date of the final rule, the agency proposes a compliance date of 21 months after the effective date of the final rule. For new drug and biologic product applications submitted on or after the effective date of the final rule, the agency proposes a compliance date of 15 months after the effective date of the final rule. The agency solicits comments on the proposed effective date and proposed compliance dates.

VIII. Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The title, description, and respondent description of the information collection provisions are shown below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions,

searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Pediatric Safety and Effectiveness Reporting Requirements for Certain Drugs and Biological Products.

Description: FDA is proposing reporting requirements that include: (1) Reports on planned pediatric studies in investigational new drug applications (IND's) (proposed § 312.23(a)(10)(iii)); (2) Reports assessing the safety and effectiveness of certain drugs and

biological products for pediatric use in new drug applications (NDA's) and biologic license applications (BLA's) or in supplemental applications (proposed § 314.50(g)(1)); (3) Analyses of data on pediatric safety and effectiveness in NDA's (proposed § 314.50(d)(7)); (4) Postmarketing reports of analyses of data on pediatric safety and effectiveness (proposed § 314.81(b)(2)(vi)(C)); (5) Postmarketing reports on patient exposure to certain marketed drug products, analyzed and age (proposed § 314.81(b)(2)(i)); (6) Postmarketing reports on labeling changes initiated in response to new pediatric data (proposed § 314.81(b)(2)(vi)(C)); and (7) Postmarketing reports on the status of required postapproval studies in pediatric patients (proposed § 314.81(b)(2)(vii)). The purpose of these reporting requirements is to address the lack of adequate pediatric labeling of drugs and biological products by requiring the submission of evidence on pediatric safety and effectiveness for products with clinically significant use in children.

Description of Respondents: Sponsors and manufacturers of drugs and biological products.

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN

CFR section	Number of respondents	Annual frequency per response	Total annual responses	Hours per response	Total hours
201.23	2	1	2	16	32
314.50(d)(7)	150	1	150	8	1,200
314.50(g)(1)	10	1	10	16	160
314.50(g)(2)	9	1	9	8	72
314.50(g)(3)	15	1	15	8	120
314.81(b)(2)(i)	625	1	625	1.5	937.5
314.81(b)(2)(vi)(c)	625	1	625	1.5	937.5
314.81(b)(2)(vii)	625	1	625	1.5	937.5
601.27(a)	1	1	1	16	16
601.27(b)	1	1	1	16	16
601.27(c)	1	1	1	16	16
Total:					4,444.5

There are no capital or operating and maintenance costs associated with this collection of information.

The agency has submitted the information collection provisions of this proposed rule to OMB for review. Interested persons are requested to send comments regarding information collection by September 15, 1997 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.

IX. Environmental Impact

The agency has determined under 21 CFR 25.24 (a)(8), (a)(11), and (e)(6) 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.

X. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order

12866, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act (Pub. L. 104-4). 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). Under the Regulatory Flexibility Act, unless an agency certifies that a rule will not have

a significant economic impact on a substantial number of small entities, the agency must analyze regulatory options that would minimize the impact of the rule on small entities. The Unfunded Mandates Reform Act (Pub. L. 104-4) (in section 202) requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in an annual expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation).

The agency has reviewed this proposed rule and has determined that the proposed rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866, and these two statutes. This proposal is a significant regulatory action as defined by the Executive Order due to the novel policy issues it raises. With respect to the Regulatory Flexibility Act, the Commissioner certifies that the rule will not have a significant economic impact on a substantial number of small entities. Since the proposed rule does not impose any mandates on State, local, or tribal governments, or the private sector that will result in an annual expenditure of \$100,000,000 or more, FDA is not required to perform a cost-benefit analysis according to the Unfunded Mandates Reform Act.

A. Purpose

The FDA is proposing that a limited class of important new drugs and biologicals that are likely to be used in pediatric patients contain sufficient data and information to support directions for this use. As the approved labeling for many of these new products lack relevant pediatric information, any use in children greatly increases the risk of inappropriate dosing, unexpected adverse effects, and suboptimal therapeutic outcomes. The proposed rule is designed to ensure that new drugs, including biological drugs, that are therapeutically important and/or likely to be widely used in children contain adequate pediatric labeling at the time of, or soon after, approval.

B. Number of Affected Products and Required Studies

Neither the precise number of new drugs that would require additional pediatric studies nor the cost of these studies can be predicted with certainty. To develop plausible estimates, FDA examined the pediatric labeling status at time of approval for each NME and important biological approved from 1991 to 1995, and used these estimates to project the cost that would have occurred had the proposed rule been in

place over that period. The agency assumes that future costs would be reasonably similar. As shown in Table 2, each new drug was assigned to one of three categories: (1) Therapeutically important, some potential pediatric use, (2) other approvals, potential for wide pediatric use, and (3) all other approvals. (The first two categories include all products that the agency believes would have met the therapeutic importance and pediatric use threshold criteria set forth in this proposed rule. The third category includes all products that would not have met these criteria.) For NME's, these category assignments were based on pediatric pages completed by CDER's reviewing division at the time of each approval, the priority review designation for each drug, and 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 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.

²IMS, 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.

TABLE 2.—ESTIMATED NUMBER OF NME'S AND BIOLOGICALS APPROVED IN 1991–95

[That Would Have Been Affected by the Proposed Rule]

Pediatric labeling status	Number of approved drugs	Percent of approved drugs
Therapeutically important, some potential pediatric use	47	33
Some pediatric labeling	16	
No pediatric labeling	31	
Other approvals, potential for wide pediatric use	13	9
Some pediatric labeling	7	
No pediatric labeling	6	
Subtotal	60	42
Some pediatric labeling	23	
No pediatric labeling	137	
All other approvals	82	58
Total Approvals	142	100

¹ Pediatric page shows seven ongoing pediatric studies.

In assessing the amount of additional research that would have been required for the 60 drugs from the first two categories (those that would have potentially been affected by the proposed rule), FDA believes that most would not have required extensive additional clinical trials. As FDA explained in the 1994 final rule (59 FR 64240), extrapolations from adult effectiveness data based on pharmacokinetics studies and other safety data can be sufficient to provide the necessary dosing pediatric information for those drugs that work by similar mechanisms in adults and children. The agency estimates that the majority of these 60 drugs could, to some extent, rely on such extrapolations. Although the proposed rule identifies four pediatric subgroups: (1) Neonates, (2) infants, (3) children, and (4) adolescents, the need for studies in more than one age group depends on the likely use of the drug in each age group and on whether relevant data can be extrapolated to other age groups. As a rule, individual clinical trials would rarely be required for each age group for a given drug.

Estimates of the size of the studies that would have been required to support pediatric labeling for these 60 drugs vary from 20 patients where the simplest type of pharmacokinetic study

would be adequate, to 70 to 120 pediatric patients for studies where some safety and effectiveness data would be needed, to several hundred pediatric patients for studies where more substantial safety and effectiveness data would be required. Thus, for the purpose of developing order-of-magnitude cost estimates, FDA further subdivided the 60 potentially affected drugs into three distinct groupings. The first group of 30 drugs would have required the least amount of new data and includes both the 7 drugs for which the CDER pediatric pages indicate that pediatric trials were already underway and the 23 drugs that already had at least some pediatric labeling at the time of approval. Based on a review of those labels at approval time, FDA estimated that up to half, or 15 of these 30 drugs may have needed limited additional data that would have involved new studies with, on average, 50 pediatric patients each.

Next, FDA assumed that 23 drugs (about three quarters of the remaining 30) would have required new pediatric studies with data from about 100 patients each. Finally, FDA assumed that the remaining 7 drugs would have needed more extensive safety and effectiveness data, requiring 300 pediatric patients for each drug. Consequently, FDA estimates that, if this proposed rule had been in effect from 1991 to 1995, sponsors of 45 of the 60 potentially affected drugs would have needed to obtain additional data from about 5,150 pediatric patients (15 drugs $\times$ 50 patients + 23 drugs $\times$ 100 patients + 7 drugs $\times$ 300 patients). The proposed regulation, therefore, would have required additional pediatric research for an estimated average of 9 new drugs and about 1,030 pediatric patients per year.

In addition, the proposed rule permits the agency to request pediatric data for certain drugs that are already marketed. While the precise impact of this regulatory provision is uncertain, FDA expects that it would affect no more than two drugs per year. If the submission for one of these drugs relied on data from 100 pediatric patients and the other from 300 pediatric patients, the total number of drugs that would have required additional research reaches 11 per year and the total number of pediatric patients about 1,430 per year.

Other costs for pediatric research may accrue to drugs that ultimately fail to gain regulatory approval. Although many drug sponsors would wait until they are relatively certain that their product will be shown safe and effective for the indicated use in adults before

spending substantial resources on pediatric uses, other sponsors may need to begin pediatric examinations earlier to have data included with the new drug or product licence application. It is difficult for FDA to judge how much additional pediatric research would be directed towards products that are not approvable. The agency notes, however, that because only about 65 percent of all NME's that enter phase III trials are eventually approved, the number of drugs entering phase III trials is about 54 percent greater than the number of actual approvals ($100/65 = 1.54$). Since some, but not all, of these unapprovable drugs would initiate some pediatric research, FDA has increased its estimate of the annual number of affected drugs and pediatric patients by 30 percent, to a projected total of 14 drugs and about 1,850 pediatric patients per year.

The agency is aware that forecasting future trends based on historical data can be imprecise. For example, over time, even in the absence of this rule, the percentage of new drugs with labels that provide adequate pediatric use information could change. At this time, however, FDA is not aware of any marked trend. Also, the above estimates ignore those pediatric studies that were promised, but not yet underway at the time of drug approval. To the extent that these commitments are honored, the above estimates of research attributable to the regulation are overstated. Finally, the methodology implies that the standards used by FDA to judge the 1991-1995 approvals would remain unchanged. While subsequent change is possible, FDA does not anticipate that its present views would differ substantially. Thus, while acknowledging substantial uncertainty, the agency's cost estimates are based on the assumption that the proposed rule would require additional research on about 14 drugs, involving a total of 1,850 pediatric patients per year.

C. Cost of Studies

The agency finds that the cost of conducting clinical research with pediatric patients varies directly with the size, duration, and complexity of the clinical research. Although FDA has little detailed information on the cost to drug sponsors of conducting research on clinical patients, one private consulting firm reports that the costs of hiring clinical investigators to conduct phase IV pediatric drug trials ranges from \$300-\$500 per patient for studies on vaccines or fevers to \$3,600 and \$5,000 per patient for renal disease and epilepsy, respectively.³ Similarly, a

number of academic researchers have reported average costs of from \$1,500 to \$3,400 per patient for pediatric trials. These estimates, however, do not account for the many administrative, monitoring, data analysis, and document preparation tasks that would be required of a drug sponsor. Since a published study suggests that a total accounting of all sponsor costs may be three times as great as investigator costs,⁴ FDA has assumed that the average costs of conducting the newly required studies would range from \$5,000 to \$9,000 per pediatric patient. As a result, the estimated 1,850 additional pediatric patients that would need to be studied annually suggests new research costs to the pharmaceutical industry of between \$9.25 million and \$16.65 million per year.

In addition, the testing of a new drug in children would sometimes require the development of a new pediatric dosage form. (Typically a liquid or suspension formulation in place of a tablet or capsule.) Of the 47 drugs identified in the first category of Table 2 (therapeutically important with some potential pediatric use), 14 (30 percent) were available only in tablets or hard capsules at the time of approval. (Manufacturers of 4 of these 14 have since developed oral suspensions.) It seems reasonable, therefore, to assume that, of the 14 new drugs per year estimated to require additional pediatric research, about 4 might require new formulations. The agency solicits comment on the estimate that four new formulations would be required per year.

The effort and cost of developing such formulations could be substantial. Drug developers and manufacturers would have to find appropriate solvents and develop additional data for demonstrating adequate product stability, bioavailability, and production process validation. While such costs would vary with the particular drug type, one industry consultant suggests that per drug laboratory costs could average from \$300,000 to \$500,000 and corresponding regulatory requirements could bring this figure close to \$1 million. Moreover, this estimate assumes the availability of adequate preclinical data on animal toxicity and metabolic rates. Since the proposed rule permits FDA to waive the requirement for reformulation where reasonable attempts have failed, the agency assumes that the additional costs would not exceed \$1 million apiece for 4

³DataEdge, LLC, Faxed data, March 7, 1997.

⁴Thomas Hill, "Calculating the Cost of Clinical Research," *Scrip Magazine*, p. 29, March 1994.

drugs, or an additional \$4 million per year.

Finally, the rule will impose additional paperwork burdens related to new label content, postmarket reporting requirements, and written requests for deferred submissions and waivers. As shown above, FDA estimates that these paperwork activities will require about 4,400 hours annually. At an average compensation rate of \$50 an hour, this cost amounts to about \$220,000 per year.

In sum, FDA anticipates that the annual costs of this proposed rule will total between \$13.5 and \$20.9 million per year.

D. Other Impacts

Other potential impacts would occur if the requirements contributed to delays in the submittal of NDA's. Extended drug development times would be associated with significant additional industry costs. FDA has attempted to minimize the likelihood of regulatory delays through plans for early consultation with drug sponsors and a willingness to consider deferred submissions for pediatric studies. However, the agency recognizes the importance of this issue and solicits public comment on the best means to obtain adequate and timely pediatric information without slowing the process for bringing new drugs to market. Also, as noted earlier in this preamble, the agency is aware that new pediatric supplements could impose additional user fees on drug sponsors and is considering means to alleviate this added burden. All user fee issues will be resolved before issuance of the final rule. Overall, therefore, compared to the hundreds of millions of dollars typically required to bring a new drug to market, FDA believes that the added regulatory impact imposed by this rule would be unlikely to threaten the economic viability of any promising research and development project.

E. Benefits

This proposed rule is aimed at addressing two problems associated with inadequate directions for pediatric uses of drugs: (1) Avoidable adverse drug reactions in children, i.e., drug reactions that occur because of the use of inadvertent drug overdoses or other drug administration problems that could have been avoided with better information on appropriate pediatric use; and (2) undertreatment of children with a potentially safe and effective drug, because the physician either prescribed an inadequate dosage or regimen, prescribed a less effective drug, or did not prescribe a drug, due

to the physician's uncertainty about whether the drug or the dose was safe and effective in children. Thus, the primary benefits expected from this proposed rule are the reductions in avoidable adverse drug reactions and undertreatments that would result from better informing physicians about whether, and in what dosages, a given drug was safe and effective for use in children.

FDA is aware of no systematic data in the literature that evaluate the magnitude of harm that results from inadequate information on the use of drugs in children, although numerous anecdotes and case examples exist. Physicians who care for HIV-infected children, for example, have expressed frustration at their inability to treat these children with drugs known to be effective in adults, because they lack information on how to do so safely or effectively.⁵ As mentioned previously in this preamble, history is replete with examples of children who have died or suffered other serious adverse effects as a result of the use of drugs that have not been tested in children and for which better, alternative treatments were available. Many of these adverse events (e.g., "gray baby syndrome" in babies treated with chloramphenicol) develop quickly and would be detected in early clinical studies.

While FDA could not develop a quantitative estimate of the potential benefits of the proposed rule, the agency attempted to gain some more systematic insight into the benefits that might accrue by examining the rate at which each of 20 NME's (approved between 1991 and 1995) were mentioned in the 1996 IMS National Drug and Therapeutics Index (an outpatient drug use data base). The drugs examined were all of those that could be analyzed in this IMS data base, lack full pediatric labeling, were considered to need further pediatric studies at the time of approval, and would have been affected by the proposed rule. FDA found that, after adjusting for the prevalence of the relevant diagnoses in children and adults, 15 of the 20 drugs were mentioned less frequently in association with pediatric treatments than with adult treatments for the same set of approved indications. In 11 of these 15 drugs, pediatric treatment mentions were less than half as frequent. Although it is not possible to conclude, based on these data, that children with those diagnoses are necessarily undertreated relative to adults, these data are consistent with the hypothesis

that the lack of pediatric labeling leads to suboptimal treatment of children.

FDA also examined the number of adverse drug events (ADE's) reported to the agency from 1991 through 1996 for all NME's approved during that time. Of the 25 NME's associated with the highest number of ADE's in children, 8 NME's (responsible for 1,273 pediatric ADE's sufficiently severe to be reported to FDA) had no labeling for use in children at all. An additional 5 NME's (responsible for 434 pediatric ADE's) were labeled for use only in children age 12 and over. Furthermore, of these 13 NME's, 11 would probably have been required to be the subject of further pediatric studies (or of a justification for the lack of studies) under the conditions of this proposed rule if it had been in place at the time of the drug's approval. While it is not possible to conclude that all (or even most) of these ADE's would have been avoided had these drugs been fully labeled for pediatric use, these data confirm that there is substantial pediatric use of drugs not labeled for such use; that this use is associated with ADE's, including serious ADE's; and that the improved knowledge and labeling that would result from this proposed rule could bring significant benefits to children treated with these drugs. The agency solicits information on any available studies or data related to the incidence and costs of either undertreatment or avoidable ADE's in pediatric age groups due to the lack of information on the effects of pharmaceuticals.

F. Small Entities

FDA believes that this proposed rule will not have a significant economic impact on a substantial number of small entities. New drug development is typically an activity completed by large multinational drug firms. FDA reviewed the size of every company that submitted the 60 new drug and biological applications that would likely have been affected by this rule between 1991 and 1995 (see the first two categories in Table 1). Over this 5-year period, only two were for products sponsored by small businesses as defined by the Small Business Administration. Because so few small firms are likely to be significantly affected in any given year, the Commissioner certifies that this rule will not have a significant economic impact on a substantial number of small entities. Therefore, no further analysis is required under the Regulatory Flexibility Act. The agency notes, however, that where pediatric use qualifies as an orphan indication, some of these added research costs could be

⁵ Time, March 1997.

reimbursed under the various grant and tax deduction provisions of the Orphan Drug Act.

XI. Request for Comments

Interested persons may, on or before November 13, 1997, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday. Submit written comments on the information collection provisions 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.

XII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Committee on Drugs, American Academy of Pediatrics, Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations, *Pediatrics*, 95(2):286-294, 1995.

2. Pina, L. M., Drugs widely used off label in pediatrics, Report of the pediatric use survey working group of the pediatric subcommittee. Draft.

3. Cote, C. J. et al., "Is the therapeutic orphan about to be adopted?" *Pediatrics*, 98(1):118-123, 1996.

4. Koren, G. et al., "Unexpected alterations in fentanyl pharmacokinetics in pediatric patients undergoing cardiac surgery: age related or disease related?" *Developmental Pharmacology Therapeutics*, 9:183-191, 1986.

5. Gauntlett, I. S. et al., "Pharmacokinetics of fentanyl in neonatal humans and lambs: Effects of age," *Anesthesiology*, 69:683-687, 1988.

6. Powell, D. A. et al., "Chloramphenicol: New perspectives on an old drug," *Drug Intelligences & Clinical Pharmacy*, 16:295-300, 1982.

7. Oski, F. A. et al., *Principles and Practice of Pediatrics*, 2d Edition, J. B. Lippincott Co., Philadelphia, p. 864, 1994.

8. Nathan, D. G. et al., *Hematology of Infancy and Childhood*, 4th Edition, W. B. Saunders Co., Philadelphia, p. 92, 1993.

9. Kauffman, R. E., "Fentanyl, fads, and folly: who will adopt the therapeutic orphans?" *Journal of Pediatrics*, 119:588-589, 1991.

10. McCloskey, J. J. et al., "Bupivacaine toxicity secondary to continuous caudal epidural infusion in pediatric patients," *Anesthesia and Analgesia*, 75:287-290, 1992.

11. Fisher, D. M. et al., "Neuromuscular effects of vecuronium (ORG NC45) in infants and pediatric patients during N₂O halothane anesthesia," *Anesthesiology*, 58:519-523, 1983.

12. Agarwal, R. et al., "Seizures occurring in pediatric patients receiving continuous infusion of bupivacaine," *Anesthesia and Analgesia*, 75:284-286, 1992.

13. Mevorach, D. L. et al., "Bupivacaine toxicity secondary to continuous caudal epidural infusion in pediatric patients," *Anesthesia and Analgesia*, 77:13005-1306, 1993.

14. Editorial: "Cystic fibrosis and colonic strictures," *Journal of Clinical Gastroenterology*, 21(1):2-5, 1995.

15. Oikola, K. T. et al., "A potentially hazardous interaction between erythromycin and midazolam," *Clinical Pharmacology Therapeutics*, 53:298-305, 1993.

16. Hiller, A. et al., "Unconsciousness associated with midazolam and erythromycin," *British Journal of Anaesthesia*, 65:826-828, 1994.

List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, and Safety.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

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, it is proposed that 21 CFR parts 201, 312, 314, and 601 be 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. New § 201.23 is added to subpart A to read as follows:

§ 201.23 Required pediatric studies.

(a) A manufacturer of a drug product, including a biological drug product, that is widely used in pediatric patients, or that is indicated for a very significant or life threatening illness, but whose label does not provide adequate information to support its safe and effective use in pediatric populations for the claimed indications may, in compelling circumstances, be required to submit an application containing data adequate to assess whether the drug product is safe and effective in pediatric populations. The application may be required to contain adequate evidence to support dosage and administration in some or all pediatric subpopulations, including neonates, infants, children, and adolescents, depending upon the known or appropriate use of the drug product in such subpopulations. The applicant may be required to develop a pediatric formulation for a drug product that is indicated for a very significant or life threatening illness for which a pediatric formulation is necessary, unless the manufacturer demonstrates that reasonable attempts to produce a pediatric formulation have failed.

(b) The Food and Drug Administration (FDA) may, by order issued by the Center for Drug Evaluation and Research (CDER) or Center for Biologic Evaluation and Research (CBER) Center Director, after notifying the manufacturer of its intent and offering an opportunity for a written response and a meeting, which may include an advisory committee meeting, require a manufacturer to submit an application containing the information described in paragraph (a) of this section within a time specified in the letter, if FDA finds that:

(1) The drug product is widely used in pediatric populations for the claimed indications and the absence of adequate labeling could pose significant risks to pediatric patients; or

(2) The drug product is indicated for a very significant or life threatening illness, but additional dosing or safety information is needed to permit its safe and effective use in pediatric patients.

(c)(1) FDA may grant a full or partial waiver of the requirements of paragraph (a) of this section on its own initiative or at the request of an applicant.

(2) An applicant may request a full waiver of the requirements of paragraph (a) of this section if the applicant certifies that:

(i) Necessary studies are impossible or highly impractical, e.g., because the number of such patients is so small or geographically dispersed; or

(ii) There is evidence strongly suggesting that the drug product would

be ineffective or unsafe in all pediatric age groups.

(3) An applicant may request a partial waiver of the requirements of paragraph (a) of this section with respect to a specified pediatric age group, if the applicant certifies that:

(i) The drug product:

(A) Is not indicated for a very significant or life threatening illness; and

(B) Is not likely to be used in a substantial number of patients in that age group; or

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed; or

(iii) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in that age group; or

(iv) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(4) The request for a waiver must provide an adequate justification.

(5) FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver specified in paragraph (c)(2) or (c)(3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

(d) If a manufacturer fails to submit a supplemental application containing the evidence described in paragraph (a) of this section within the time specified by FDA, and the Center Director of CDER or CBER, under the requirements of paragraph (c) of this section, has not granted a waiver, the drug product may be considered misbranded or an unapproved new drug.

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

3. The authority citation for 21 CFR part 312 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371); sec. 351 of the Public Health Service Act (42 U.S.C. 262).

4. Section 312.23 is amended by redesignating paragraph (a)(10)(iii) as paragraph (a)(10)(iv) and adding new paragraph (a)(10)(iii) to read as follows:

§ 312.23 IND content and format.

(a) * * *

(10) * * *

(iii) *Pediatric studies.* If the drug is a new chemical entity, plans for assessing pediatric safety and effectiveness.

5. Section 312.47 is amended by revising paragraph (b)(1)(i) and the second sentence of paragraph (b)(2) and by adding a new sentence after the fifth sentence to paragraph (b)(1)(v) to read as follows:

§ 312.47 Meetings.

* * * * *

(b) * * *

(1) *End-of-Phase 2 meetings—(i) Purpose.* The purpose of an end-of-phase 2 meeting is to determine the safety of proceeding to phase 3, to evaluate the phase 3 plan and protocols and the adequacy of plans to assess pediatric safety and effectiveness, and to identify any additional information necessary to support a marketing application for the uses under investigation.

* * * * *

(v) *Conduct of meeting.* * * * FDA will also provide its best judgment, at that time, of the pediatric studies that will be required for the drug product and their timing. * * *

(2) *"Pre-NDA" meetings.* * * * The primary purpose of this kind of exchange is to uncover any major unresolved problems, to identify those studies that the sponsor is relying on as adequate and well-controlled to establish the drug's effectiveness, to identify current or planned studies adequate to assess pediatric safety and effectiveness, to acquaint FDA reviewers with the general information to be submitted in the marketing application (including technical information), to discuss appropriate methods for statistical analysis of the data, and to discuss the best approach to the presentation and formatting of data in the marketing application. * * *

* * * * *

6. Section 312.82 is amended by revising the last sentence of paragraph (a) and the second sentence of paragraph (b) to read as follows:

§ 312.82 Early consultation.

* * * * *

(a) *Pre-investigational new drug (IND) meetings.* * * * The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, plans for studying the drug product in pediatric populations, and the best approach for presentation and formatting of data in the IND.

(b) *End-of-phase 1 meetings.* * * * The primary purpose of this meeting is to review and reach agreement on the design of phase 2 controlled clinical trials, with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support a decision on its approvability for marketing, and to discuss the need for, as well as the design and timing of, studies of the drug in pediatric patients. * * *

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

7. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 374, 379e).

8. Section 314.50 is amended in subpart B by redesignating paragraphs (g) through (k) as paragraphs (h) through (l) and by adding new paragraphs (d)(7) and (g) to read as follows:

§ 314.50 Content and format of an application.

* * * * *

(d) * * *

(7) *Pediatric use section.* A section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, and a reference to the full descriptions of such studies provided under paragraphs (d)(3) and (d)(5) of this section.

* * * * *

(g) *Pediatric use information—(1) General requirements.* Except as provided in paragraphs (d)(2) and (d)(3) of this section, each application for a new chemical entity shall contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in pediatric populations, including neonates, infants, children, and adolescents, and to support dosing and administration information for each pediatric subpopulation for which the drug is safe and effective. Where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-

controlled studies in adults based on other information, such as pharmacokinetic studies. Studies may not have to be carried out in each pediatric age group, if data from one age group can be extrapolated to others. Assessments of safety and effectiveness required under this section for a drug product that represents a meaningful therapeutic benefit over existing treatments for pediatric patients must be carried out using appropriate formulations for each age group(s) for which the assessment is required.

(2) *Deferred submission.* FDA may, on its own initiative or at the request of an applicant, defer submission of some or all assessments of safety and effectiveness described in paragraph (g)(1) of this section until after approval of the drug product for use in adults. If an applicant requests deferred submission, the request must provide a certification from the applicant of the grounds for delaying pediatric studies, a description of the planned or ongoing studies, and evidence that the studies are being or will be conducted with due diligence and at the earliest possible time. If FDA determines that there is an adequate justification for temporarily delaying the submission of assessments of pediatric safety and effectiveness, the drug product may be approved for use in adults subject to the requirement that the applicant submit the required assessments within a specified time.

(3) *Waivers.*—(i) FDA may grant a full or partial waiver of the requirements of paragraph (g)(1) of this section on its own initiative or at the request of an applicant.

(ii) An applicant may request a full waiver of the requirements of paragraph (g)(1) of this section if the applicant certifies that:

(A) The drug product:

(1) Does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients; and
(2) Is not likely to be used in a substantial number of pediatric patients; or

(B) Necessary studies are impossible or highly impractical, e.g., because the number of such patients is so small or geographically dispersed; or

(C) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups.

(iii) An applicant may request a partial waiver of the requirements of paragraph (g)(1) of this section with respect to a specified pediatric age group, if the applicant certifies that:

(A) The drug product:

(1) Does not represent a meaningful therapeutic benefit over existing

treatments for pediatric patients in that age group; and

(2) Is not likely to be used in a substantial number of patients in that age group; or

(B) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed; or

(C) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in that age group; or

(D) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(iv) The request for a waiver must provide an adequate justification.

(v) FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver specified in paragraph (g)(2) or (g)(3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

* * * * *

9. Section 314.81 is amended by adding two new sentences at the end of paragraph (b)(2)(i) and a new paragraph (b)(2)(vi)(c) and by revising paragraph (b)(2)(vii) to read as follows:

§ 314.81 Other postmarketing reports.

* * * * *

(b) * * *

(2) * * *

(i) *Summary.* * * * The summary shall briefly state whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) should be provided, including dosage form.

* * * * *

(vi) * * *

(c) Analysis of available safety and efficacy data conducted or obtained by the applicant in the pediatric population and changes proposed in the label based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population should be included.

(vii) *Status reports.* A statement on the current status of any postmarketing studies performed by, or on behalf of, the applicant. The statement shall include the status of postmarketing clinical studies in pediatric populations required or agreed to, e.g., to be initiated, ongoing (with projected completion date), completed (including date), completed and results submitted to the NDA (including date). To facilitate communications between FDA and the applicant, the report may, at the applicant's discretion, also contain a list of any open regulatory business with FDA concerning the drug product subject to the application.

* * * * *

PART 601—LICENSING

10. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 513–516, 518–520, 701, 704, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381); secs. 215, 301, 351, 352 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263); secs. 2–12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451–1461).

11. New § 601.27 is added to subpart C to read as follows:

§ 601.27 Pediatric studies.

(a) *General requirements.* Except as provided in paragraphs (b) and (c) of this section, each application for a new biological product for which the applicant has not previously obtained approval shall contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in pediatric populations, including neonates, infants, children, and adolescents, and to support dosing and administration information for each pediatric subpopulation for which the product is safe and effective. Where the course of the disease and the effects of the product are similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled effectiveness studies in adults, based on other information, such as pharmacokinetic studies. In addition, studies may not have to be carried out in each pediatric age group, if data from one age group can be extrapolated to others. Assessments required under this section for a product that represents a meaningful therapeutic benefit over existing treatments must be carried out using appropriate formulations for the age group(s) for which the assessment is required.

(b) *Deferred submission.* FDA may, on its own initiative or at the request of an applicant, defer submission of some or all assessments of safety and effectiveness described in paragraph (a) of this section until after licensing of the product for use in adults. If an applicant requests deferred submission, the request must provide an adequate justification for delaying pediatric studies, a description of the planned or ongoing studies, and evidence that the studies are being or will be conducted with due diligence and at the earliest possible time. If FDA determines that there is an adequate justification for temporarily delaying the submission of assessments of pediatric safety and effectiveness, the product may be licensed for use in adults subject to the requirement that the applicant submit the required assessments within a specified time.

(c) *Waivers.* (1) FDA may grant a full or partial waiver of the requirements of paragraph (a) of this section on its own initiative or at the request of an applicant.

(2) An applicant may request a full waiver of the requirements of paragraph (a) of this section if:

(i) The product:

(A) Does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and

(B) Is not likely to be used in a substantial number of pediatric patients; or

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed; or

(iii) There is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups.

(3) An applicant may request a partial waiver of the requirements of paragraph (a) of this section with respect to a specified pediatric age group, if:

(i) The product:

(A) Does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and

(B) Is not likely to be used in a substantial number of patients in that age group; or

(ii) Necessary studies are impossible or highly impractical, e.g., because the number of patients in that age group is so small or geographically dispersed; or

(iii) There is evidence strongly suggesting that the product would be

ineffective or unsafe in that age group; or

(iv) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(4) The request for a waiver must provide an adequate justification.

(5) FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver specified in paragraph (c) (2) or (3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

Dated: July 24, 1997.

Michael A. Friedman,

Lead Deputy Commissioner for the Food and Drug Administration.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 97-21646 Filed 8-13-97; 2:00 pm]

BILLING CODE 4160-01-P

Proposed Rules

Federal Register

Vol. 62, No. 189

Tuesday, September 30, 1997

This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 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; Public Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notification of a public meeting.

SUMMARY: The Food and Drug Administration (FDA) is announcing a public meeting to discuss issues related to the agency's proposed rule on regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients. The proposed rule, previously announced in the Federal Register, requested written comments and proposed new regulations requiring pediatric studies of certain new drug and biological products. The purpose of the meeting is to provide experts in the field and interested individuals an opportunity to discuss specific issues raised by the proposed rule. The agency is seeking comment and specific data on the proposed rule.

DATES: The public meeting will be held on October 27, 1997, from 9 a.m. to 6 p.m. Please arrive no later than 8:30 a.m. to allow time for security clearance. Written requests for oral presentations should be received by the agency on or before October 14, 1997. Written comments must be submitted on or before November 13, 1997.

ADDRESSES: The public meeting will be held at the Cohen Bldg., auditorium, 330 C St. SW., Washington, DC. Submit written requests for oral presentations to Lisa Barclay, Office of Policy (HF-22), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. To expedite processing, fax written

requests for oral presentations to 301-594-6777. To ensure timely handling, the outer envelope or facsimile cover sheet should be clearly marked with: Docket No. 97N-0165, "Pediatric Labeling Meeting." ATTN: Lisa Barclay. Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Khyati N. Roberts, Center for Drug Evaluation and Research (HFD-6), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-6779, FAX 301-594-5493, e-mail robertsk@cder.fda.gov, or Elaine C. Esber, Center for Biologics Evaluation and Research (HFM-30), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-0641, FAX 301-827-0644, e-mail esber@1.cber.fda.gov.

SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of August 15, 1997 (62 FR 43900), the agency published a proposed rule for new regulations requiring pediatric studies of certain new drug and biological products. The proposed rule would attempt to partially address a lack of pediatric use information by requiring that manufacturers of a limited class of new drug and 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 already marketed drugs and biologics would also, in compelling circumstances, have to provide such data. The proposed rule is part of a comprehensive effort to increase the number of new drug and biological products with clinically significant use in children that carry adequate labeling for use in that subpopulation.

Because of the importance of ensuring the safety and effectiveness of the medications administered to children and the need to address the absence of pediatric labeling in the most effective manner possible, FDA, in cooperation with the American Academy of Pediatrics, is announcing a public meeting at which recognized experts in the field, members of the

pharmaceutical industry, and other interested parties will have an opportunity to discuss certain issues raised by the proposed rule. FDA will consider information presented and discussed at the meeting and written comments submitted to the Dockets Management Branch in the development of the final rule. There is no fee for this public meeting.

II. Scope of Meeting

The purpose of this meeting is to complement the process for gathering written comments and recommendations on certain issues raised by the proposed rule. The meeting will provide recognized experts in the field, members of the pharmaceutical industry, and other interested parties an opportunity to discuss these issues. The agency is specifically seeking comment and data on the following:

- (1) What should be considered a "substantial number" of pediatric patients?
- (2) Whether the rule should be restricted to new chemical entities, including new (never-before-approved) drugs, antibiotics and biological products, or whether it should be applied more broadly (e.g., to applications for chemical variations of approved products, new indications, new dosage forms or routes of administration)?
- (3) Whether the proposed grounds for waiving the pediatric study requirement are adequate and whether additional grounds may exist?
- (4) What would constitute sufficient data or an adequate pediatric clinical trial? and
- (5) How should dose and safety levels for each of the different pediatric age groups or stages of development be established? Relevant to this issue, the agency solicits comment on special problems associated with studies in neonates and young infants.

III. Requests for Oral Presentations

Persons who wish to participate in the meeting must file a written or facsimile request for oral presentation with the Office of Policy (address and fax numbers above). The request for oral presentation should contain the speaker's name, address, telephone and fax numbers, title, business affiliation, if any, topic, a brief summary of the

presentation, and approximate amount of time requested for the presentation.

The agency requests that persons or groups having similar interests consolidate their presentations and present them through a single representative. Because presentations will be limited to 1 day, the agency may not be able to accommodate all requests for oral presentations. FDA will allocate the time available for the meeting among the persons who properly file requests for oral presentations. If time permits at the conclusion of the meeting, FDA may allow participation from both interested persons attending the meeting who did not submit a written request for an oral presentation and those who requested an opportunity to make a presentation, but, due to the time limitations, were not granted the request.

IV. Requests for Comments

Interested persons may, on or before November 13, 1997, submit written comments to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

V. Special Accommodations

In order to accommodate the need for space or technical support, persons who are planning on using audiovisual equipment during their oral presentations are urged to provide advance notice of their planned attendance to one of the contact persons identified above. If you need special accommodations due to a disability, please contact one of the contact persons listed above at least 7 days in advance.

VI. Transcripts

Transcripts of the meeting may be requested in writing from the Freedom of Information Office (HFI-35), Food and Drug Administration, 5600 Fishers Lane, rm. 12A-16, Rockville, MD 20857, approximately 15 working days after the meeting at a cost of 10 cents per page.

Dated: September 24, 1997.

William K. Hubbard,

*Associate Commissioner for Policy
Coordination.*

[FR Doc. 97-25937 Filed 9-29-97; 8:45 am]

BILLING CODE 4160-01-F

FDA TALK PAPER

Food and Drug Administration
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, MD 20857

FDA Talk Papers are prepared by the Press Office to guide FDA personnel in responding with consistency and accuracy to questions from the public on subjects of current interest. Talk Papers are subject to change as more information becomes available.

T97-46
Sept. 23, 1997

Susan M. Cruzan: 301-827-6242
Broadcast Media: 301-827-3434
Consumer Hotline: 800-532-4440

FDA PROPOSES RULE ON WOMEN IN CLINICAL TRIALS

FDA today proposed a rule that would ensure that women are not excluded from participating in early studies of drugs and biologics to treat life-threatening diseases just because of their reproductive potential. The following may be used to respond to inquiries.

In a notice to be published in tomorrow's Federal Register, the agency is requesting public comment on a proposal that would prevent the routine exclusion of either men or women from clinical studies because of potential risks of toxicity to offspring or reproductive organs.

The proposed rule would permit FDA to place a trial on clinical hold (not allow the study to be conducted or to continue) if a sponsor proposes to exclude or is excluding women from a trial for inappropriate reasons.

FDA's proposal reflects a significant evolution of thought about participation of women of reproductive potential in clinical studies during the past two decades, and is in keeping with the agency's 1993 guideline encouraging women's participation in all phases of clinical trials.

FDA prepared this proposal after the National Task Force on AIDS Drug Development and the Presidential Advisory Council on HIV/AIDS recommended that women with HIV or AIDS, particularly those of reproductive potential, not be excluded from investigational trials intended to study a therapy for a life-threatening disease.

Many of the women who are affected by HIV and AIDS are young women with reproductive potential.

The council's recommendation, along with limited surveys of some applications showing the exclusion of women of reproductive age in some clinical trials, including some trials of drugs for

life-threatening illness, led to today's proposal.

In developing this proposal FDA focused on several important factors:

First, FDA is committed to expanding access to and accelerating approval of new therapies for life-threatening diseases. FDA recognizes that physicians and patients are generally willing to accept greater potential risks or side effects from medical products to treat life-threatening diseases.

Second, FDA believes that patients, including women of reproductive potential, in concert with their partners and doctors, can make their own risk/benefit decision when provided with thorough information about risks and potential benefits by the clinical investigator. The informed consent process, required by law for participation in all studies, provides information intended to describe known and potential risks, including potential risks to the embryo or fetus, should a woman become pregnant.

By encouraging diversity at all stages of a drug's development, FDA hopes that drug sponsors will generate better data about how the drug will affect the populations that will receive it once it is marketed. The agency believes it is important to identify important information about a drug during the investigational phase, such as dosages for different age groups, genders, and racial subgroups, and to use that information to refine labeling information, patient selection, and dose selection.

It is important to note that the proposed rule would not require specific recruitment goals for women, nor would it apply to all clinical trials. For example, it would not apply to:

-- Clinical trials designed to look at healthy volunteers exclusively;

-- trials designed to test drugs for special circumstances, such as in gender specific populations such as drugs for prostate cancer; or

-- trials designed exclusively for men so long as a companion study in women of reproductive potential has been planned or is being conducted.

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**DEPARTMENT OF HEALTH AND
HUMAN SERVICES****Food and Drug Administration****21 CFR Part 312****[Docket No. 97N-0030]****Investigational New Drug Applications;
Proposed Amendment to Clinical Hold
Regulations for Products Intended for
Life-Threatening Diseases****AGENCY:** Food and Drug Administration,
HHS.**ACTION:** Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the provisions of its regulations governing investigational new drug applications (IND's) to permit FDA to place a clinical hold on one or more studies under an IND involving a drug that is intended to treat a life-threatening disease affecting both genders if men or women with reproductive potential who have the disease and are otherwise eligible but are excluded from participation in an

investigation only because of a risk or potential risk of reproductive or developmental toxicity from use of the investigational drug. Women have been excluded in the past from early clinical trials because of a risk or potential risk of reproductive or developmental toxicity. Therefore, the primary goal of this proposed amendment is to ensure that women with reproductive potential who have a life-threatening disease are not automatically excluded in the future for that reason. The proposed rule would not impose requirements to enroll or recruit a specific number of men or women with reproductive potential.

The proposal would implement a recommendation of both the National Task Force on AIDS Drug Development (the AIDS Task Force) and the Presidential Advisory Council on Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS).

DATES: Submit written comments by December 23, 1997. FDA proposes that any final rule that may issue based on this proposal become effective 60 days after its date of publication in the *Federal Register*.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Nancy E. Derr, Center for Drug Evaluation and Research (HFD-5), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5400, FAX 301-594-6197.

SUPPLEMENTARY INFORMATION:

I. Introduction

On January 19, 1995, the AIDS Task Force made a series of recommendations related to women's participation in the drug development process, including the recommendation that women with reproductive potential not be excluded from studies of drugs being tested for use against life-threatening diseases, particularly HIV- and AIDS-related diseases. This recommendation was based, in part, on data provided by the HIV Law Project of the AIDS Service Center (Ref. 1). The data demonstrated that participation of women in AIDS clinical drug trials was low.¹

¹ As of January 1992, 14,799 participants were enrolled in U.S. AIDS Clinical Trial Group studies sponsored by the National Institute of Allergy and Infectious Diseases, of whom only 1,151 were adult women. (Pearl, M., et al., "Women in U.S. Government Clinical Trials," VIII International Conference on AIDS, 8(2): B235, 1992.)

In 1993, 21,598 participants were enrolled, while only 1,952 were adult women. (Korrick, J.A.,

In the view of members of the AIDS Task Force, this low rate of participation raised doubts as to whether a sufficient number of women were being included in these clinical trials to provide clinically meaningful information about the effects of HIV and AIDS drugs in the women who would be using them. These data also raised questions and concerns among women with HIV regarding their ability to participate in trials for promising new experimental therapies. On December 8, 1995, the Presidential Advisory Council on HIV/AIDS adopted the AIDS Task Force's recommendation that FDA amend its regulations to prevent the exclusion of women who have a life-threatening disease from any phase of clinical investigations for that disease because of their reproductive potential. If adopted, this proposed rule would implement that recommendation.

FDA's policies regarding the participation of women in clinical investigations have evolved over time. The agency now believes it is important to codify its policies regarding the participation of women with reproductive potential in clinical investigations of drug products intended to treat life-threatening diseases. The proposed amendments to the clinical hold regulations address the exclusion from clinical trials of members of either gender who have a life-threatening disease. The primary intent, however, is to ensure that women who have a life-threatening disease are not automatically excluded from investigational trials of drug products for that disease due to a perceived risk or potential risk of reproductive or developmental toxicity from the use of the investigational drug. The proposal would not apply to clinical studies conducted: (1) Exclusively in healthy volunteers; (2) under special circumstances, such as studies of a single-gender population (e.g., studies evaluating the excretion of a drug in semen or its effects on menstrual function); or (3) in men, as long as a study that does not exclude subjects with reproductive potential has been planned or is being conducted in women. For the purposes of this rulemaking, FDA does not intend the phrase "women with reproductive potential" to include pregnant women. The agency acknowledges the need for more information on the safety and effectiveness of drugs and biological products in pregnant women and is

continuing to explore this complex issue in other forums.

II. Clinical Hold Regulations

A clinical hold is an order, under § 312.42 (21 CFR 312.42), that FDA may issue to a sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation for the development of a new drug, antibiotic drug, or biological product. A clinical hold may apply to one or more of the investigations under an IND. When FDA places a proposed study on clinical hold, subjects in that study may not be given the investigational drug. When FDA places an ongoing study on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; subjects already in the study should be taken off the therapy involving the investigational drug unless FDA specifically permits continuation of the therapy in the interest of patient safety.

FDA may place a clinical hold on a proposed or ongoing phase 1, phase 2, or phase 3 investigation (§ 312.42(b)(1) and (b)(2)), a proposed or ongoing treatment IND or treatment protocol (§ 312.42(b)(3)), or any investigation that is not designed to be adequate and well controlled (§ 312.42(b)(4)). Generally, FDA will attempt to discuss and resolve the matter with the sponsor before issuing a clinical hold order unless subjects are exposed to immediate and serious risk (§ 312.42(c)). When the deficiency that prompts a clinical hold is corrected by the sponsor, the investigation generally may resume (§ 312.42(e)).

III. Evolution of FDA Policy Regarding Participation of Women in Clinical Investigations

Although the proposed amendments to the clinical hold regulations address the exclusion from trials for drug products to treat a life-threatening disease of members of either gender who have the disease, the primary intent of the proposed amendments is to ensure that women who have a life-threatening disease are not excluded from clinical trials solely because of their reproductive potential. Since 1977, when FDA first issued guidance on the participation of women in clinical trials, women with reproductive potential often have been excluded from early clinical trials due to the perceived risk or potential risk of reproductive or developmental toxicity. As the following discussion shows, however, views on the participation of women, as well as corresponding FDA guidance and regulations pertaining to clinical trials of investigational drugs, reflect a

"Trends in Federally Sponsored Clinical Trials," *Until the Cure: Caring for Women With HIV*, A. Kurth, editor, pp. 94-103, 1993).

significant evolution of thought during the past two decades within the agency and the scientific community. In addition, during this period considerable public attention has been paid to questions about the participation of women in general in clinical trials. The following background information highlights key FDA statements on the inclusion of women, especially women with reproductive potential, in the clinical drug testing process. Throughout, the phrase "reproductive toxicity" refers to toxicities to reproductive organs, while the term "developmental toxicity" refers to toxicities to potential offspring.

The agency first provided formal guidance on the participation of women with reproductive potential in clinical trials in a 1977 guideline entitled "General Considerations for the Clinical Evaluation of Drugs" (the 1977 guideline). Developed within the protective environment brought on by the thalidomide experience a decade earlier, the 1977 guideline stated that women of childbearing potential should not be included in phase 1 and early phase 2 trials because of the potential for reproductive or developmental toxicity. Women with childbearing potential could be included in later phase 2 and phase 3 studies, as long as animal teratogenicity and the female part of animal fertility studies had been completed and there was some evidence of effectiveness from earlier studies. The 1977 guideline made an exception to this recommendation for early trials involving drug products intended to treat life-threatening diseases, even in the absence of adequate reproduction studies in animals. Despite this exception, however, the exclusion of women of reproductive potential from early trials was in some cases applied to trials for drug products to treat life-threatening diseases.

Since the 1977 guideline was issued, views have evolved about the participation of women in clinical trials. Views also have evolved about informed individuals assuming the risks of investigational products. Recognition has increased in the agency and among the public that patients, especially those with a life-threatening disease, are willing to accept considerable risks to participate in studies that may benefit them. There is increased public recognition of ethical issues such as fairness and an individual patient's ability to participate in decisions that involve personal risk. There is growing understanding that information about population subgroups, e.g., subsets grouped by age, gender, or race, is needed to evaluate the safety and

effectiveness of therapies and to refine labeling, patient selection, and dose selection in those groups. Failure to obtain such information may limit the usefulness of a treatment or expose a segment of the population to risk. These perspectives have influenced FDA policy since the early 1980's.

In the **Federal Register** of July 22, 1993 (58 FR 39406), FDA issued a "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs" (the 1993 guideline). That guideline revoked the 1977 guideline's recommendation regarding restrictions on the participation of women with reproductive potential in early clinical trials, including clinical pharmacology studies (e.g., dose tolerance, bioavailability, and mechanism of action studies) and early therapeutic studies. The 1993 guideline left the determination about whether the risks and benefits support the participation of women with reproductive potential to patients, investigators, sponsors, and institutional review boards (IRB's).

Although the 1993 guideline does not require participation of women in any particular trial, it sets forth FDA's general expectations regarding the inclusion of both women and men in drug development, analyses of clinical data by gender, assessment of potential pharmacokinetic differences between genders, and conduct of specific additional studies in women, where indicated. The 1993 guideline is consistent with an earlier guideline, issued in 1988 and entitled, "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications" published in the **Federal Register** of October 7, 1988 (53 FR 39524), in which FDA advised that new drug applications (NDA's) should include analyses of data for population subsets, including age, gender, and race, to identify subgroup differences in effectiveness and adverse reactions to investigational drugs. The 1993 guideline notes that participants in clinical studies should, in general, reflect the population that will receive the drug once it is marketed and encourages the participation of women, whether or not they have a serious disease, in early phases of all clinical trials. It points out that including women early is particularly important when a drug is intended for a serious disease and may become available rapidly, for example, through distribution under a treatment IND (§§ 312.34 and 312.35 (21 CFR 312.34 and 312.35)), or marketing under subpart E of part 601 (21 CFR part 601) and consisting of §§ 601.40 through

601.46 or subpart H of part 314 (21 CFR part 314) and consisting of §§ 314.500 through 314.560. (See section IV.A. of this document for a description of these procedures.)

FDA has long recognized the importance of gender data in evaluating the safety and efficacy of a drug. This is reflected in other FDA guidances issued in 1993 ("New Drug Evaluation Guidance Document: Refusal to File" and "Center for Biologics Evaluation and Research (CBER): Refusal to File (RTF) Guidance for Product License Applications (PLA's) and Establishment License Applications (ELA's)" (58 FR 38770, July 20, 1993). These documents state that FDA may refuse to file an application if it contains inadequate evaluation of the safety and/or effectiveness of a drug, biological therapeutic, or vaccine in specific populations, such as in women, intended to use the product.

FDA also recently proposed a rule that would codify expectations regarding presentation in NDA's of safety and effectiveness data by gender as described in the 1993 guideline. Although it would not require the inclusion of women with reproductive potential in clinical investigations, the rule would require the presentation in NDA's of certain data by specific population subgroups, including women, who are likely to receive the drug once it is marketed (60 FR 46794, September 8, 1995).

The 1977 guideline never recommended excluding women with reproductive potential from trials for drugs to treat life-threatening diseases. Moreover, the 1993 guideline recommended that the exclusion of such women be removed from all trials. Nevertheless, a recent limited agency review of clinical trial protocols dealing with antiviral drugs revealed that women with reproductive potential are still being excluded from some protocols of some investigational trials for drug products intended to treat HIV, a life-threatening disease. The agency believes that this violates ethical principles and in some cases could lead to inadequate data on use in women prior to wide availability of the drug. The agency has concluded that women with reproductive potential who have a life-threatening disease should no longer be excluded from investigational clinical trials for drug products to treat that disease because of a risk or potential risk of reproductive or developmental toxicity from use of the investigational drug, as long as patient volunteers are fully informed of the risks, in compliance with informed

consent regulations in part 50 (21 CFR part 50).

IV. Rationale for the Proposed Rule

In the past, women with a life-threatening disease who have reproductive potential often have been excluded from early investigational clinical trials for that disease because of the potential risk of reproductive or developmental toxicity. As a result, although it applies to the exclusion of either gender, the primary goal of this proposed rule is to ensure that women who have a life-threatening disease are not excluded from investigational drug studies for that disease because of their reproductive potential.

In lengthy discussions with representatives of industry and the public during the development of this proposal (Ref. 2), the view was expressed that many early clinical studies involving life-threatening diseases offer the potential for therapeutic benefit. In some cases, for example, participation in an early clinical study is a prerequisite for enrollment in later studies. Based on these discussions, FDA has concluded that all trials involving patients with life-threatening diseases should, for purposes of this proposed rule, be considered to have therapeutic potential and that this proposal would apply to studies in any phase of a clinical investigation that enroll participants with a life-threatening disease.

In developing this proposal, FDA focused on four important factors: (1) FDA is committed to expanding access to and accelerating approval of new therapies for life-threatening diseases; (2) important ethical principles underlie the belief that neither gender should be excluded from early clinical trials involving a life-threatening disease because of their reproductive potential; (3) the mechanisms are in place, or are available, to protect individuals who participate in clinical trials from potential risks; and (4) FDA is committed to expanding the collection of gender-specific data on investigational therapies, especially for those populations who ultimately will be using the therapies. These four factors are discussed in detail in the following sections of this document.

A. Expanding Access and Accelerating Approval

FDA is committed to expanded patient access to potentially beneficial therapies for life-threatening and serious diseases, such as cancer and AIDS, through the IND process. Mechanisms for expanding access include treatment IND's (§§ 312.34 and 312.35), parallel

track protocols (57 FR 13250, April 15, 1992), and other open-label protocols either for groups of patients or for one patient. Tens of thousands of patients have received promising pharmaceuticals under expanded access mechanisms.

In many cases, the risk-benefit assessment for investigational drugs for life-threatening or even serious diseases differs from that for investigational drugs for treating diseases not considered life-threatening or serious. In establishing procedures for the investigation of drugs for life-threatening diseases, FDA has recognized that physicians and patients are generally willing to accept greater risks or side effects from these medical products than they would accept from products that treat less serious diseases (53 FR 41516 at 41518, October 21, 1988).

FDA also is committed to expediting the approval of investigational drugs for treatment of life-threatening and serious diseases. The agency has issued regulations for the expedited development of new therapies intended to treat persons with life-threatening or severely debilitating diseases (subpart E of part 312 (21 CFR part 312) procedures in §§ 312.80 through 312.88), especially where no satisfactory alternative therapies exist. In addition, FDA has issued regulations for the accelerated approval of certain new drugs (subpart H of part 314 procedures in §§ 314.500 through 314.560) and biological products (subpart E of part 601 procedures in §§ 601.40 through 601.46) for serious or life-threatening diseases. For instance, accelerated approval can be based on a surrogate endpoint that reasonably suggests clinical benefit or on evidence of the drug's effect on a clinical endpoint other than survival or irreversible morbidity. On March 29, 1996, President Clinton announced a major initiative undertaken by FDA to make promising new therapies available sooner to American cancer patients with intractable or unresponsive malignancies. Under this initiative, FDA proposes, among other things, to shorten approval times for cancer treatments by recognizing that tumor shrinkage is often an early indication of a treatment's effectiveness and by basing approval of investigational drugs for refractory tumors on evidence of tumor shrinkage.

In view of the agency's commitment to provide expanded access to and accelerated approval of new therapies for life-threatening and serious diseases, this proposed rule is intended to ensure that women with reproductive potential who have a life-threatening disease are not excluded from volunteering for and

being included in clinical investigational trials for drug products intended to treat their disease. Although a risk or potential risk of reproductive or developmental toxicity might exist, FDA recognizes that the potential benefits that may be accrued by these women from participation in a study for their disease may outweigh such risks and that the availability of certain safeguards can reduce these risks. (See section IV.C. of this document for a discussion regarding minimizing risks.)

B. Ethical Principles

In developing this proposal, FDA has carefully considered the evolution of thought within the agency and the scientific community and among the public regarding the participation of women in clinical trials and the related risks or potential risks. The agency also has considered the basic ethical principles that underlie clinical research. Current FDA and Department of Health and Human Services regulations related to informed consent and IRB's are based, in large part, on the three ethical principles relevant to human subject research discussed in the Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the Belmont Report) (44 FR 23192, April 18, 1979). These principles include respect for persons, beneficence, and justice.

The principle of respect for persons usually is cited within the context of being certain that individuals are included in clinical research voluntarily after being fully informed. The principle recognizes the ability of autonomous individuals to make their own decisions about participating in clinical research.

The principle of beneficence requires that the risks associated with a clinical research activity be reasonable in the light of expected benefits. Beneficence also requires that the chance for benefits from participation be maximized, and the risk of possible harms be minimized, consistent with sound research design. In weighing risks and benefits, beneficence also recognizes the results of research as a potential benefit, so long as the rights of research participants are protected.

The principle of justice requires that the burdens and benefits of participation in clinical research be equitably distributed across the entire population in the place or region where the clinical research is conducted. In general, racial, ethnic, gender, and economic status should not be used as a basis for excluding participation in clinical research. Furthermore, persons who are eligible for participation in the

clinical research because of their disease or condition should be provided a reasonable opportunity to be included in the research until the research cohort is fully recruited.

An Institute of Medicine committee recently examined the issue of women in health research (Ref. 3). As part of their deliberations, they highlighted the ethical principle of justice and recommended that the scientific community and the institutions that support it ensure that scientific advances in medicine and public health fairly benefit all people, regardless of gender, race, ethnicity, or age. The committee concluded that clinical trials should be conducted consistent with the principle that medical research promotes the health and well-being of both women and men. This proposed rule would help achieve that goal by ensuring that women with a life-threatening disease are not denied the opportunity to contribute to the body of scientific knowledge about their disease and its manifestations in women.

The proposed rule is consistent with the three ethical principles in the Belmont Report and would help to ensure that women with reproductive potential who suffer from a life-threatening disease are no longer excluded from early clinical research.

C. Informed Consent and Other Mechanisms for Protecting People With a Life-Threatening Disease in Early Clinical Trials

A number of mechanisms are in place to protect participants in early clinical trials, including requirements for sound study design, the use of sound research procedures, and the proper use of the informed consent process. In addition to the sponsors, who have the responsibility of designing safe clinical trials, and the investigators, who carry them out, institutional review boards (IRB's) play an important role in ensuring participant safety in clinical trials. It is the responsibility of the involved IRB to determine that specific criteria for the protection of study participants are met before approving research subject to the IND regulations (§ 56.111(a) (21 CFR 56.111(a))). For example, the IRB must determine that risks to study participants are minimized by the use of procedures consistent with sound research design and that risks to study participants are reasonable in relation to anticipated benefits (§ 56.111(a)(1) and (a)(2)). The IRB also is responsible for ensuring that information given to study participants as part of the informed consent process is in accordance with FDA's regulations under part 50 (see § 56.111(a)(4)).

Elements of informed consent require that potential study participants be adequately informed that the study involves research (§ 50.25(a)(1)) and of any foreseeable risks or discomforts (§ 50.25(a)(2)). In addition, prospective study participants must be informed, when appropriate, of certain unforeseeable risks, including potential risks to the embryo or fetus, should a female study participant become pregnant (§ 50.25(b)(1)). As FDA noted in the 1993 guideline, if animal reproductive toxicity studies are complete, the results and an explanation of their significance in humans should be presented as part of the informed consent process (58 FR 39406 at 39411). If these studies are not complete, that fact should be communicated along with any other pertinent information, such as a general assessment of reproductive and fetal toxicity associated with other drugs that have related chemical structures or pharmacological effects. If no relevant information is available, the informed consent should explicitly state that fact and make clear that the potential exists for reproductive risks and/or developmental risks to a fetus. If needed, the IRB should require that a specific period of time lapse between when the potential study participants receive relevant information and when they must decide whether to participate in the study. If in the IRB's judgment, additional information to that required by § 50.25 would add meaningfully to the protection of the rights and welfare of study participants, the IRB may require the imparting of that information to the study participants (21 CFR 56.109(b)).

It is also the responsibility of the IRB to determine that the study is designed in such a way as to minimize the risk of fetal exposure to possibly harmful agents. Developmental toxicity has been linked to maternal exposure to certain drugs. Although a link between paternal drug exposure and developmental toxicity has not been conclusively established, results of some studies suggest that paternal exposure to certain drugs might be associated with developmental toxicity (Ref. 4). In particular, low-level, chronic genotoxic exposures that maintain fertility might lead to fetal developmental abnormalities, particularly when there is exposure of post-stem cell stages of spermatozoal development. Although the agency has not issued formal guidance on this issue, in such cases, it might be prudent to take precautions to prevent impregnation of women by men

participating in such investigational studies.

The risk of fetal exposure can be eliminated by preventing pregnancy (except in those studies designed to test a drug's effect during pregnancy). The risk of fetal exposure also can be minimized by sponsors and IRB's, who can require the use of pregnancy testing to detect unsuspected pregnancy prior to initiation of study treatment or at intervals during the course of drug exposure. When the study design permits, sponsors can minimize potential developmental risks by short-term timing of studies to coincide with the early follicular phase of the menstrual cycle. Thus, in most of these short-term studies, the investigational agent would be eliminated from a woman's body prior to conception, should she inadvertently become pregnant. When the teratogenic effects of a drug are well established, the agency, sponsor, or IRB may require the use of contraception to prevent pregnancy in sexually active individuals of childbearing potential.

Women and men can eliminate the possibility of pregnancy through abstinence and reduce the possibility of pregnancy through the use of contraception for the duration of drug exposure (which may exceed the length of the study). In part because the cooperation of the individual's sexual partner may be needed to ensure that abstinence occurs, or that appropriate contraceptive methods are used, it is important for potential study participants to be provided with an opportunity to discuss their involvement in a clinical trial with their sexual partner prior to deciding whether to participate in the study.

The agency believes that, through the proper use of the informed consent process and the use of other study design mechanisms, risks to participants in early clinical trials can be reduced. When deciding whether to participate in a clinical trial for an investigational drug, potential participants should be able to weigh, in consultation with their spouse or partner, their health care provider, and their researcher, the potential risks of their participation.

D. Expanding the Collection of Gender-Specific Data

As noted previously, the need for gender specific data was the subject of guidances developed by the agency in 1988 and 1993 and was addressed in a proposed rule issued in 1995. Recently, medical and scientific issues related to gender analyses were the subject of an FDA-sponsored workshop on "Gender Studies in Product Development:

Scientific Issues and Approaches" held from November 6 to 7, 1995 (Ref. 5). Workshop participants, including representatives from industry, academia, government agencies, consumer groups, and patient communities, concluded that women should be included in all stages of drug development to fully characterize the safety and efficacy profile of the product. It was noted by numerous participants that use of gender-specific data from early trials may improve the efficiency of phase 3 trials by aiding in the interpretation of expected variations among gender groups.

In the 1993 guideline, FDA acknowledged that although drugs often behave similarly in demographic (age, gender, race) and other (concomitant disease, concomitant drugs) subsets of the population, there are many differences within such subsets, for example, in dose-response, in maximum size of effect, or in the risk of an adverse effect (58 FR 39406 at 39409). To identify such potential differences and to help refine labeling information, patient selection, and dose selection, the agency believes that it is important that those women who are likely to use an investigational agent once it is marketed be included in clinical investigations that may identify potential gender differences. In the case of HIV and AIDS, many of the women who are affected are young women with reproductive potential. Therefore, early participation by these women in clinical trials for such diseases will help ensure that needed gender-specific safety and effectiveness data are available for the women affected by the disease (Ref. 6).

V. Legal Authority

Section 505(i) (21 U.S.C. 355(i)) of the Federal Food, Drug, and Cosmetic Act (the act) confers broad authority upon the Secretary of Health and Human Services (the Secretary) (and by delegation to FDA) to issue regulations governing the clinical investigation of new drugs to protect the rights, safety, and welfare of human subjects (including through informed consent provisions) and otherwise to protect the public health. In addition, section 701 of the act (21 U.S.C. 371) provides that the Secretary has authority to issue regulations for the efficient enforcement of the act (including the drug-related provisions, such as the misbranding and approval provisions of sections 502 (21 U.S.C. 352) and 505 of the act).

The proposed amendment to the clinical hold regulations is intended to protect human subjects against being categorically excluded, based on reproductive potential, from the

opportunity to participate in clinical trials investigating potentially beneficial treatments for a life-threatening disease. In addition, the proposed amendment would enhance public health protection by expanding opportunities to generate data concerning the safety and efficacy of investigational drugs for the treatment of life-threatening diseases.

The agency believes that prohibiting the exclusion of women with reproductive potential who have a life-threatening disease from clinical trials also is consistent with congressional efforts to prevent unwarranted discrimination against women. In the employment context, for example, the Civil Rights Act of 1964, as amended by the Pregnancy Discrimination Act (42 U.S.C. 2000e(k), 2000e-2(e)(1)) and as interpreted by the U.S. Supreme Court in the landmark case of *International Union, United Automobile, Aerospace and Agricultural Implement Workers, UAW v. Johnson Controls, Inc.*, 111 S.Ct. 1196 (1991), prohibits the exclusion of women with childbearing capacity from jobs they are qualified to perform solely because the working conditions of those jobs pose potential risks to exposed fetuses. Although the Court did not consider or hold that the Civil Rights Act applies to clinical drug trials, which are manifestly different in nature and purpose from private employment, FDA believes it is appropriate to consider the Court's opinion when developing policy on the eligibility of women with reproductive potential for participation in clinical trials for a life-threatening disease.

VI. Description of the Proposed Rule

Current § 312.42(b)(1) identifies the grounds for placing a clinical hold on proposed or ongoing phase 1 studies under an IND, and current § 312.42(b)(2) identifies the grounds for placing a clinical hold on proposed or ongoing phase 2 or phase 3 studies. FDA is proposing to amend §§ 312.42(b)(1) and (b)(2) to provide an additional ground for placing a phase 1, phase 2, or phase 3 study under an IND on clinical hold. Under proposed §§ 312.42(b)(1)(v) and (b)(2)(i), FDA may issue a clinical hold on any proposed or ongoing clinical trial for a life-threatening illness or disease that affects both genders if men or women with reproductive potential who have the disease being studied are excluded from eligibility in any phase of clinical investigation because of a risk or potential risk of reproductive toxicity (i.e., toxicity to reproductive organs) or developmental toxicity (i.e., toxicity to potential offspring) from use of the investigational drug. FDA believes that such risks would be outweighed by the

potential benefits that may be accrued by participants in a study for the treatment of their disease and that fully informed potential participants should be able to make their own risk-benefit determination. FDA also believes that, in the case of developmental toxicity, potential risks can be minimized by the prevention of pregnancy through contraception or abstinence.

The clinical hold under proposed §§ 312.42(b)(1)(v) and (b)(2)(i) would not apply to clinical studies conducted: (1) Exclusively in healthy volunteers; (2) under special circumstances, such as studies of a single-gender population (e.g., studies evaluating the excretion of a drug in semen or its effects on menstrual function); or (3) in men, as long as a study that does not exclude subjects with reproductive potential has been planned or is being conducted in women.

The phrase "women with reproductive potential" as used in the proposed rule does not include pregnant women. The proposed rule also would not impose requirements to enroll or recruit a specific number of men or women with reproductive potential.

As is true for clinical holds on any basis, FDA ordinarily would issue a clinical hold only after attempts to convince the sponsor to remove an exclusion had failed (§ 312.42(c)).

Under proposed § 312.42(b)(1)(v), "life-threatening illnesses or diseases" are defined as "diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted." The proposed definition is consistent with the definition of "life-threatening" in the IND regulations governing drugs intended to treat life-threatening illnesses (21 CFR 312.81(a)(1)).

The proposed definition of life-threatening illnesses or diseases is intended to include those fatal diseases where death itself may not be imminent, but where treatment is necessary to prevent premature death. For example, an anti-retroviral drug might be found, on the basis of phase 2 studies, to delay progression from the asymptomatic state to the symptomatic state and then to AIDS when used early after infection with HIV. Although this progression ordinarily would take more than 12 months to occur in most patients, this condition would be within the definition of life-threatening. Other examples of life-threatening illnesses include cancer, certain cardiac arrhythmias, intracranial hemorrhage, or amyotrophic lateral sclerosis.

The exclusion of subjects with reproductive potential addressed by this proposed rule not only includes explicit

exclusion but also de facto exclusion. For example, a de facto exclusion might result from setting study entry criteria that require sterilization and would have the effect of precluding enrollment of participants with reproductive potential. De facto exclusions also might result from setting criteria that are inherently difficult for subjects to meet, such as weight, or other physical requirements that generally differ between women and men.

VII. Environmental Impact

The agency has determined under 21 CFR 25.30(h) 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. Paperwork Reduction Act of 1995

This proposed rule does not contain any information collection provisions that would be subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).

IX. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601-612). 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 Regulatory Flexibility Act requires agencies to analyze regulatory options if the proposed rule is expected to have a significant impact on a substantial number of small entities.

The Unfunded Mandates Reform Act (Pub. L. 104-4) requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in an annual expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation). This proposed rule does not impose any mandates on State, local, or tribal governments, or the private sector that will result in an annual expenditure of \$100,000,000 or more. The data for the impacts analysis were developed by FDA's Economics Staff, Office of Management and Systems, Office of Planning and Evaluation, and their full

report is on file at the Dockets Management Branch (address above).

A. Costs

Implementation of this proposed rule could impart additional direct costs to the industry in one area—the cost associated with testing for pregnancy in women with reproductive potential who volunteer to participate in clinical trials that would have previously excluded them.

As fully described in its detailed study (Ref. 7), FDA estimated the direct cost in the following manner. Using an FDA protocol database, the agency estimated the number of clinical trials for drug products for life-threatening diseases from which women with reproductive potential are being excluded. The agency then determined the total number of subjects recruited for those clinical trials. Using published information, the agency estimated the relative incidence among women with reproductive potential for the specific life-threatening diseases compared to the incidence in the general population. Using the estimates of relative incidence among women with reproductive potential for the specific disease, it was estimated how many women would be participating in clinical trials for the specific disease, were they not being excluded. Finally, using the approximate length of each phase of clinical trials (phases 1, 2, and 3), the agency calculated the number of pregnancy tests that would be necessary to test for pregnancy in this volunteering population subset.

FDA conducted its analysis using data extracted from the majority of the clinical trial protocols submitted to four review divisions in the Center for Drug Evaluation and Research (CDER) during a 20-month period between August 1, 1993, and March 31, 1995: Cardio-Renal; Anti-Viral; Medical Imaging, Surgical and Dental; and the former Pilot Drug Evaluation. The protocol data base includes information on the phase of the studies (whether they are phase 1, 2, or 3), the planned size of the trials, and the indications for which the therapies are being studied. Data from this data base were analyzed to estimate how many protocols were submitted to these four FDA divisions involving life-threatening illnesses that excluded women with reproductive potential. Forty-three protocols involving life-threatening illnesses and excluding women with reproductive potential were identified as having been submitted to FDA during this 20-month period.

Projecting the number of submissions from the four review divisions across the entire agency required additional analysis because it could not be assumed that all review divisions receive protocols for life-threatening diseases at the same rate. To adjust for the difference from division to division, the agency calculated the number of NDA approvals that were granted in each division for drugs to treat life-threatening and severely debilitating illnesses under the accelerated approval procedures of subpart E of part 312. Using the results of this analysis and the annualized numbers from the four analyzed review divisions, it was possible to calculate approximately how many protocols for life-threatening diseases that exclude women are submitted to individual review divisions each year. It was projected that approximately 62 protocols are submitted to FDA per year for life-threatening diseases that exclude women with reproductive potential.

Next it was assumed that, once they are no longer excluded, women with reproductive potential would enter clinical trials in proportion to the relative incidence of the disease occurrence in that population at diagnosis. Using published data on the relative incidence among women with reproductive potential at diagnosis of AIDS, HIV, and coronary heart disease and the number of protocols submitted to the four divisions projected across the entire agency and annualized, the agency estimated how many women (ages 13 to 49 years) are excluded per year from phase 1, phase 2, and phase 3 clinical studies in the United States. The results showed that approximately 90 women with reproductive potential are excluded from phase 1 studies, 266 from phase 2 studies, and 40 from phase 3 studies annually in the United States.

If one assumes further that phase 1 studies last approximately 2 weeks, phase 2 studies approximately 3 months, and phase 3 studies about a year, the costs for pregnancy testing can be assessed. During phase 1 studies, approximately 1 pregnancy test would be required for each woman with reproductive potential entering the study; during phase 2 studies, approximately 3 tests would be required; and, during phase 3 studies, approximately 12 tests would be required. At a cost of \$30 per test, the annual cost to industry is estimated to be at most about \$41,000. This estimate is summarized in Table 1.

TABLE 1.—ESTIMATED ANNUAL COSTS OF TESTING FOR PREGNANCY IN WOMEN WITH REPRODUCTIVE POTENTIAL IN U.S. CLINICAL TRIALS FOR THERAPIES FOR LIFE-THREATENING ILLNESSES

Study Phase	Tests Required per Woman	Estimated Number of Women Annually	Cost per Test	Annual Costs
1	1	90		
2	3	266	\$30	\$2,700
3	12	40	\$30	\$23,940
Totals		396	\$30	\$14,400
				\$41,040

The largest cost encountered in the 43 analyzed protocols was a phase 2 trial from which an estimated 45 women with reproductive potential were excluded. The cost of pregnancy testing for this trial, if women with reproductive potential had been included, would have been about \$4,050. Of the 43 protocols analyzed, 6 had estimated costs of pregnancy testing exceeding \$1,000.

The agency is aware of industry's concerns about the liability exposure associated with the inclusion of women with reproductive potential in clinical trials, particularly prior to completion of animal reproductive studies. FDA believes, however, that the inclusion in investigational studies of women with reproductive potential who have a life-threatening disease and who have given informed consent is not likely to lead to increased liability. Informed consent means that a study participant has agreed to participate despite recognition and appreciation of known or potential risks, an agreement that should minimize the legal risks associated with drug development. Careful use of study design and informed consent is likely to minimize exposure to liability (Refs. 8 and 9). There is, of course, no way to guarantee this, but there have been few instances of liability assessed against drug manufacturers for the conduct of clinical trials.

As already stated, if a deficiency exists in a clinical investigation that may be grounds for the imposition of a clinical hold, FDA will generally attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order (§ 312.42(c)). An IND would be placed on clinical hold for specifically excluding women with reproductive potential only as a last resort. Only for those few protocols could there be an increase in cost, due primarily to a delay in starting the clinical trials.

The agency believes that the societal benefits more than outweigh the potential minimal additional costs because a considerable patient population (women with reproductive potential who have a life-threatening

disease) could receive a potentially beneficial new therapy.

B. Small Entities

The protocol analysis identified protocols sponsored by small businesses. The largest additional pregnancy testing cost incurred by a small business in the reviewed protocols under the proposed rule was \$990. Projected across all CDER/CBER review divisions and annualized, we expect no more than nine protocol submissions per year from small businesses that might incur additional costs under the proposed rule. Few small firms are likely to be affected in any given year and most of these would incur no significant additional costs. Therefore, under the Regulatory Flexibility Act, the Commissioner of Food and Drugs certifies that this rule will not have a significant effect on a substantial number of small entities.

X. Request for Comments

Interested persons may, on or before December 23, 1997, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

XI. References

Copies of the following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. McGovern, T., "Proposal to Eliminate Obstacles Facing Women in the Drug Development Process: A Recommendation to the National Task Force on AIDS Drug Development," HIV Law Project of the AIDS Service Center, June 30, 1994.

2. Transcript of the meeting of the National Task Force on AIDS Drug Development, October 26, 1994 (see discussion on pp. 25 to 70).

3. Mastroianni, A. C., R. Faden, and D. Federman, editors, *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Vol. 1, National Academy Press, Washington, pp. 75-83, 1994.

4. DeLap, R. J., J. L. Fourcroy, and G. A. Fleming, "Fetal Harm Due to Paternal Drug Exposure: A Potential Issue in Drug Development," *Drug Information Journal*, 30:359-364, 1996.

5. Transcript of the FDA workshop "Gender Studies in Product Development: Scientific Issues and Approaches," November 6-7, 1995.

6. Sherman, L. A., R. Temple, and R. B. Merkatz, "Women in Clinical Trials: An FDA Perspective," *Science*, 269:793-795, 1995.

7. Food and Drug Administration, Office of Management and Systems, Office of Planning and Evaluation, *Impacts of Not Excluding Women with Reproductive Potential Who Have Life-threatening Illnesses from Clinical Trials*, January 10, 1997.

8. Flannery, E., and S. N. Greenberg, "Liability Exposure for Exclusion and Inclusion of Women as Subjects in Clinical Studies," in *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Vol. 2, edited by A. C. Mastroianni, R. Faden, and D. Federman, National Academy Press, Washington, pp. 96-97, 1994.

9. Clayton, E. W., "Liability Exposure When Offspring Are Injured Because of Their Parents' Participation in Clinical Trials," in *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Vol. 2, edited by A. C. Mastroianni, R. Faden, and D. Federman, National Academy Press, Washington, pp. 108-109, 1994.

List of Subjects in 21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

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, it is proposed that 21 CFR part 312 be amended as follows:

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

1. The authority citation for 21 CFR part 312 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug,

and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371); sec. 351 of the Public Health Service Act (42 U.S.C. 262).

2. Section 312.42 is amended by adding new paragraph (b)(1)(v) and by revising paragraph (b)(2)(i) to read as follows:

§ 312.42 Clinical holds and requests for modification.

* * * * *

(b) * * *

(1) * * *

(v) The IND is for the study of an investigational drug intended to treat a life-threatening illness or disease that affects both genders, and men or women with reproductive potential who have the disease being studied are excluded from eligibility in any phase of clinical investigation because of a risk or potential risk of reproductive (i.e., toxicities to reproductive organs) or developmental (i.e., toxicities to potential offspring) toxicity from use of the investigational drug. The phrase "women with reproductive potential" does not include pregnant women. For purposes of this paragraph, "life-threatening illnesses or diseases" are defined as "diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted." The clinical hold would not apply under this paragraph to clinical studies conducted:

(A) Under special circumstances, such as studies of a single-gender population (e.g., studies evaluating the excretion of a drug in semen or the effects on menstrual function); or

(B) In men, as long as a study that does not exclude subjects with reproductive potential has been planned or is being conducted in women.

(2) * * *

(i) Any of the conditions in paragraphs (b)(1)(i) through (b)(1)(v) of this section apply; or

* * * * *

Dated: September 16, 1997.

Michael A. Friedman,

Lead Deputy Commissioner for the Food and Drug Administration.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 97-25268 Filed 9-23-97; 8:45 am]

BILLING CODE 4160-01-F

HHS NEWS

U.S. Department of Health and Human Services

P97-33

FOR IMMEDIATE RELEASE

September 26, 1997

FOOD AND DRUG ADMINISTRATION

Media Press: (301) 827-6242

Broadcast Media: (301) 827-3434

Consumer Hotline: (800) 532-4440

FDA WARNS CONSUMERS ABOUT TWO UNAPPROVED HOME-USE TEST KITS

FDA is advising consumers and pharmacists about two unapproved, fraudulently marketed home-use test kits distributed by Lei-Home Access Care, a division of Jin-Greene Biotechnology, Inc. in Sunnyvale, Calif. One test kit is advertised on the internet as the "Personal HIV Test Kit" and is labeled the "Lei-Home Access HIV Test." The other test kit is labeled as an "In-home Hepatitis A Test Kit." Results from any unapproved tests for home use are unreliable.

The human immunodeficiency virus (HIV) is the virus that causes the disease AIDS. The hepatitis A virus, usually a food-borne illness, causes a mild, rarely serious, liver disease.

FDA is recommending that pharmacists remove any of these unapproved test kits from their stores.

Currently, the only approved HIV home collection system being marketed in the United States is the Home Access HIV-1 Test System (also called the Home Access Express HIV-1 Test System), manufactured by the Home Access Health Corporation, Hoffman Estates, Ill. With this home system, the user mails a dried blood sample obtained from a finger prick to a laboratory for analysis. Confidential, highly accurate test results are obtained by telephone, with a trained counselor available. FDA has not approved a hepatitis A home test kit.

FDA is advising consumers who purchased the "Lei-Home Access HIV Test" or the "In-Home Hepatitis A Test Kit" to consult with a health professional about other available approved tests that detect antibodies to the HIV virus and the hepatitis A virus.

ATTENTION TV BROADCASTERS: Please use open caption for the hearing impaired.

FDA HOME PAGE

Unpasteurized Cider and Juice Can Contain Bacteria That Make Children and Some Other People Sick

People in the
following
high-risk
groups should
drink *only*
pasteurized
cider and juice:

- Children
- Older adults
- People with weakened immune systems, such as those with HIV, AIDS, or cancer.

Some kinds of juice and cider have not been pasteurized and may contain harmful bacteria. Unpasteurized juice and cider may not be labeled with a statement saying they are unpasteurized and warning of the risk of unpasteurized juice.

Frozen concentrate, shelf-stable juice in hermetically sealed containers, and canned juice are processed to eliminate harmful bacteria. Fresh unpasteurized juices normally are found in the groceries' refrigerated sections. Unpasteurized apple cider may also be found at cider mills and farm markets.

Parents of children in day-care centers and schools that serve cider and juice may want to ask if the products are pasteurized. Children on field trips to apple cider mills or farm markets should not drink unpasteurized cider.

If you or someone in your family is in one of the high-risk groups and you cannot determine if a juice product has been processed to destroy harmful bacteria, either don't use the product or bring it to a boil to kill any possible harmful bacteria.

For other food safety information, go to
<http://vm.cfsan.fda.gov/list.html>

FDA

FDA TALK PAPER

Food and Drug Administration

U.S. Department of Health and Human Services

Public Health Service 5600 Fishers Lane Rockville, MD 20857

FDA Talk Papers are prepared by the Press Office to guide FDA personnel in responding with consistency and accuracy to questions from the public on subjects of current interest. Talk Papers are subject to change as more information becomes available.

T97-49
Sept. 29, 1997

Ivy Fleischer Kupec: 301-827-6242
Broadcast Media: 301-827-3434
Consumer Inquiries: 800-532-4440

FDA APPROVES FIRST COMBINATION DRUG FOR AIDS

On Friday, Sept. 26, FDA approved a combination of AZT (zidovudine) and 3TC (lamivudine) for treating AIDS and HIV infection. Combining these two drugs, which are commonly prescribed with one another, into one tablet could decrease the number of pills people with HIV have to take daily. The following can be used to answer questions:

Combivir, as the new drug is called, given twice a day provides an alternative regimen to 150 mg 3TC twice a day plus AZT 600 mg per day in divided doses. This drug form reduces pill intake for these two drugs to two per day instead of up to eight.

AZT and 3TC are members of the nucleoside analogue class of drug compounds, and both interfere with the replication of HIV, the virus that causes AIDS. These drugs are frequently part of the "drug cocktails" used to attack the virus in people with HIV.

Adverse events continue to be those associated with nucleoside analogue drugs: nausea, diarrhea, anemia, low white blood cells, pancreatitis and neuropathy.

AZT has been available for people with AIDS since 1987; 3TC was approved in 1995 for use in combination with AZT.

All three drugs are manufactured and marketed by Glaxo Wellcome of Research Triangle, N.C.

####

FDA HOME PAGE

Liposomal daunorubicin is not recommended in patients with less than advanced HIV-related Kaposi's sarcoma

A recent report [1] described results of a small randomized crossover study that compared liposomal daunorubicin with observation in patients with early Kaposi's sarcoma. Liposomal daunorubicin appeared to delay disease progression by about 8 weeks. Data from this and other studies of liposomal daunorubicin were submitted to the US Food and Drug Administration (FDA) and presented at a public meeting of the FDA Oncologic Drugs Advisory Committee on 8 June 1995. These data included information on survival and the rate of opportunistic infections in this study that were not included in the published report, but are pertinent to the interpretation of the study results.

As described in the report, patients in the study had early Kaposi's sarcoma (< 20 mucocutaneous lesions; no visceral disease) and were randomized to two groups, one to receive liposomal daunorubicin for six cycles (12 weeks) followed by observation off treatment for 12 weeks, the other to be observed off treatment for 12 weeks or until progression occurred, then crossed over to receive six cycles (12 weeks) of liposomal daunorubicin. The study was intended to determine whether liposomal daunorubicin delayed progression of Kaposi's sarcoma, as indicated by the rate of appearance of new lesions or increase in size of existing lesions. According to the study protocol,

accrual of 40 patients (20 per arm) was planned, but the study was terminated after accrual of 29 patients.

The study showed as reported that liposomal daunorubicin has biological activity against early AIDS-related Kaposi's sarcoma. As reported, patients randomized to receive initial treatment with liposomal daunorubicin had a significantly prolonged time to progression (≥ 90 days) compared with patients who were initially observed (31 days) and later crossed over to receive this treatment (log-rank and Wilcoxon tests, $P = 0.0001$).

The crossover nature of the study limits inferences about long-term outcomes (i.e., survival and occurrence of opportunistic infections), because they occur, for the most part, well after the study at a time when both groups have received the experimental treatments. An effective therapy could, however, lead to a delay in such outcomes in the group treated first. Data on these long-term outcomes were not included in the published report, but were presented at the 1995 FDA Advisory Committee meeting. These data do not suggest a benefit of early treatment on these long-term outcomes.

The median survival for patients initially treated with liposomal daunorubicin was 359 days, compared with a

median survival of 586 days for patients who initially received no treatment, a nominally significant difference (log-rank, $P = 0.16$; Wilcoxon, $P = 0.02$). The median time to the first opportunistic infection following study entry was also shorter in the patients who received initial liposomal daunorubicin treatment, 145 versus 371 days in patients who initially received no treatment (log-rank, $P = 0.068$; Wilcoxon, $P = 0.038$).

As the only treatment difference between the two groups in this crossover study was a delay in liposomal daunorubicin of at most 84 days, it is not easy to see how a difference of more than 84 days could result from treatment. The 32-week difference in survival and time to first opportunistic infection thus appears at least partly due to chance. The direction of the result should remind us, however, that administration of immunosuppressive cytotoxic drugs to patients with HIV might decrease resistance to infection and shorten survival. It may be reasonable to accept this risk in

advanced Kaposi's sarcoma that is interfering with patients' lives, but available data do not support use of liposomal daunorubicin at earlier stages.

The indications and usage section of the FDA-approved prescribing information for DaunoXome (liposomal daunorubicin) includes the statement, 'DaunoXome is not recommended in patients with less than advanced HIV-related Kaposi's sarcoma'.

R. M. White, Medical Officer, Division of Oncology Drug Products FDA, Center for Drug Evaluation and Research, HFD-150, Rockville, Maryland, USA.

Reference

- 1 Uthayakumar S, Bower M, Money-Kyrle J, et al.: Randomized cross-over comparison of liposomal daunorubicin versus observation for early Kaposi's sarcoma. *AIDS* 1996, 10:515-519.

PLEASE HELP US

We would appreciate it if you would help us update our mailing list by answering the following questions and returning the questionnaire in the envelope provided. Please type/print clearly.

Your organization's name: _____

1. Do you wish to continue receiving mailings from our office?

_____ YES

_____ NO

2. If the name and address on this mailing is not correct please list the corrected information:

3. Please list the names of the organization's contact person(s) and his/her title(s):

4. What are the telephone, FAX, and e-mail numbers of your organization?

Telephone: () _____

FAX: () _____

E-Mail: _____

5. Please add us to your mailing list as follows:

Richard Klein
HIV/AIDS Program Director
Food and Drug Administration
Parklawn Building - HF-12
Room 9-49
5600 Fishers Lane
Rockville, MD 20857

E-Mail: Rklein@oc.fda.gov

Telephone: (301) 827-4460

FAX: (301) 443-4555

THANK YOU FOR YOUR COOPERATION
PLEASE MAIL, FAX OR E-MAIL US YOUR CORRECTIONS TO THE ABOVE ADDRESS



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

October 10, 1997

Food and Drug Administration
Rockville MD 20857

Dear Colleague:

I am enclosing information pertaining to recent and upcoming Food and Drug (FDA) activities related to HIV/AIDS. Please share this information with your colleagues and distribute it to your constituents. This mailing contains:

- Summary Minutes, Antiviral Drugs Advisory Committee, which discussed the utility of plasma HIV RNA measurement as an endpoint in clinical trials for drugs to treat HIV infection, July 14 and 15, 1997.
- Pediatric Patients; Regulations Requiring Manufacturers To Assess the Safety and Effectiveness of New Drugs and Biological Products; Proposed Rule, Federal Register, August 15, 1997
- FDA is announcing a public meeting on October 27, 1997 to discuss issues related to the agency's proposed rule on regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients. The meeting will be held at the Cohen Building Auditorium, 330 C Street SW, Washington, DC.
- FDA approved Famvir (famciclovir, Smithkline Beecham Pharmaceuticals) for the new indication of suppression of recurrent episodes of genital herpes in immunocompetent adults, September 17, 1997
- FDA Proposed Rule on Women in Clinical Trials, Talk Paper T97-46, September 23, 1997
- Investigational New Drug Applications; Proposed Amendment to Clinical Hold Regulations for Products Intended for Life-Threatening Diseases, Federal Register, September 24, 1997
- FDA approved Combivir, a combination of AZT (zidovudine) and 3TC (lamivudine) for treating AIDS and HIV infection, Talk Paper T97-29, September 26, 1997
- Unpasteurized Cider and Juice Alert, People with weakened immune systems, such as those with HIV, AIDS or cancer, should drink only pasteurized cider and juice.
- FDA Warns Consumers About Two Unapproved Home-Use Test Kits, HHS News, P97-33, September 26, 1997
- Liposomal daunorubicin is not recommended in patients with less than advanced HIV-related Kaposi's sarcoma, R. M. White, Medical Officer, Division of Oncology Drug Products, FDA, AIDS 1997, Vol 11 No 11, November 1997

We are updating our HIV/AIDS mailing list. If you wish to continue receiving these mailings, please complete the enclosed form and mail or FAX it back to my attention. You may contact me either by phone (1.301.827.4460) or by e-mail (Rklein@oc.fda.gov) if you have any questions or comments about these or other HIV/AIDS-related issues pertaining to the Food and Drug Administration.

Yours truly,

Richard Klein
HIV/AIDS Program Director
Office of Special Health Issues
5600 Fishers Lane, HF-12
Rockville, MD 20857

ENCLOSURES

Food and Drug Administration
Center for Drug Evaluation and Research

SUMMARY MINUTES
ANTIVIRAL DRUGS ADVISORY COMMITTEE
July 14-16, 1997
Armory Place, Silver Spring, MD

Antiviral Drugs Advisory Committee

Scott M. Hammer, MD, Chair
Wm. Christopher Mathews, MD, MSPH
Pamela Diaz, MD
Judith Feinberg, MD
Wafaa El-Sadr, MD
James J. Lipsky, MD

Ermona McGoodwin, Acting Executive Secretary (7/14)

FDA SGE Consultants

John Modlin, MD (7/14-15)
Fred Valentine, MD (7/14-15)
Vernon Chinchilli, PhD (7/14-15)
Joel Verter, PhD (7/14-15)
Janet Elashoff, PhD (7/16)
Brian Wong, MD (7/16)

FDA Guests

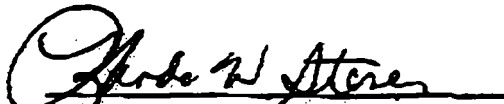
Mark Harrington (7/14-15)
Brenda Lein (7/14-15)
Virginia Kam, MD (7/16)

FDA Participants

David Feigal, MD, MPH
Donna Freeman, MD (7/14-15)
Mark Goldberger, MD, MPH (7/16)
Jeffrey Murray, MD
Michael Elashoff, PhD (7/14-15)
Paul Flyer, PhD (7/14-15)
Lauren Iacono-Connors, PhD (7/14-15)
Joyce Korvick, MD (7/16)
Thomas Hammerstrom, PhD (7/16)

These summary minutes for the July 14-16, 1997 Antiviral Drugs Advisory Committee meeting were approved on 9/15/97

I certify that I attended the July 14-16, 1997 Antiviral Drugs Advisory Committee meeting and that these minutes accurately reflect what transpired.


Rhonda W. Stover, RPh
Executive Secretary


Scott M. Hammer, MD
Chair

The July 14-16, 1997 meeting of the Antiviral Drugs Advisory Committee consisted of three open session days. On July 14 and 15, 1997, the committee discussed the utility of plasma human immunodeficiency virus (HIV) RNA measurement as an endpoint in clinical trials for drugs to treat HIV infection. On July 16, 1997, the committee discussed NDA 50-740, AmBisome® (liposomal amphotericin B, Fujisawa, USA), as empirical therapy for presumed fungal infection in febrile neutropenic patients.

MEETING PROCEEDINGS-OPEN SESSION-JULY 14, 1997

Topic: The utility of plasma human immunodeficiency virus (HIV) RNA measurement as an endpoint in clinical trials for drugs to treat HIV infection.

Approximately 350 persons were in attendance. A briefing memorandum from the FDA was the only background material sent to the committee prior to the meeting.

Call to Order

The meeting was called to order by Dr. Scott Hammer, Chair, at 8:30 a.m. The committee members, guests, and the FDA participants at the table introduced themselves.

Conflict of Interest

The conflict of interest statement was read by Ermona McGoodwin, Acting Executive Secretary. General matters waivers were granted to all committee participants with interests in companies or organizations that could be affected by the committee's discussion of the meeting topic.

Introduction

Dr. David Feigal, Director, Office of Drug Evaluation IV, FDA, reviewed the history of surrogate markers and the accelerated approval of HIV medications. The purpose of this cooperative meeting was to examine the effects of HIV medications on viral load and treatment response issues.

Presentations-HIV RNA Assays

Lauren Iacono-Connors, PhD (FDA), gave an overview of HIV-RNA measurements. Don Brambilla, PhD (New England Research Institute), discussed the assay characteristics of the Chiron ES bDNA, Organon Teknika NASBA, and Roche Amplicor HIV Monitor assays. Winston Cavert, MD (University of Minnesota), presented data on the comparative tissue compartment activity for plasma RNA and lymphoid tissue RNA.

Presentations-Review of Pediatric Data

Lynne Mofenson, MD, (NICHD), presented the natural history of HIV infection in pediatric patients. Paul Palumbo, MD (University of Medicine and Dentistry of New Jersey), discussed the virology data from the ACTG study 152. The virology data from the ACTG study 300 was given by George Johnson, MD (Medical University of South Carolina).

Open Public Hearing

The following 7 open public hearing speakers presented data, information, and views to the Committee on the meeting topic and other HIV treatment issues. The speakers were requested to make presentations of approximately 5 minutes and to disclose their financial associations.

- Victor DeGruttola, PhD, Harvard School of Public Health
- David Scondras, Search for Cure, Boston, MA
- Alan Norburn, AIDS Treatment Project, London, England
- Francois Houyez, European AIDS Treatment Group (EATG), Paris, France
- Bill Bahlman, ACT-UP, New York
- Iris Long, PhD, ACT-UP, Mount Sinai ACTG-CAP
- Ronald Baker, San Francisco AIDS Foundation, (BETA)

Presentations-Clinical Confirmation of HIV-RNA Changes

After a review of the current antiretroviral guidelines by Sherilyn Stanley, MD, (NIAID), the presentations on clinical confirmation of HIV-RNA changes were introduced by Jeffrey Murray, MD (FDA). Dr. Murray gave the rationale for the agency's decision to explore plasma HIV-RNA as a clinical endpoint in HIV trials. Plasma HIV-RNA as a clinical endpoint would be less complex than current endpoints, more reflective of current medical practice, and allow treatment switches before clinical failure. However, the agency must be confident that HIV-RNA reduction is associated with a decreased clinical progression rate as well as other related issues.

Ian Marschner, PhD, (Harvard School of Public Health/ACTG) presented a cross-protocol analysis of 7 ACTG studies (116A, 116B/117, 175, 197, 229, 241, 259) involving a variety of treatment regimens. After an introduction by Lynn Smiley, MD (GlaxoWellcome), Ralph DeMasi, PhD, (GlaxoWellcome) discussed data from 6 controlled trials (CAESAR, NUCA3001, NUCA3002, NUCB3001, NUCB3002, AVANTI-01) of ZDV+3TC (67%) versus control treatments (33%).

Christy Chuang-Stein, PhD, (Pharmacia and UpJohn), presented combined data from studies 0017 (DLV+ddI versus ddI) and 0021 (DLV+ZDV versus ZDV). Data from the intent to treat population of trial NV14256 (ddC, saquinavir, and ddC+saquinavir) was

given by Lesley Struthers (Hoffman La Roche) and Mike Shear (Hoffman La Roche). Margo Heath Chiozzi, MD (Abbott Laboratories), reviewed data from study M94-247 of ritonavir treated patients.

Michael Elashoff, PhD (FDA), gave a summary of the 5 presentations. Overall, the data that comprised many studies, regimens, and methods of analysis, supported an association between RNA changes and clinical event rates. A reduction of 0.5 log, the smallest decrease studied across trials, was associated with clinical benefit and greater decreases resulted in lower clinical event-rates. Dr. Elashoff stated that there was an association between longer suppression and lower clinical event rates. However, the effect of long-term durability remains to be characterized since durable responses past 24 weeks were rare in these trials.

The committee was given the opportunity to ask questions of the presenters and the FDA representatives. The agency's formal discussion points were posed to the committee on the second day of the meeting-July 15, 1997, after additional presentations and discussion.

The meeting was adjourned at 4:30 p.m. to reconvene at 8:00 a.m. on July 15, 1997.

MEETING PROCEEDINGS-OPEN SESSION-JULY 15, 1997

Topic: The utility of plasma human immunodeficiency virus (HIV) RNA measurement as an endpoint in clinical trials for drugs to treat HIV infection.

Approximately 300 persons were in attendance. A briefing memorandum from the FDA was the only background material sent to the committee prior to the meeting.

Call to Order

The meeting was called to order by Dr. Scott Hammer, Chair, at 8:00 a.m. The committee members, guests, and the FDA participants at the table introduced themselves.

Conflict of Interest

The conflict of interest statement was read by Rhonda Stover, RPh, Executive Secretary. General matters waivers were granted to all committee participants with interests in companies or organizations that could be affected by the committee's discussion of the meeting topic.

Introduction

Paul Flyer, PhD (FDA), stated that the previous day's presentations indicated that there is a strong relationship between the treatment induced changes in HIV RNA and clinical outcome. He discussed the use of HIV RNA as a surrogate marker and its proposed use as a clinical endpoint. The FDA proposes adding a new treatment indication, the suppression of HIV RNA, to serve as the confirmatory trial for a drug approved under accelerated approval. Dr. Flyer stated that the focus of this meeting day would be trial design issues in evaluating HIV RNA response.

Presentations-Viral Changes in Response to Antiretroviral Treatment

The four presentations utilized study data to address issues that included time to virologic response and durability of virologic response. Jeff Chodakewitz, MD (Merck Laboratories), presented data from indinavir protocols 028, 033, and 035. Barry Quart, PharmD (Agouron Pharmaceuticals), discussed Viracept study 511. The results of nevirapine trial BI 1046 were given by David Hall, PhD (Boehringer Ingelheim Pharmaceuticals). The final industry presentation consisted of ZDV+3TC data from 6 controlled trials (CAESAR, NUCA3001, NUCA3002, NUCB3001, NUCB3002, AVANTI-01) and was given by Lynn Smiley, MD (GlaxoWellcome) and Ralph DeMasi, PhD, (GlaxoWellcome).

Michael Elashoff, PhD, (FDA) discussed the design of an RNA-based clinical trial and summarized the four presentations. Dr. Elashoff stated that a primary study endpoint of

time to loss of response could include RNA as well as CD4 and other clinical endpoints. The initial phase of the RNA-based clinical trial could be used for accelerated approval on the basis of percent response and the long-term followup would address the durability of the drugs. Furthermore, the RNA-based clinical trial should allow patients to switch if they do not experience an initial or sustained response and to exit the study, if appropriate.

Dr. Elashoff commented on the utility of the data from the four presentations in defining treatment response for an RNA-based clinical trial. In these studies, a response was considered to be achieving the assay limit, although a less stringent response definition and a flexible loss of response definition may be needed in some trials. The time of response may be as long as 16 to 24 weeks and the time of loss of response may exceed 48 weeks after response.

Open Public Hearing

The following 7 open public hearing speakers presented data, information, and views to the Committee on the meeting topic and other HIV treatment issues. The speakers were requested to make presentations of approximately 5 minutes and to disclose their financial associations.

- Ben Cheng, Project Inform
- Jules Levin, National AIDS Treatment Advocacy Project (NATAP)
- Spencer Cox, Treatment Action Group, New York, New York
- Bill Bahlman, ACT-UP, New York
- John S. James, AIDS Treatment News
- Mike Donnelly, ACT-UP, Golden Gate
- Beverly Dale, Roche Molecular Systems

Charge to the Committee

Dr. David Feigal, Director, Office of Drug Evaluation IV, FDA, discussed HIV trial design issues. He commented on the emergence of individualizing HIV therapy and the need for decision rules versus only following surrogate markers. Dr. Feigal informed the committee that the agency hopes to change product labeling from a label which only states that an agent is approved to treat HIV infection to a label that would describe the performance characteristics of a product.

Committee Discussion

The committee posed questions to the presenters and discussed all the issues that arose from the presentations. The committee was asked by the agency to **comment** (no formal vote) on the following discussion points:

1. Does the available information support our conclusion that a durable reduction in plasma HIV-RNA is evidence of clinical benefit?

Yes, the committee agreed that the data presented suggested correlation between a durable reduction in plasma HIV-RNA and clinical benefit. Several committee members stated that a durable reduction in plasma HIV-RNA predicts (versus is evidence of) clinical benefit.

2. For the purpose of evaluating drug efficacy;
 - A. What is the most appropriate definition of a clinically meaningful virological response?
 - B. Should the definition differ for subpopulations such as:
Children
Antiretroviral experienced patients or
Baseline disease status
 - C. Given this definition what would constitute a loss of that response?
 - D. How long should responders be followed to assess a durable virologic response?

The committee decided to answer this question grouped as 2A and 2B and 2C and 2D.

2A and 2B

The majority of the committee stated that the definition would vary based on the treatment population. The definitions of a clinically meaningful response ranged from the minimum of a 0.5 log reduction from baseline to a maximum of below quantifiable levels. It was also stated that the definition may have to be a composite inclusive of time to response, CD4 counts, and resistance issues.

2C and 2D

The definition of a loss of response was dependent on the definition of a clinically meaningful virological response. Therefore, the committee's views ranged from an increase to within 0.5 log of baseline to any quantifiable amounts of HIV-RNA. The agency's proposed time to failure was also cited as a reasonable endpoint. The committee agreed that patients should be followed for at least 48 weeks. Additionally, it was suggested that patients be followed 48-52 weeks past the last enrolled patient as the minimum and for as long as possible as the maximum.

3.
 - A. What events should prompt altering randomized therapy during a clinical trial?
 - B. Are there circumstances in which this would differ from the virologic endpoint?

The committee stated that there are clinical and immunologic factors that differ from the virologic endpoint that could prompt altering randomized therapy during a clinical trial. Progressive CD4 decline, toxicity, and changes in standard clinical practice were cited as some of these factors. Several committee members cautioned that the therapy switch

criteria be conservative to allow time for the patient to achieve maximal benefit on the randomized regimen.

The meeting was adjourned at 2:55 p.m. to reconvene at 8:30 a.m., July 16, 1997, to discuss NDA 50-740, AmBisome® (liposomal amphotericin B, Fujisawa, USA), as empirical therapy for presumed fungal infection in febrile neutropenic patients.

federal register

Friday
August 15, 1997

Part V

Department of Health and Human Services

Food and Drug Administration

**21 CFR Parts 201, 312, 314, and 601
Pediatric Patients; Regulations Requiring
Manufacturers To Assess the Safety and
Effectiveness of New Drugs and
Biological Products; Proposed Rule**

**DEPARTMENT OF HEALTH AND
HUMAN SERVICES**

Food and Drug Administration

21 CFR Parts 201, 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 November 13, 1997. Written comments on the information collection provisions should be submitted by September 15, 1997. For further information of the agency's implementation plan, see section VII of **SUPPLEMENTARY INFORMATION** in 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 times to pediatric patients under 2; aerosol prescribed 399,000 times to pediatric patients under 5); Zoloft for treatment of depression (prescribed 248,000 times 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 (m²)). 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. CDER 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 other 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 supplements containing pediatric use studies for which FDA granted a request to defer submission until after approval.

Finally, FDA has issued a policy statement describing the types of evidence necessary to support supplements. In that policy, FDA provides guidance to manufacturers on the circumstances in which FDA may approve a supplement in which confirmation of the results of an adequate and well-controlled trial is provided by information other than a second adequate and well-controlled trial precisely replicating the first trial, or by studies without the extensive documentation ordinarily required.

The agency believes that financial and other incentives to manufacturers, although largely beyond FDA's current authority, could further increase the number of drugs and biologics with adequate pediatric labeling.

IV. Public Hearing

Because of the importance of ensuring the safety and effectiveness of the medications administered to children and the need to address the absence of pediatric labeling in the most effective manner possible, FDA intends to hold a public hearing at which recognized experts in the field, members of the pharmaceutical industry, and other interested parties will have an opportunity to discuss the issues raised by this proposal.

V. Description of the Proposed Rule

The proposed rule is designed to ensure that new drugs and biological products that are likely to be commonly used in children or that represent a meaningful therapeutic benefit over existing treatments for children contain adequate pediatric labeling for the approved indications at the time of, or soon after, approval. The rule would therefore require a manufacturer of a drug classified as a "new chemical entity" or a new (never-before-approved) biological product to submit, before approval, safety and effectiveness information on relevant pediatric age groups for the claimed indications. The

submission of information could be deferred until after approval if, for example, pediatric studies should not begin until information on adults was collected, or where the collection and filing of pediatric data would delay the availability of a product that provides a significant therapeutic advantage to adults. The requirement would be waived for some or all pediatric age groups, if: (1) The product did not represent a meaningful therapeutic benefit over existing treatments for pediatric patients and was unlikely to be used in a substantial number of pediatric patients, (2) studies on the product were impossible or highly impractical because, for example, the population was too small or geographically dispersed, (3) the product were likely to be unsafe or ineffective in pediatric patients, or (4) reasonable efforts to develop a pediatric formulation (if one were needed) had failed.

The rule is also intended to assist in improving pediatric use information for already marketed drugs and biological products where there is a compelling need for more information. The rule would therefore codify FDA's authority, discussed in the 1994 rule, to require, in compelling circumstances, that manufacturers of already marketed drugs and biological products conduct studies to support pediatric use labeling for the claimed indications.

The proposed rule also contains provisions designed to encourage discussions of the need for pediatric studies early in the drug development process, as well as postmarketing reporting requirements designed to assist FDA in determining whether pediatric studies are needed for particular products and whether required studies are being carried out with due diligence.

FDA notes that the Federal Food, Drug, and Cosmetic Act (the act) authorizes FDA, under certain circumstances, to grant periods of exclusive marketing to manufacturers who obtain approval of labeling supplements adding pediatric use information to a drug's label. First, a manufacturer is entitled to 3 years of exclusive marketing under section 505(c)(3)(D)(iii) and (j)(4)(D)(iv) of the act (21 U.S.C. 355(c)(3)(D)(iii) and (j)(4)(D)(iv)) for obtaining approval of pediatric use labeling based on clinical studies, other than bioavailability studies. Second, a manufacturer may be entitled to 7 years of exclusive marketing under the Orphan Drug Amendments for obtaining approval of an application for use of a drug to treat a disease or condition affecting a

pediatric population of less than 200,000.

A. Scope

The proposed rule would cover only original applications for those drugs classified as "new chemical entities," including antibiotics, and new biological drug products that have never been approved for any indication. A "new chemical entity," defined in 21 CFR 314.108(a), is a drug that contains no previously approved active moiety. (An "active moiety," also defined in § 314.108(a), is the molecule or ion, excluding certain appendages, that is responsible for the physiological or pharmacological action of the drug.) New chemical entities and new biological products are generally the most innovative and therapeutically significant of the new drug products approved by FDA.

In an effort to limit the scope of the rule to those products for which pediatric labeling is most urgently needed and to minimize the burden on manufacturers and on agency resources available to review new product applications, FDA has tentatively concluded that the pediatric study requirement would not apply to subsequent applications for the drug or biological product, e.g. to supplements for new indications or dosage forms. FDA recognizes that, in some cases, a change to an approved product, particularly a new indication, may have clinically significant use in children. FDA seeks comment on whether the requirement should apply more broadly, e.g., to applications for minor chemical variations of approved products, new indications, new dosage forms or new routes of administration, and, if so, how the rule could be applied in a manner that does not impose undue burdens on manufacturers or agency resources.

The proposed rule would require an assessment of safety and effectiveness in one subpopulation (pediatric patients) only for the indications already claimed by the manufacturer. It would 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 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, or at the earliest appropriate opportunity, 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 been collected. FDA believes that in certain cases it may be appropriate to defer submission of pediatric studies. For example, in such cases, an NDA or biological product license could be ready for approval for adult use before pediatric studies were completed. Also, where a product was needed to treat a serious or life-threatening disease for which there were not satisfactory alternative therapies or where the product represented a meaningful therapeutic benefit over existing therapies, it would be contrary to the public health to delay approval until pediatric studies were submitted.

Proposed §§ 314.50(g)(2) and 601.27(b) would permit FDA to defer the submission of some or all of the

required pediatric data until after approval of the product for adult use, on its own initiative or at the request of the applicant. If the applicant requested deferral, the request would be required to contain an adequate justification for delaying pediatric studies. If FDA concluded that there were adequate justification for deferring the submission of pediatric use studies, the agency could approve the product for use in adults subject to a requirement that the applicant submit the required pediatric studies within a specified time after approval. FDA would consult with the sponsor in determining a deadline for the deferred submission, but would ordinarily require the submission not more than 2 years after the date of the initial approval. The deadline for submission of studies would take account of likely or actual difficulties encountered in recruiting pediatric 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, or (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 immature 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 Index¹, 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 than 15,000 patients in that age group were affected by the disease or condition. FDA seeks comment on these methods of assessing expected pediatric exposure and on the specific numerical thresholds suggested.

5. Section 314.50(d)(7)—Pediatric Use Section of Application

Under proposed § 314.50(d)(7), applicants would be required to include in their applications a section summarizing and analyzing the data supporting pediatric use information for the claimed indications. The proposed new section of the application would contain an integrated summary of the clinical pharmacology studies, controlled clinical studies, uncontrolled clinical studies, or other data or information that are relevant to the safety and effectiveness, and benefits and risks of the drug in pediatric populations. Because full descriptions of all such studies must already be provided under § 314.50(d)(3) and (d)(5), the new pediatric use section would be required to contain only brief summaries of the studies together with a reference to the full description of each provided elsewhere in the application.

C. Marketed Drug and Biological Products

1. Section 201.23—Required Studies

As discussed in the preamble to the 1994 rule, FDA has the authority, under certain circumstances, to require the manufacturers of marketed drugs that are used in pediatric patients to submit pediatric studies assessing safety and effectiveness for the already approved

indications (59 FR 64240 at 64243). Proposed § 201.23 would authorize FDA to require a manufacturer of a marketed drug or biological drug product to submit an application containing data evaluating the safety and effectiveness of the product in pediatric populations, in compelling circumstances. FDA has tentatively concluded that it should impose such a requirement only where the agency made one of two findings that: (1) The product was widely used in pediatric populations and the absence of adequate labeling could pose significant risks to pediatric patients; or (2) the product was indicated for a very significant or life threatening illness, but additional dosing or safety information was needed to permit its safe and effective use in pediatric patients.

Before requiring a study under § 201.23, the appropriate center, CDER or CBER, would consult with the manufacturer on the type of studies needed and on the length of time necessary to complete them and would notify the manufacturer, by letter, of the center's tentative conclusion that such a study was needed and provide the manufacturer an opportunity to provide a written response and to have a meeting with the center. At the center's discretion, such a meeting could be an advisory committee meeting. If, after reviewing any written response and conducting any requested meeting, CDER or CBER determined that additional pediatric use information were necessary, the center director would issue an order requiring the manufacturer to submit a supplemental application containing pediatric safety and effectiveness data within a specified time. The manufacturer would be able to request reconsideration by the Commissioner for Food and Drugs (the Commissioner) of the order under the provisions at 21 CFR 10.33.

Proposed § 201.23(c) would require FDA to grant full or partial waivers of study requirements on their own initiative or at request of the applicant for reasons analogous to those which would entitle not-yet-marketed drug and biologic products to waivers.

FDA seeks comment on whether it should codify its authority to require the manufacturers of marketed drugs to conduct pediatric studies, and, if so, the circumstances under which the agency should exercise that authority. The agency also solicits comment on the proposed grounds for waiving the pediatric study requirement for already marketed drug and biological products and whether additional ground may exist, such as whether cost should justify waiver of the pediatric study requirement. Comment is also sought on

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

defining the term "very significant illness".

D. Studies in Different Pediatric Age Groups

Because the pharmacokinetics and pharmacodynamics of a drug or biological product may be different in different pediatric age groups or stages of development, it could be necessary to conduct studies in more than one pediatric age group. The following age categories for the pediatric population are commonly distinguished: (1) Neonates; (2) infants; (3) children, and (4) adolescents. In the 1994 rule, FDA defined neonates as birth up to 1 month, infants as 1 month to 2 years, children as 2 years to 12 years, and adolescents as 12 years to 16 years (59 FR 64242). The need for studies in more than one age group would depend on whether the drug or biological product was likely to be used in each age group (see "Waivers," in sections V.B.4 and V.C.1 of this document) and whether safety and effectiveness in one age group could be extrapolated to other age groups. The metabolism and elimination of the drug and the stage of development of the child may be important in determining which age groups should be tested. There would generally need to be sufficient data, including pharmacokinetic data to establish dosing and safety for each group. (Pharmacokinetic data are generally collected from pediatric patients receiving the drug or biologic as treatment rather than from healthy children.) In cases where the product was expected to have similar pharmacokinetics in more than one age group, pharmacokinetic data from one age group could be sufficient to support labeling for other age groups. Such extrapolation would not be routine.

FDA recognizes that studies in neonates and young infants present special problems. On one hand, failure to adequately test drugs in this age group has led to both under treatment and, conversely, some of the most serious therapeutic mishaps known to have occurred among pediatric patients. On the other hand, studies in this age group may be significantly more difficult to carry out in the period before or soon after approval than studies in older age groups. However, FDA recognizes that for some conditions, early study would be advantageous. FDA would therefore expect to apply the study requirement to patients in this age group with caution and would, whenever appropriate, permit such studies to occur after the product has been successfully studied in older children. The agency seeks comment on

the issues raised by requiring studies in this age group.

E. Pediatric Formulations

In some cases, testing of a product in pediatric patients could require the development of a pediatric formulation. Many children below a certain age are unable to swallow pills and may require a liquid, chewable or injectable form of the product. The need to develop a pediatric formulation does not necessarily mean that the product would not have been used in children in its adult dosage form. In many cases, physicians prescribing tablets to young children direct the parent to grind up the tablet and sprinkle the powder into the child's food. In other cases, pharmacists may compound tablets into pediatric formulations of their own choosing. These methods of administering adult dosage forms to children may be unsatisfactory, however, because the bioavailability of any particular product in this form is untested and dosing may be highly variable. A standardized pediatric formulation ensures bioavailability and consistency of dosing, and permits meaningful testing of safety and effectiveness.

FDA has tentatively concluded that it would be reasonable to expect a manufacturer of a product to produce a pediatric formulation, if one were necessary, only in those cases where a new drug or new biological product provided a meaningful therapeutic benefit over existing treatments, and where the study requirement had not been waived in the age group requiring the pediatric formulation. Proposed §§ 201.23, 314.50(g)(1) and 601.27(a) contain this requirement. The type of formulation needed would vary depending on the age group in which the product were to be used and the disease being treated. Young children unaccustomed to taking drugs may need liquid or chewable formulations, while children with serious and chronic diseases may need only smaller tablets.

The difficulty and cost of producing a pediatric formulation may vary greatly depending upon such factors as solubility of the compound and taste. FDA would waive the requirement for pediatric studies (see "Waivers," in section V.B.4 of this document) in age groups requiring a pediatric formulation, if the manufacturer provided evidence that reasonable attempts to produce a pediatric formulation had failed.

FDA solicits comment on whether it is appropriate to require a manufacturer to develop a pediatric formulation and, if so, the circumstances in which it

would be appropriate to impose such a requirement. For example, should the cost of developing a pediatric formulation justify a waiver of the pediatric study requirement? Should the number of patients affected by the disease or condition in the relevant age group be considered in determining whether to require the development of a pediatric formulation for that age group? Is it appropriate to ask the manufacturer of a not-yet-approved product to allocate resources to developing pediatric formulation(s)? Where cost is a significant issue, would it be appropriate to defer development of a pediatric formulation until after approval of the product? What should be considered "reasonable attempts" to develop a pediatric formulation?

As noted above, FDA was unable to quantify the potential benefits of this rule due to the unavailability of relevant data and studies. Nevertheless, the agency will attempt to assess the benefits of the final rule and solicits comment on the appropriate design and methodology of such measurement. In particular, FDA seeks information and data that would help the agency to: (1) Quantify the societal costs of the adverse drug events experienced by pediatric populations and (2) assess the proportion of these adverse drug events that would be eliminated by the new information that would result from the rule. In addition, FDA seeks information and data that would help the agency to: (1) Quantify the societal costs of the underused or inadequate drug therapies prescribed to pediatric populations and to (2) assess the proportion of these costs that would be eliminated by the new information that would result from the rule.

F. Ethical Issues

Ethical concerns may have contributed to reluctance to conduct studies in pediatric patients. To address these concerns, both the American Academy of Pediatrics (Ref. 1) and the Department of Health and Human Services, 45 CFR part 46, subpart D, have developed guidelines or regulations for the ethical conduct of clinical studies in pediatric patients. Because pediatric patients represent a vulnerable population, special protections are needed to protect their rights and to shield them from undue risk. As the American Academy of Pediatrics has observed, however, administration of untested drugs "may place more children at risk than if the drugs were administered as part of well-designed, controlled clinical trials" (Ref. 1 at p. 286). The ethical guidelines currently in place are designed to

protect children's rights and protect them from undue risk. Sponsors should adhere to these guidelines for pediatric studies conducted under this rule. The agency seeks comment on ethical issues that may be raised by this proposal.

G. Remedies

FDA has tentatively concluded that the most practical remedy for failure to submit a required study is an injunctive action brought under the "misbranding" or "new drug" provisions of the act. Denying or withdrawing approval of an otherwise safe and effective drug or biological product is not a satisfactory remedy, because removal of a product from the marketplace could deprive other patients of the benefits of a useful medical product. FDA does not intend to deny or withdraw approval of a product for failure to conduct pediatric studies, except possibly in rare circumstances.

If a manufacturer failed, in the time allowed, to submit adequate studies to evaluate pediatric safety and effectiveness, under proposed §§ 201.23(d) or 314.50(g), FDA could consider the product misbranded under section 502 of the act (21 U.S.C. 352) or an unapproved new drug under section 505(a) of the act (see "Legal Authority," in section VI of this document). When a product is misbranded or an unapproved new drug, sections 302, 303, and 304 of the act (21 U.S.C. 332, 333, and 334) authorize injunction, prosecution or seizure. For violations of this rule, should it become final, FDA would ordinarily expect to file an enforcement action for an injunction, asking a Federal court to require the company to submit an assessment of pediatric safety and effectiveness for the product. Violation of the injunction would result in a contempt proceeding or such other penalties as the court ordered, e.g., fines.

To assist FDA in determining whether pediatric assessments are needed or are being carried out with due diligence, FDA is proposing to amend § 314.81 (other postmarketing reports) to require that annual reports filed by the manufacturer contain information on labeling changes that have been initiated in response to new pediatric data, analysis of clinical data that have been gathered on pediatric use, assessment of data needed to ensure appropriate labeling for the pediatric population, and information on the status of ongoing pediatric studies. Where possible, the annual report would also contain an estimate of patient exposure to the drug product, with special reference to the pediatric population.

FDA seeks comment on appropriate remedies for failure to conduct a required pediatric study and the circumstances, if any, in which the agency should deny or withdraw approval of a drug product.

VI. Legal Authority

Therapeutic tragedies in pediatric patients have prompted some of the most important federal legislation to ensure that drugs are safe and effective. For example, the act was enacted in 1938 in the wake of a tragedy in which many pediatric patients died after taking an untested medicine called Elixir of Sulfanilamide. The legislative history of this enactment demonstrates that Congress intended to ensure that children, as well as adults, received adequately tested and appropriately labeled drugs. (See, e.g., 78 Congressional Record 567-573 (1934) (statement of Sen. Copeland).)

Every mother is anxious that the food and medicine given her baby shall be above suspicion. The welfare of every man, woman, and child is involved in the quality and preparation of the foods and drugs sold in America * * *. [T]he purpose of this legislation * * * is to protect the public, to protect the mothers and the children * * *

81 Congressional Record 7312 (1937) (remarks of Rep. Coffee)

The agency has stated, in the context of both pediatric studies and studies in women, that an application for marketing approval should contain data on a reasonable sample of the patients likely to be given a drug or biological product once it is marketed (59 FR 64240 at 64243; 58 FR 39406 at 39409, July 22, 1993). The agency has further stated that in some cases it could require studies in pediatric patients and in women for both not-yet-approved products and marketed products (*Id.*).

The primary rationale for such a requirement is the same for women and pediatric patients. In most cases, drugs and biological products behave similarly in demographic subgroups, including age and gender subgroups, even though there may be variations among the subgroups, based on, for example, differences in pharmacokinetics. Thus, where a drug or biological product is indicated for a disease suffered equally by men, women, and children, and is not contraindicated in women or pediatric patients, the product will be widely prescribed for all three subgroups even if it were studied only in, or labeled only for, men. As described above, there is extensive evidence that many drugs labeled only for adult use are in fact widely used in pediatric patients for the same indications.

FDA notes that this proposal addresses only use of drug products for their approved indications in a significant subpopulation. The proposed rule does not address "off-label" or unapproved uses of approved drugs and biological products, in which an approved product is used for diseases or conditions other than those in the label. This rule would apply only where a product was expected to have clinically significant use in pediatric populations for the indications already claimed by the manufacturer.

In addition to the provisions cited below as authority for the proposed rule, the agency relies on section 701(a) of the act (21 U.S.C. 371(a)), which authorizes FDA to issue regulations for the efficient enforcement of the act.

A. New Drug and Biological Products

Biological drug products are subject both to section 351 of the Public Health Service Act (the PHS Act) and to the provisions of the act and implementing regulations applicable to drugs, except that manufacturers of biological products covered by approved BLA's are not required to submit NDA's under section 505 of the act. References to "drugs" in the following sections include biological drugs.

1. Sections 502(a), 502(f), 505(d)(7), and 201(n) of the Act

A drug is misbranded under section 502(a) of the act if its labeling is "false or misleading in any particular." Similarly, a new drug application must contain labeling that is not false or misleading (section 505(d)(7) of the act). Section 201(n) of the act (21 U.S.C. 321(n)) defines labeling as misleading if it "fails to reveal facts material * * * with respect to consequences which may result" not only from use of the product as labeled, but "from the use of the [product] * * * under such conditions of use as are customary or usual." Information on dosing and adverse effects are facts "material" to the consequences that may result from customary use in pediatric patients. A drug product is misbranded under section 502(f) of the act, if its label fails to provide adequate directions for each intended use. 21 CFR 201.5 states that adequate directions must be provided for each use recommended in the labeling and each use "for which the drug is commonly used." Thus, FDA may require a product to carry labeling that provides safety and effectiveness information on use in subpopulations in which the product is customarily or commonly used.

There is extensive evidence that drugs for diseases that affect both adults and pediatric patients are routinely used in pediatric patients despite the absence of pediatric labeling, and even in the face of disclaimers stating that safety and effectiveness have not been established in children. FDA may therefore consider pediatric use to be "customary or usual" or "commonly used" where the drug is indicated for a disease or condition that affects both adults and children, and the drug is not contraindicated in pediatric patients. In many cases, the use in pediatric patients of a drug labeled only for adults will increase over time, as physicians become aware of the drug's potential usefulness in children and familiar with the drug's uses and effects. Thus, FDA may conclude that a drug that was appropriately labeled for adult use at the time of approval is, at some later date, no longer appropriately labeled.

2. Sections 201(p), 301(a), and 505(a) of the Act

Under section 301 (a) and (d) of the act (21 U.S.C. 331 (a) and (d)) and section 505(a) of the act, a drug product is subject to enforcement action if it is a "new drug" for which no NDA has been approved. A product is a new drug under section 201(p) of the act if it is not recognized to be safe and effective under the conditions "prescribed, recommended, or suggested" in the drug's labeling. There is widespread evidence that, despite the absence of pediatric labeling, drugs are routinely used in pediatric patients for the labeled indications. FDA may therefore consider pediatric use to be "suggested" in a drug's labeling where the drug is indicated for a disease or condition that affects both adults and pediatric patients, unless the drug is specifically contraindicated for pediatric patients. As described above, because pediatric use of new drugs often increases over time, FDA may conclude that labeling that is appropriate at the time of approval is later no longer appropriate.

3. Section 502(j) of the Act

Section 502(j) of the act defines as misbranded those drugs that are dangerous to health when used in the manner prescribed, recommended, or suggested in their labeling. FDA may consider pediatric use to be "suggested" in a drug's labeling where the drug is indicated for a disease or condition that affects both adults and pediatric patients, unless the drug is specifically contraindicated for pediatric patients. As described earlier in this notice, the absence of pediatric testing and labeling poses risks to children including the

risk of unanticipated adverse reactions, and under- and over-dosing.

4. Section 505 (i) and (k) of the Act

Section 505(i) of the act that authorizes the issuance of regulations governing the use of investigational drugs, and the proviso in 505(k) of the act, which requires regulations issued under 505(i) to have "due regard * * * for the interests of patients," together authorize FDA to impose conditions on the investigation of new drugs, including conditions related to the ethics of a proposed investigation and to the interests of patients. Fairness in distribution of the burdens and benefits of research is one of the ethical principles underlying federal regulations on investigational drugs. (See, e.g., 44 FR 23192 at 23194, April 18, 1979 ("Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research").) Because exclusion of pediatric patients from clinical trials may deny them an equitable share of the benefits of research, section 505 (i) and (k) authorize FDA to require their inclusion in clinical trials.

5. Section 351 of the Public Health Service Act

Section 351 of the PHS Act (42 U.S.C. 262) provides authority to regulate the labeling and shipment of biological products. Under section 351(d), 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. The "potency" of a biological product includes its effectiveness (21 CFR 600.3(s)).

B. Marketed Drug Products

1. Section 502(f) of the Act and 21 CFR 201.5

A drug product is misbranded under section 502(f) of the act, if its label fails to provide adequate directions for each intended use. 21 CFR 201.5 states that adequate directions must be provided for each use recommended in the labeling and each use "for which the drug is commonly used." Where there is evidence that a drug product is widely used in pediatric patients, failure to provide adequate directions for the use could misbrand the product.

2. Sections 502(a) and 201(n) of the Act

A drug is misbranded under section 502(a) of the act if its labeling is false or misleading. Section 201(n) of the act defines labeling as misleading if it fails to reveal facts that are material in light of the consequences of the customary or

usual use of the product. Where a drug is widely used in pediatric patients, FDA may consider pediatric use to be "customary." Failure to provide adequate information on dosing and adverse effects in the pediatric population could render the product misbranded, even where the manufacturer does not promote the product for that subpopulation.

3. Section 502(j) of the Act

Section 502(j) of the act defines as misbranded those drugs that are dangerous to health when used in the manner prescribed, recommended, or suggested in their labeling. FDA may consider pediatric use to be "suggested" in a drug's labeling where the drug is indicated for a disease or condition that affects both adults and pediatric patients, unless the drug is specifically contraindicated for pediatric patients. As described earlier in this notice, the absence of pediatric testing and labeling poses risks to children including the risk of unanticipated adverse reactions, and under- and over-dosing.

4. Section 505(k) of the Act

Section 505(k) of the act authorizes FDA to order the holder of an approved NDA to submit reports of data necessary to determine whether there are grounds to withdraw approval of the NDA. FDA has in the past issued regulations under section 505(k) of the act (formerly section 505(j) of the act) requiring postapproval studies of certain drugs (see, e.g., 21 CFR 310.303 ("Continuation of long-term studies, records, and reports on certain drugs for which new drug applications have been approved") (1972); 21 CFR 310.304 ("Drugs that are subjects of approved new drug applications and that require special studies, records, and reports") (1972); and 21 CFR 310.500 ("Digoxin products for oral use; conditions for marketing") (1974)). Section 505(k) of the act also authorizes the agency to require other postmarketing reports on drug products.

5. Section 351 of the Public Health Service Act

Section 351(d) of the PHS Act authorizes FDA to ensure the "continued safety, purity, and potency" of biological products. Section 351(b) of the PHS Act prohibits false labeling of a biological product.

VII. Implementation Plan

All applications for drug and biological products covered by the final rule would be required to contain an assessment of pediatric safety and effectiveness for the claimed

indications, unless the applicant has obtained a waiver or deferral of this requirement from FDA.

FDA proposes that the final rule become effective 90 days after the date of its publication in the Federal Register. For new drug and biologic product applications submitted before the effective date of the final rule, the agency proposes a compliance date of 21 months after the effective date of the final rule. For new drug and biologic product applications submitted on or after the effective date of the final rule, the agency proposes a compliance date of 15 months after the effective date of the final rule. The agency solicits comments on the proposed effective date and proposed compliance dates.

VIII. Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520). The title, description, and respondent description of the information collection provisions are shown below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions,

searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on: (1) Whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Pediatric Safety and Effectiveness Reporting Requirements for Certain Drugs and Biological Products.

Description: FDA is proposing reporting requirements that include: (1) Reports on planned pediatric studies in investigational new drug applications (IND's) (proposed § 312.23(a)(10)(iii)); (2) Reports assessing the safety and effectiveness of certain drugs and

biological products for pediatric use in new drug applications (NDA's) and biologic license applications (BLA's) or in supplemental applications (proposed § 314.50(g)(1)); (3) Analyses of data on pediatric safety and effectiveness in NDA's (proposed § 314.50(d)(7)); (4) Postmarketing reports of analyses of data on pediatric safety and effectiveness (proposed § 314.81(b)(2)(vi)(C)); (5) Postmarketing reports on patient exposure to certain marketed drug products, analyzed and age (proposed § 314.81(b)(2)(i)); (6) Postmarketing reports on labeling changes initiated in response to new pediatric data (proposed § 314.81(b)(2)(vi)(C)); and (7) Postmarketing reports on the status of required postapproval studies in pediatric patients (proposed § 314.81(b)(2)(vii)). The purpose of these reporting requirements is to address the lack of adequate pediatric labeling of drugs and biological products by requiring the submission of evidence on pediatric safety and effectiveness for products with clinically significant use in children.

Description of Respondents: Sponsors and manufacturers of drugs and biological products.

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN

CFR section	Number of respondents	Annual frequency per response	Total annual responses	Hours per response	Total hours
201.23	2	1	2	16	32
314.50(d)(7)	150	1	150	8	1,200
314.50(g)(1)	10	1	10	16	160
314.50(g)(2)	9	1	9	8	72
314.50(g)(3)	15	1	15	8	120
314.81(b)(2)(i)	625	1	625	1.5	937.5
314.81(b)(2)(vi)(c)	625	1	625	1.5	937.5
314.81(b)(2)(vii)	625	1	625	1.5	937.5
601.27(a)	1	1	1	16	16
601.27(b)	1	1	1	16	16
601.27(c)	1	1	1	16	16
Total:					4,444.5

There are no capital or operating and maintenance costs associated with this collection of information.

The agency has submitted the information collection provisions of this proposed rule to OMB for review. Interested persons are requested to send comments regarding information collection by September 15, 1997 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.

IX. Environmental Impact

The agency has determined under 21 CFR 25.24 (a)(8), (a)(11), and (e)(6) 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.

X. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order

12866, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act (Pub. L. 104-4). 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). Under the Regulatory Flexibility Act, unless an agency certifies that a rule will not have

a significant economic impact on a substantial number of small entities, the agency must analyze regulatory options that would minimize the impact of the rule on small entities. The Unfunded Mandates Reform Act (Pub. L. 104-4) (in section 202) requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in an annual expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation).

The agency has reviewed this proposed rule and has determined that the proposed rule is consistent with the regulatory philosophy and principles identified in Executive Order 12866, and these two statutes. This proposal is a significant regulatory action as defined by the Executive Order due to the novel policy issues it raises. With respect to the Regulatory Flexibility Act, the Commissioner certifies that the rule will not have a significant economic impact on a substantial number of small entities. Since the proposed rule does not impose any mandates on State, local, or tribal governments, or the private sector that will result in an annual expenditure of \$100,000,000 or more, FDA is not required to perform a cost-benefit analysis according to the Unfunded Mandates Reform Act.

A. Purpose

The FDA is proposing that a limited class of important new drugs and biologicals that are likely to be used in pediatric patients contain sufficient data and information to support directions for this use. As the approved labeling for many of these new products lack relevant pediatric information, any use in children greatly increases the risk of inappropriate dosing, unexpected adverse effects, and suboptimal therapeutic outcomes. The proposed rule is designed to ensure that new drugs, including biological drugs, that are therapeutically important and/or likely to be widely used in children contain adequate pediatric labeling at the time of, or soon after, approval.

B. Number of Affected Products and Required Studies

Neither the precise number of new drugs that would require additional pediatric studies nor the cost of these studies can be predicted with certainty. To develop plausible estimates, FDA examined the pediatric labeling status at time of approval for each NME and important biological approved from 1991 to 1995, and used these estimates to project the cost that would have occurred had the proposed rule been in

place over that period. The agency assumes that future costs would be reasonably similar. As shown in Table 2, each new drug was assigned to one of three categories: (1) Therapeutically important, some potential pediatric use, (2) other approvals, potential for wide pediatric use, and (3) all other approvals. (The first two categories include all products that the agency believes would have met the therapeutic importance and pediatric use threshold criteria set forth in this proposed rule. The third category includes all products that would not have met these criteria.) For NME's, these category assignments were based on pediatric pages completed by CDER's reviewing division at the time of each approval, the priority review designation for each drug, and 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 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.

²IMS, 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.

TABLE 2.—ESTIMATED NUMBER OF NME'S AND BIOLOGICALS APPROVED IN 1991-95

[That Would Have Been Affected by the Proposed Rule]

Pediatric labeling status	Number of approved drugs	Percent of approved drugs
Therapeutically important, some potential pediatric use	47	33
Some pediatric labeling	16	
No pediatric labeling	31	
Other approvals, potential for wide pediatric use	13	9
Some pediatric labeling	7	
No pediatric labeling	6	
Subtotal	60	42
Some pediatric labeling	23	
No pediatric labeling	137	
All other approvals	82	58
Total Approvals	142	100

¹ Pediatric page shows seven ongoing pediatric studies.

In assessing the amount of additional research that would have been required for the 60 drugs from the first two categories (those that would have potentially been affected by the proposed rule), FDA believes that most would not have required extensive additional clinical trials. As FDA explained in the 1994 final rule (59 FR 64240), extrapolations from adult effectiveness data based on pharmacokinetics studies and other safety data can be sufficient to provide the necessary dosing pediatric information for those drugs that work by similar mechanisms in adults and children. The agency estimates that the majority of these 60 drugs could, to some extent, rely on such extrapolations. Although the proposed rule identifies four pediatric subgroups: (1) Neonates, (2) infants, (3) children, and (4) adolescents, the need for studies in more than one age group depends on the likely use of the drug in each age group and on whether relevant data can be extrapolated to other age groups. As a rule, individual clinical trials would rarely be required for each age group for a given drug.

Estimates of the size of the studies that would have been required to support pediatric labeling for these 60 drugs vary from 20 patients where the simplest type of pharmacokinetic study

would be adequate, to 70 to 120 pediatric patients for studies where some safety and effectiveness data would be needed, to several hundred pediatric patients for studies where more substantial safety and effectiveness data would be required. Thus, for the purpose of developing order-of-magnitude cost estimates, FDA further subdivided the 60 potentially affected drugs into three distinct groupings. The first group of 30 drugs would have required the least amount of new data and includes both the 7 drugs for which the CDER pediatric pages indicate that pediatric trials were already underway and the 23 drugs that already had at least some pediatric labeling at the time of approval. Based on a review of those labels at approval time, FDA estimated that up to half, or 15 of these 30 drugs may have needed limited additional data that would have involved new studies with, on average, 50 pediatric patients each.

Next, FDA assumed that 23 drugs (about three quarters of the remaining 30) would have required new pediatric studies with data from about 100 patients each. Finally, FDA assumed that the remaining 7 drugs would have needed more extensive safety and effectiveness data, requiring 300 pediatric patients for each drug. Consequently, FDA estimates that, if this proposed rule had been in effect from 1991 to 1995, sponsors of 45 of the 60 potentially affected drugs would have needed to obtain additional data from about 5,150 pediatric patients (15 drugs $\times$ 50 patients + 23 drugs $\times$ 100 patients + 7 drugs $\times$ 300 patients). The proposed regulation, therefore, would have required additional pediatric research for an estimated average of 9 new drugs and about 1,030 pediatric patients per year.

In addition, the proposed rule permits the agency to request pediatric data for certain drugs that are already marketed. While the precise impact of this regulatory provision is uncertain, FDA expects that it would affect no more than two drugs per year. If the submission for one of these drugs relied on data from 100 pediatric patients and the other from 300 pediatric patients, the total number of drugs that would have required additional research reaches 11 per year and the total number of pediatric patients about 1,430 per year.

Other costs for pediatric research may accrue to drugs that ultimately fail to gain regulatory approval. Although many drug sponsors would wait until they are relatively certain that their product will be shown safe and effective for the indicated use in adults before

spending substantial resources on pediatric uses, other sponsors may need to begin pediatric examinations earlier to have data included with the new drug or product licence application. It is difficult for FDA to judge how much additional pediatric research would be directed towards products that are not approvable. The agency notes, however, that because only about 65 percent of all NME's that enter phase III trials are eventually approved, the number of drugs entering phase III trials is about 54 percent greater than the number of actual approvals ($100/65 = 1.54$). Since some, but not all, of these unapprovable drugs would initiate some pediatric research, FDA has increased its estimate of the annual number of affected drugs and pediatric patients by 30 percent, to a projected total of 14 drugs and about 1,850 pediatric patients per year.

The agency is aware that forecasting future trends based on historical data can be imprecise. For example, over time, even in the absence of this rule, the percentage of new drugs with labels that provide adequate pediatric use information could change. At this time, however, FDA is not aware of any marked trend. Also, the above estimates ignore those pediatric studies that were promised, but not yet underway at the time of drug approval. To the extent that these commitments are honored, the above estimates of research attributable to the regulation are overstated. Finally, the methodology implies that the standards used by FDA to judge the 1991-1995 approvals would remain unchanged. While subsequent change is possible, FDA does not anticipate that its present views would differ substantially. Thus, while acknowledging substantial uncertainty, the agency's cost estimates are based on the assumption that the proposed rule would require additional research on about 14 drugs, involving a total of 1,850 pediatric patients per year.

C. Cost of Studies

The agency finds that the cost of conducting clinical research with pediatric patients varies directly with the size, duration, and complexity of the clinical research. Although FDA has little detailed information on the cost to drug sponsors of conducting research on clinical patients, one private consulting firm reports that the costs of hiring clinical investigators to conduct phase IV pediatric drug trials ranges from \$300-\$500 per patient for studies on vaccines or fevers to \$3,600 and \$5,000 per patient for renal disease and epilepsy, respectively.³ Similarly, a

number of academic researchers have reported average costs of from \$1,500 to \$3,400 per patient for pediatric trials. These estimates, however, do not account for the many administrative, monitoring, data analysis, and document preparation tasks that would be required of a drug sponsor. Since a published study suggests that a total accounting of all sponsor costs may be three times as great as investigator costs,⁴ FDA has assumed that the average costs of conducting the newly required studies would range from \$5,000 to \$9,000 per pediatric patient. As a result, the estimated 1,850 additional pediatric patients that would need to be studied annually suggests new research costs to the pharmaceutical industry of between \$9.25 million and \$16.65 million per year.

In addition, the testing of a new drug in children would sometimes require the development of a new pediatric dosage form. (Typically a liquid or suspension formulation in place of a tablet or capsule.) Of the 47 drugs identified in the first category of Table 2 (therapeutically important with some potential pediatric use), 14 (30 percent) were available only in tablets or hard capsules at the time of approval. (Manufacturers of 4 of these 14 have since developed oral suspensions.) It seems reasonable, therefore, to assume that, of the 14 new drugs per year estimated to require additional pediatric research, about 4 might require new formulations. The agency solicits comment on the estimate that four new formulations would be required per year.

The effort and cost of developing such formulations could be substantial. Drug developers and manufacturers would have to find appropriate solvents and develop additional data for demonstrating adequate product stability, bioavailability, and production process validation. While such costs would vary with the particular drug type, one industry consultant suggests that per drug laboratory costs could average from \$300,000 to \$500,000 and corresponding regulatory requirements could bring this figure close to \$1 million. Moreover, this estimate assumes the availability of adequate preclinical data on animal toxicity and metabolic rates. Since the proposed rule permits FDA to waive the requirement for reformulation where reasonable attempts have failed, the agency assumes that the additional costs would not exceed \$1 million apiece for 4

³DataEdge, LLC, Faxed data, March 7, 1997.

⁴Thomas Hill, "Calculating the Cost of Clinical Research," *Scrip Magazine*, p. 29, March 1994.

drugs, or an additional \$4 million per year.

Finally, the rule will impose additional paperwork burdens related to new label content, postmarket reporting requirements, and written requests for deferred submissions and waivers. As shown above, FDA estimates that these paperwork activities will require about 4,400 hours annually. At an average compensation rate of \$50 an hour, this cost amounts to about \$220,000 per year.

In sum, FDA anticipates that the annual costs of this proposed rule will total between \$13.5 and \$20.9 million per year.

D. Other Impacts

Other potential impacts would occur if the requirements contributed to delays in the submittal of NDA's. Extended drug development times would be associated with significant additional industry costs. FDA has attempted to minimize the likelihood of regulatory delays through plans for early consultation with drug sponsors and a willingness to consider deferred submissions for pediatric studies. However, the agency recognizes the importance of this issue and solicits public comment on the best means to obtain adequate and timely pediatric information without slowing the process for bringing new drugs to market. Also, as noted earlier in this preamble, the agency is aware that new pediatric supplements could impose additional user fees on drug sponsors and is considering means to alleviate this added burden. All user fee issues will be resolved before issuance of the final rule. Overall, therefore, compared to the hundreds of millions of dollars typically required to bring a new drug to market, FDA believes that the added regulatory impact imposed by this rule would be unlikely to threaten the economic viability of any promising research and development project.

E. Benefits

This proposed rule is aimed at addressing two problems associated with inadequate directions for pediatric uses of drugs: (1) Avoidable adverse drug reactions in children, i.e., drug reactions that occur because of the use of inadvertent drug overdoses or other drug administration problems that could have been avoided with better information on appropriate pediatric use; and (2) undertreatment of children with a potentially safe and effective drug, because the physician either prescribed an inadequate dosage or regimen, prescribed a less effective drug, or did not prescribe a drug, due

to the physician's uncertainty about whether the drug or the dose was safe and effective in children. Thus, the primary benefits expected from this proposed rule are the reductions in avoidable adverse drug reactions and undertreatments that would result from better informing physicians about whether, and in what dosages, a given drug was safe and effective for use in children.

FDA is aware of no systematic data in the literature that evaluate the magnitude of harm that results from inadequate information on the use of drugs in children, although numerous anecdotes and case examples exist. Physicians who care for HIV-infected children, for example, have expressed frustration at their inability to treat these children with drugs known to be effective in adults, because they lack information on how to do so safely or effectively.⁵ As mentioned previously in this preamble, history is replete with examples of children who have died or suffered other serious adverse effects as a result of the use of drugs that have not been tested in children and for which better, alternative treatments were available. Many of these adverse events (e.g., "gray baby syndrome" in babies treated with chloramphenicol) develop quickly and would be detected in early clinical studies.

While FDA could not develop a quantitative estimate of the potential benefits of the proposed rule, the agency attempted to gain some more systematic insight into the benefits that might accrue by examining the rate at which each of 20 NME's (approved between 1991 and 1995) were mentioned in the 1996 IMS National Drug and Therapeutics Index (an outpatient drug use data base). The drugs examined were all of those that could be analyzed in this IMS data base, lack full pediatric labeling, were considered to need further pediatric studies at the time of approval, and would have been affected by the proposed rule. FDA found that, after adjusting for the prevalence of the relevant diagnoses in children and adults, 15 of the 20 drugs were mentioned less frequently in association with pediatric treatments than with adult treatments for the same set of approved indications. In 11 of these 15 drugs, pediatric treatment mentions were less than half as frequent. Although it is not possible to conclude, based on these data, that children with those diagnoses are necessarily undertreated relative to adults, these data are consistent with the hypothesis

that the lack of pediatric labeling leads to suboptimal treatment of children.

FDA also examined the number of adverse drug events (ADE's) reported to the agency from 1991 through 1996 for all NME's approved during that time. Of the 25 NME's associated with the highest number of ADE's in children, 8 NME's (responsible for 1,273 pediatric ADE's sufficiently severe to be reported to FDA) had no labeling for use in children at all. An additional 5 NME's (responsible for 434 pediatric ADE's) were labeled for use only in children age 12 and over. Furthermore, of these 13 NME's, 11 would probably have been required to be the subject of further pediatric studies (or of a justification for the lack of studies) under the conditions of this proposed rule if it had been in place at the time of the drug's approval. While it is not possible to conclude that all (or even most) of these ADE's would have been avoided had these drugs been fully labeled for pediatric use, these data confirm that there is substantial pediatric use of drugs not labeled for such use; that this use is associated with ADE's, including serious ADE's; and that the improved knowledge and labeling that would result from this proposed rule could bring significant benefits to children treated with these drugs. The agency solicits information on any available studies or data related to the incidence and costs of either undertreatment or avoidable ADE's in pediatric age groups due to the lack of information on the effects of pharmaceuticals.

F. Small Entities

FDA believes that this proposed rule will not have a significant economic impact on a substantial number of small entities. New drug development is typically an activity completed by large multinational drug firms. FDA reviewed the size of every company that submitted the 60 new drug and biological applications that would likely have been affected by this rule between 1991 and 1995 (see the first two categories in Table 1). Over this 5-year period, only two were for products sponsored by small businesses as defined by the Small Business Administration. Because so few small firms are likely to be significantly affected in any given year, the Commissioner certifies that this rule will not have a significant economic impact on a substantial number of small entities. Therefore, no further analysis is required under the Regulatory Flexibility Act. The agency notes, however, that where pediatric use qualifies as an orphan indication, some of these added research costs could be

⁵Time, March 1997.

reimbursed under the various grant and tax deduction provisions of the Orphan Drug Act.

XI. Request for Comments

Interested persons may, on or before November 13, 1997, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday. Submit written comments on the information collection provisions 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.

XII. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Committee on Drugs, American Academy of Pediatrics, Guidelines for the Ethical Conduct of Studies to Evaluate Drugs in Pediatric Populations, *Pediatrics*, 95(2):286-294, 1995.
2. Pina, L. M., Drugs widely used off label in pediatrics, Report of the pediatric use survey working group of the pediatric subcommittee. Draft.
3. Cote, C. J. et al., "Is the therapeutic orphan about to be adopted?" *Pediatrics*, 98(1):118-123, 1996.
4. Koren, G. et al., "Unexpected alterations in fentanyl pharmacokinetics in pediatric patients undergoing cardiac surgery: age related or disease related?" *Developmental Pharmacology Therapeutics*, 9:183-191, 1986.
5. Gauntlett, I. S. et al., "Pharmacokinetics of fentanyl in neonatal humans and lambs: Effects of age," *Anesthesiology*, 69:683-687, 1988.
6. Powell, D. A. et al., "Chloramphenicol: New perspectives on an old drug," *Drug Intelligence & Clinical Pharmacy*, 16:295-300, 1982.
7. Oski, F. A. et al., *Principles and Practice of Pediatrics*, 2d Edition, J. B. Lippincott Co., Philadelphia, p. 864, 1994.
8. Nathan, D. G. et al., *Hematology of Infancy and Childhood*, 4th Edition, W. B. Saunders Co., Philadelphia, p. 92, 1993.
9. Kauffman, R. E., "Fentanyl, fads, and folly: who will adopt the therapeutic orphans?" *Journal of Pediatrics*, 119:588-589, 1991.
10. McCloskey, J. J. et al., "Bupivacaine toxicity secondary to continuous caudal epidural infusion in pediatric patients," *Anesthesia and Analgesia*, 75:287-290, 1992.

11. Fisher, D. M. et al., "Neuromuscular effects of vecuronium (ORG NC45) in infants and pediatric patients during N₂O halothane anesthesia," *Anesthesiology*, 58:519-523, 1983.

12. Agarwal, R. et al., "Seizures occurring in pediatric patients receiving continuous infusion of bupivacaine," *Anesthesia and Analgesia*, 75:284-286, 1992.

13. Mevorach, D. L. et al., "Bupivacaine toxicity secondary to continuous caudal epidural infusion in pediatric patients," *Anesthesia and Analgesia*, 77:13005-1306, 1993.

14. Editorial: "Cystic fibrosis and colonic strictures," *Journal of Clinical Gastroenterology*, 21(1):2-5, 1995.

15. Olkkola, K. T. et al., "A potentially hazardous interaction between erythromycin and midazolam," *Clinical Pharmacology Therapeutics*, 53:298-305, 1993.

16. Hiller, A. et al., "Unconsciousness associated with midazolam and erythromycin," *British Journal of Anaesthesia*, 65:826-828, 1994.

List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, and Safety.

21 CFR Part 314

Administrative practice and procedure, Confidential business information, Drugs, Reporting and recordkeeping requirements.

21 CFR Part 601

Administrative practice and procedure, Biologics, Confidential business information.

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, it is proposed that 21 CFR parts 201, 312, 314, and 601 be 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. New § 201.23 is added to subpart A to read as follows:

§ 201.23 Required pediatric studies.

(a) A manufacturer of a drug product, including a biological drug product, that is widely used in pediatric patients, or that is indicated for a very significant or life threatening illness, but whose label does not provide adequate information to support its safe and effective use in pediatric populations for the claimed indications may, in compelling circumstances, be required to submit an application containing data adequate to assess whether the drug product is safe and effective in pediatric populations. The application may be required to contain adequate evidence to support dosage and administration in some or all pediatric subpopulations, including neonates, infants, children, and adolescents, depending upon the known or appropriate use of the drug product in such subpopulations. The applicant may be required to develop a pediatric formulation for a drug product that is indicated for a very significant or life threatening illness for which a pediatric formulation is necessary, unless the manufacturer demonstrates that reasonable attempts to produce a pediatric formulation have failed.

(b) The Food and Drug Administration (FDA) may, by order issued by the Center for Drug Evaluation and Research (CDER) or Center for Biologic Evaluation and Research (CBER) Center Director, after notifying the manufacturer of its intent and offering an opportunity for a written response and a meeting, which may include an advisory committee meeting, require a manufacturer to submit an application containing the information described in paragraph (a) of this section within a time specified in the letter, if FDA finds that:

(1) The drug product is widely used in pediatric populations for the claimed indications and the absence of adequate labeling could pose significant risks to pediatric patients; or

(2) The drug product is indicated for a very significant or life threatening illness, but additional dosing or safety information is needed to permit its safe and effective use in pediatric patients.

(c)(1) FDA may grant a full or partial waiver of the requirements of paragraph (a) of this section on its own initiative or at the request of an applicant.

(2) An applicant may request a full waiver of the requirements of paragraph (a) of this section if the applicant certifies that:

(i) Necessary studies are impossible or highly impractical, e.g., because the number of such patients is so small or geographically dispersed; or

(ii) There is evidence strongly suggesting that the drug product would

be ineffective or unsafe in all pediatric age groups.

(3) An applicant may request a partial waiver of the requirements of paragraph (a) of this section with respect to a specified pediatric age group, if the applicant certifies that:

(i) The drug product:

(A) Is not indicated for a very significant or life threatening illness; and

(B) Is not likely to be used in a substantial number of patients in that age group; or

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed; or

(iii) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in that age group; or

(iv) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(4) The request for a waiver must provide an adequate justification.

(5) FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver specified in paragraph (c)(2) or (c)(3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

(d) If a manufacturer fails to submit a supplemental application containing the evidence described in paragraph (a) of this section within the time specified by FDA, and the Center Director of CDER or CBER, under the requirements of paragraph (c) of this section, has not granted a waiver, the drug product may be considered misbranded or an unapproved new drug.

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

3. The authority citation for 21 CFR part 312 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371); sec. 351 of the Public Health Service Act (42 U.S.C. 262).

4. Section 312.23 is amended by redesignating paragraph (a)(10)(iii) as paragraph (a)(10)(iv) and adding new paragraph (a)(10)(iii) to read as follows:

§ 312.23 IND content and format.

(a) * * *

(10) * * *

(iii) *Pediatric studies.* If the drug is a new chemical entity, plans for assessing pediatric safety and effectiveness.

* * * * *

5. Section 312.47 is amended by revising paragraph (b)(1)(i) and the second sentence of paragraph (b)(2) and by adding a new sentence after the fifth sentence to paragraph (b)(1)(v) to read as follows:

§ 312.47 Meetings.

* * * * *

(b) * * *

(1) *End-of-Phase 2 meetings—(i) Purpose.* The purpose of an end-of-phase 2 meeting is to determine the safety of proceeding to phase 3, to evaluate the phase 3 plan and protocols and the adequacy of plans to assess pediatric safety and effectiveness, and to identify any additional information necessary to support a marketing application for the uses under investigation.

* * * * *

(v) *Conduct of meeting.* * * * FDA will also provide its best judgment, at that time, of the pediatric studies that will be required for the drug product and their timing. * * *

(2) *"Pre-NDA" meetings.* * * * The primary purpose of this kind of exchange is to uncover any major unresolved problems, to identify those studies that the sponsor is relying on as adequate and well-controlled to establish the drug's effectiveness, to identify current or planned studies adequate to assess pediatric safety and effectiveness, to acquaint FDA reviewers with the general information to be submitted in the marketing application (including technical information), to discuss appropriate methods for statistical analysis of the data, and to discuss the best approach to the presentation and formatting of data in the marketing application. * * *

* * * * *

6. Section 312.82 is amended by revising the last sentence of paragraph (a) and the second sentence of paragraph (b) to read as follows:

§ 312.82 Early consultation.

* * * * *

(a) *Pre-investigational new drug (IND) meetings.* * * * The meeting may also provide an opportunity for discussing the scope and design of phase 1 testing, plans for studying the drug product in pediatric populations, and the best approach for presentation and formatting of data in the IND.

(b) *End-of-phase 1 meetings.* * * * The primary purpose of this meeting is to review and reach agreement on the design of phase 2 controlled clinical trials, with the goal that such testing will be adequate to provide sufficient data on the drug's safety and effectiveness to support a decision on its approvability for marketing, and to discuss the need for, as well as the design and timing of, studies of the drug in pediatric patients. * * *

PART 314—APPLICATIONS FOR FDA APPROVAL TO MARKET A NEW DRUG OR AN ANTIBIOTIC DRUG

7. The authority citation for 21 CFR part 314 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701, 704, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371, 374, 379e).

8. Section 314.50 is amended in subpart B by redesignating paragraphs (g) through (k) as paragraphs (h) through (l) and by adding new paragraphs (d)(7) and (g) to read as follows:

§ 314.50 Content and format of an application.

* * * * *

(d) * * *

(7) *Pediatric use section.* A section describing the investigation of the drug for use in pediatric populations, including an integrated summary of the information (the clinical pharmacology studies, controlled clinical studies, or uncontrolled clinical studies, or other data or information) that is relevant to the safety and effectiveness and benefits and risks of the drug in pediatric populations for the claimed indications, and a reference to the full descriptions of such studies provided under paragraphs (d)(3) and (d)(5) of this section.

* * * * *

(g) *Pediatric use information—(1) General requirements.* Except as provided in paragraphs (d)(2) and (d)(3) of this section, each application for a new chemical entity shall contain data that are adequate to assess the safety and effectiveness of the drug product for the claimed indications in pediatric populations, including neonates, infants, children, and adolescents, and to support dosing and administration information for each pediatric subpopulation for which the drug is safe and effective. Where the course of the disease and the effects of the drug are sufficiently similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-

controlled studies in adults based on other information, such as pharmacokinetic studies. Studies may not have to be carried out in each pediatric age group, if data from one age group can be extrapolated to others. Assessments of safety and effectiveness required under this section for a drug product that represents a meaningful therapeutic benefit over existing treatments for pediatric patients must be carried out using appropriate formulations for each age group(s) for which the assessment is required.

(2) *Deferred submission.* FDA may, on its own initiative or at the request of an applicant, defer submission of some or all assessments of safety and effectiveness described in paragraph (g)(1) of this section until after approval of the drug product for use in adults. If an applicant requests deferred submission, the request must provide a certification from the applicant of the grounds for delaying pediatric studies, a description of the planned or ongoing studies, and evidence that the studies are being or will be conducted with due diligence and at the earliest possible time. If FDA determines that there is an adequate justification for temporarily delaying the submission of assessments of pediatric safety and effectiveness, the drug product may be approved for use in adults subject to the requirement that the applicant submit the required assessments within a specified time.

(3) *Waivers*—(i) FDA may grant a full or partial waiver of the requirements of paragraph (g)(1) of this section on its own initiative or at the request of an applicant.

(ii) An applicant may request a full waiver of the requirements of paragraph (g)(1) of this section if the applicant certifies that:

(A) The drug product:

(1) Does not represent a meaningful therapeutic benefit over existing treatments for pediatric patients; and
(2) Is not likely to be used in a substantial number of pediatric patients; or

(B) Necessary studies are impossible or highly impractical, e.g., because the number of such patients is so small or geographically dispersed; or

(C) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in all pediatric age groups.

(iii) An applicant may request a partial waiver of the requirements of paragraph (g)(1) of this section with respect to a specified pediatric age group, if the applicant certifies that:

(A) The drug product:

(1) Does not represent a meaningful therapeutic benefit over existing

treatments for pediatric patients in that age group; and

(2) Is not likely to be used in a substantial number of patients in that age group; or

(B) Necessary studies are impossible or highly impractical because, e.g., the number of patients in that age group is so small or geographically dispersed; or

(C) There is evidence strongly suggesting that the drug product would be ineffective or unsafe in that age group; or

(D) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(iv) The request for a waiver must provide an adequate justification.

(v) FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver specified in paragraph (g)(2) or (g)(3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

9. Section 314.81 is amended by adding two new sentences at the end of paragraph (b)(2)(i) and a new paragraph (b)(2)(vi)(c) and by revising paragraph (b)(2)(vii) to read as follows:

§ 314.81 Other postmarketing reports.

* * * * *

(b) * * *

(2) * * *

(i) *Summary.* * * * The summary shall briefly state whether labeling supplements for pediatric use have been submitted and whether new studies in the pediatric population to support appropriate labeling for the pediatric population have been initiated. Where possible, an estimate of patient exposure to the drug product, with special reference to the pediatric population (neonates, infants, children, and adolescents) should be provided, including dosage form.

* * * * *

(vi) * * *

(c) Analysis of available safety and efficacy data conducted or obtained by the applicant in the pediatric population and changes proposed in the label based on this information. An assessment of data needed to ensure appropriate labeling for the pediatric population should be included.

(vii) *Status reports.* A statement on the current status of any postmarketing studies performed by, or on behalf of, the applicant. The statement shall include the status of postmarketing clinical studies in pediatric populations required or agreed to, e.g., to be initiated, ongoing (with projected completion date), completed (including date), completed and results submitted to the NDA (including date). To facilitate communications between FDA and the applicant, the report may, at the applicant's discretion, also contain a list of any open regulatory business with FDA concerning the drug product subject to the application.

* * * * *

PART 601—LICENSING

10. The authority citation for 21 CFR part 601 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 513–516, 518–520, 701, 704, 721, 801 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 360c–360f, 360h–360j, 371, 374, 379e, 381); secs. 215, 301, 351, 352 of the Public Health Service Act (42 U.S.C. 216, 241, 262, 263); secs. 2–12 of the Fair Packaging and Labeling Act (15 U.S.C. 1451–1461).

11. New § 601.27 is added to subpart C to read as follows:

§ 601.27 Pediatric studies.

(a) *General requirements.* Except as provided in paragraphs (b) and (c) of this section, each application for a new biological product for which the applicant has not previously obtained approval shall contain data that are adequate to assess the safety and effectiveness of the product for the claimed indications in pediatric populations, including neonates, infants, children, and adolescents, and to support dosing and administration information for each pediatric subpopulation for which the product is safe and effective. Where the course of the disease and the effects of the product are similar in adults and pediatric patients, FDA may conclude that pediatric effectiveness can be extrapolated from adequate and well-controlled effectiveness studies in adults, based on other information, such as pharmacokinetic studies. In addition, studies may not have to be carried out in each pediatric age group, if data from one age group can be extrapolated to others. Assessments required under this section for a product that represents a meaningful therapeutic benefit over existing treatments must be carried out using appropriate formulations for the age group(s) for which the assessment is required.

(b) *Deferred submission.* FDA may, on its own initiative or at the request of an applicant, defer submission of some or all assessments of safety and effectiveness described in paragraph (a) of this section until after licensing of the product for use in adults. If an applicant requests deferred submission, the request must provide an adequate justification for delaying pediatric studies, a description of the planned or ongoing studies, and evidence that the studies are being or will be conducted with due diligence and at the earliest possible time. If FDA determines that there is an adequate justification for temporarily delaying the submission of assessments of pediatric safety and effectiveness, the product may be licensed for use in adults subject to the requirement that the applicant submit the required assessments within a specified time.

(c) *Waivers.* (1) FDA may grant a full or partial waiver of the requirements of paragraph (a) of this section on its own initiative or at the request of an applicant.

(2) An applicant may request a full waiver of the requirements of paragraph (a) of this section if:

(i) The product:

(A) Does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients; and

(B) Is not likely to be used in a substantial number of pediatric patients; or

(ii) Necessary studies are impossible or highly impractical because, e.g., the number of such patients is so small or geographically dispersed; or

(iii) There is evidence strongly suggesting that the product would be ineffective or unsafe in all pediatric age groups.

(3) An applicant may request a partial waiver of the requirements of paragraph (a) of this section with respect to a specified pediatric age group, if:

(i) The product:

(A) Does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in that age group; and

(B) Is not likely to be used in a substantial number of patients in that age group; or

(ii) Necessary studies are impossible or highly impractical, e.g., because the number of patients in that age group is so small or geographically dispersed; or

(iii) There is evidence strongly suggesting that the product would be

ineffective or unsafe in that age group; or

(iv) The applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

(4) The request for a waiver must provide an adequate justification.

(5) FDA shall grant a full or partial waiver, as appropriate, if the agency finds that there is a reasonable basis on which to conclude that one or more of the grounds for waiver specified in paragraph (c) (2) or (3) of this section have been met. If a waiver is granted on the ground that it is not possible to develop a pediatric formulation, the waiver will cover only those pediatric age groups requiring that formulation. If a waiver is granted because there is evidence that the product would be ineffective or unsafe in pediatric populations, this information will be included in the product's labeling.

Dated: July 24, 1997.

Michael A. Friedman,

Lead Deputy Commissioner for the Food and Drug Administration.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 97-21646 Filed 8-13-97; 2:00 pm]

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Proposed Rules

Federal Register

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Tuesday, September 30, 1997

This section of the FEDERAL REGISTER contains notices to the public of the proposed issuance of rules and regulations. The purpose of these notices is to give interested persons an opportunity to participate in the rule making prior to the adoption of the final rules.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 201, 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; Public Meeting

AGENCY: Food and Drug Administration, HHS.

ACTION: Notification of a public meeting.

SUMMARY: The Food and Drug Administration (FDA) is announcing a public meeting to discuss issues related to the agency's proposed rule on regulations requiring manufacturers to assess the safety and effectiveness of new drugs and biological products in pediatric patients. The proposed rule, previously announced in the Federal Register, requested written comments and proposed new regulations requiring pediatric studies of certain new drug and biological products. The purpose of the meeting is to provide experts in the field and interested individuals an opportunity to discuss specific issues raised by the proposed rule. The agency is seeking comment and specific data on the proposed rule.

DATES: The public meeting will be held on October 27, 1997, from 9 a.m. to 6 p.m. Please arrive no later than 8:30 a.m. to allow time for security clearance. Written requests for oral presentations should be received by the agency on or before October 14, 1997. Written comments must be submitted on or before November 13, 1997.

ADDRESSES: The public meeting will be held at the Cohen Bldg., auditorium, 330 C St. SW., Washington, DC. Submit written requests for oral presentations to Lisa Barclay, Office of Policy (HF-22), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. To expedite processing, fax written

requests for oral presentations to 301-594-6777. To ensure timely handling, the outer envelope or facsimile cover sheet should be clearly marked with: Docket No. 97N-0165, "Pediatric Labeling Meeting," ATTN: Lisa Barclay. Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT:

Khyati N. Roberts, Center for Drug Evaluation and Research (HFD-6), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-6779, FAX 301-594-5493, e-mail robertsk@cder.fda.gov, or

Elaine C. Esber, Center for Biologics Evaluation and Research (HFM-30), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-0641, FAX 301-827-0644, e-mail esber@1.cber.fda.gov.

SUPPLEMENTARY INFORMATION:

I. Background

In the Federal Register of August 15, 1997 (62 FR 43900), the agency published a proposed rule for new regulations requiring pediatric studies of certain new drug and biological products. The proposed rule would attempt to partially address a lack of pediatric use information by requiring that manufacturers of a limited class of new drug and 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 already marketed drugs and biologics would also, in compelling circumstances, have to provide such data. The proposed rule is part of a comprehensive effort to increase the number of new drug and biological products with clinically significant use in children that carry adequate labeling for use in that subpopulation.

Because of the importance of ensuring the safety and effectiveness of the medications administered to children and the need to address the absence of pediatric labeling in the most effective manner possible, FDA, in cooperation with the American Academy of Pediatrics, is announcing a public meeting at which recognized experts in the field, members of the

pharmaceutical industry, and other interested parties will have an opportunity to discuss certain issues raised by the proposed rule. FDA will consider information presented and discussed at the meeting and written comments submitted to the Dockets Management Branch in the development of the final rule. There is no fee for this public meeting.

II. Scope of Meeting

The purpose of this meeting is to complement the process for gathering written comments and recommendations on certain issues raised by the proposed rule. The meeting will provide recognized experts in the field, members of the pharmaceutical industry, and other interested parties an opportunity to discuss these issues. The agency is specifically seeking comment and data on the following:

- (1) What should be considered a "substantial number" of pediatric patients?
- (2) Whether the rule should be restricted to new chemical entities, including new (never-before-approved) drugs, antibiotics and biological products, or whether it should be applied more broadly (e.g., to applications for chemical variations of approved products, new indications, new dosage forms or routes of administration)?
- (3) Whether the proposed grounds for waiving the pediatric study requirement are adequate and whether additional grounds may exist?
- (4) What would constitute sufficient data or an adequate pediatric clinical trial? and
- (5) How should dose and safety levels for each of the different pediatric age groups or stages of development be established? Relevant to this issue, the agency solicits comment on special problems associated with studies in neonates and young infants.

III. Requests for Oral Presentations

Persons who wish to participate in the meeting must file a written or facsimile request for oral presentation with the Office of Policy (address and fax numbers above). The request for oral presentation should contain the speaker's name, address, telephone and fax numbers, title, business affiliation, if any, topic, a brief summary of the

presentation, and approximate amount of time requested for the presentation.

The agency requests that persons or groups having similar interests consolidate their presentations and present them through a single representative. Because presentations will be limited to 1 day, the agency may not be able to accommodate all requests for oral presentations. FDA will allocate the time available for the meeting among the persons who properly file requests for oral presentations. If time permits at the conclusion of the meeting, FDA may allow participation from both interested persons attending the meeting who did not submit a written request for an oral presentation and those who requested an opportunity to make a presentation, but, due to the time limitations, were not granted the request.

IV. Requests for Comments

Interested persons may, on or before November 13, 1997, submit written comments to the Dockets Management Branch (address above). Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

V. Special Accommodations

In order to accommodate the need for space or technical support, persons who are planning on using audiovisual equipment during their oral presentations are urged to provide advance notice of their planned attendance to one of the contact persons identified above. If you need special accommodations due to a disability, please contact one of the contact persons listed above at least 7 days in advance.

VI. Transcripts

Transcripts of the meeting may be requested in writing from the Freedom of Information Office (HFI-35), Food and Drug Administration, 5600 Fishers Lane, rm. 12A-16, Rockville, MD 20857, approximately 15 working days after the meeting at a cost of 10 cents per page.

Dated: September 24, 1997.

William K. Hubbard,

*Associate Commissioner for Policy
Coordination.*

[FR Doc. 97-25937 Filed 9-29-97; 8:45 am]

BILLING CODE 4160-01-F

FDA TALK PAPER

Food and Drug Administration
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, MD 20857

FDA Talk Papers are prepared by the Press Office to guide FDA personnel in responding with consistency and accuracy to questions from the public on subjects of current interest. Talk Papers are subject to change as more information becomes available.

T97-46
Sept. 23, 1997

Susan M. Cruzan: 301-827-6242
Broadcast Media: 301-827-3434
Consumer Hotline: 800-532-4440

FDA PROPOSES RULE ON WOMEN IN CLINICAL TRIALS

FDA today proposed a rule that would ensure that women are not excluded from participating in early studies of drugs and biologics to treat life-threatening diseases just because of their reproductive potential. The following may be used to respond to inquiries.

In a notice to be published in tomorrow's Federal Register, the agency is requesting public comment on a proposal that would prevent the routine exclusion of either men or women from clinical studies because of potential risks of toxicity to offspring or reproductive organs.

The proposed rule would permit FDA to place a trial on clinical hold (not allow the study to be conducted or to continue) if a sponsor proposes to exclude or is excluding women from a trial for inappropriate reasons.

FDA's proposal reflects a significant evolution of thought about participation of women of reproductive potential in clinical studies during the past two decades, and is in keeping with the agency's 1993 guideline encouraging women's participation in all phases of clinical trials.

FDA prepared this proposal after the National Task Force on AIDS Drug Development and the Presidential Advisory Council on HIV/AIDS recommended that women with HIV or AIDS, particularly those of reproductive potential, not be excluded from investigational trials intended to study a therapy for a life-threatening disease.

Many of the women who are affected by HIV and AIDS are young women with reproductive potential.

The council's recommendation, along with limited surveys of some applications showing the exclusion of women of reproductive age in some clinical trials, including some trials of drugs for

life-threatening illness, led to today's proposal.

In developing this proposal FDA focused on several important factors:

First, FDA is committed to expanding access to and accelerating approval of new therapies for life-threatening diseases. FDA recognizes that physicians and patients are generally willing to accept greater potential risks or side effects from medical products to treat life-threatening diseases.

Second, FDA believes that patients, including women of reproductive potential, in concert with their partners and doctors, can make their own risk/benefit decision when provided with thorough information about risks and potential benefits by the clinical investigator. The informed consent process, required by law for participation in all studies, provides information intended to describe known and potential risks, including potential risks to the embryo or fetus, should a woman become pregnant.

By encouraging diversity at all stages of a drug's development, FDA hopes that drug sponsors will generate better data about how the drug will affect the populations that will receive it once it is marketed. The agency believes it is important to identify important information about a drug during the investigational phase, such as dosages for different age groups, genders, and racial subgroups, and to use that information to refine labeling information, patient selection, and dose selection.

It is important to note that the proposed rule would not require specific recruitment goals for women, nor would it apply to all clinical trials. For example, it would not apply to:

-- Clinical trials designed to look at healthy volunteers exclusively;

-- trials designed to test drugs for special circumstances, such as in gender specific populations such as drugs for prostate cancer; or

-- trials designed exclusively for men so long as a companion study in women of reproductive potential has been planned or is being conducted.

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END HOME PAGE

**DEPARTMENT OF HEALTH AND
HUMAN SERVICES**

Food and Drug Administration

21 CFR Part 312

[Docket No. 97N-0030]

**Investigational New Drug Applications;
Proposed Amendment to Clinical Hold
Regulations for Products Intended for
Life-Threatening Diseases**

AGENCY: Food and Drug Administration,
HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the provisions of its regulations governing investigational new drug applications (IND's) to permit FDA to place a clinical hold on one or more studies under an IND involving a drug that is intended to treat a life-threatening disease affecting both genders if men or women with reproductive potential who have the disease and are otherwise eligible but are excluded from participation in an

investigation only because of a risk or potential risk of reproductive or developmental toxicity from use of the investigational drug. Women have been excluded in the past from early clinical trials because of a risk or potential risk of reproductive or developmental toxicity. Therefore, the primary goal of this proposed amendment is to ensure that women with reproductive potential who have a life-threatening disease are not automatically excluded in the future for that reason. The proposed rule would not impose requirements to enroll or recruit a specific number of men or women with reproductive potential.

The proposal would implement a recommendation of both the National Task Force on AIDS Drug Development (the AIDS Task Force) and the Presidential Advisory Council on Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS).

DATES: Submit written comments by December 23, 1997. FDA proposes that any final rule that may issue based on this proposal become effective 60 days after its date of publication in the *Federal Register*.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1-23, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: Nancy E. Derr, Center for Drug Evaluation and Research (HFD-5), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5400, FAX 301-594-6197.

SUPPLEMENTARY INFORMATION:

I. Introduction

On January 19, 1995, the AIDS Task Force made a series of recommendations related to women's participation in the drug development process, including the recommendation that women with reproductive potential not be excluded from studies of drugs being tested for use against life-threatening diseases, particularly HIV- and AIDS-related diseases. This recommendation was based, in part, on data provided by the HIV Law Project of the AIDS Service Center (Ref. 1). The data demonstrated that participation of women in AIDS clinical drug trials was low.¹

¹ As of January 1992, 14,799 participants were enrolled in U.S. AIDS Clinical Trial Group studies sponsored by the National Institute of Allergy and Infectious Diseases, of whom only 1,151 were adult women. (Pearl, M., et al., "Women in U.S. Government Clinical Trials," VIII International Conference on AIDS, 8(2): B235, 1992.)

In 1993, 21,598 participants were enrolled, while only 1,952 were adult women (Korvick, J.A.,

In the view of members of the AIDS Task Force, this low rate of participation raised doubts as to whether a sufficient number of women were being included in these clinical trials to provide clinically meaningful information about the effects of HIV and AIDS drugs in the women who would be using them. These data also raised questions and concerns among women with HIV regarding their ability to participate in trials for promising new experimental therapies. On December 8, 1995, the Presidential Advisory Council on HIV/AIDS adopted the AIDS Task Force's recommendation that FDA amend its regulations to prevent the exclusion of women who have a life-threatening disease from any phase of clinical investigations for that disease because of their reproductive potential. If adopted, this proposed rule would implement that recommendation.

FDA's policies regarding the participation of women in clinical investigations have evolved over time. The agency now believes it is important to codify its policies regarding the participation of women with reproductive potential in clinical investigations of drug products intended to treat life-threatening diseases. The proposed amendments to the clinical hold regulations address the exclusion from clinical trials of members of either gender who have a life-threatening disease. The primary intent, however, is to ensure that women who have a life-threatening disease are not automatically excluded from investigational trials of drug products for that disease due to a perceived risk or potential risk of reproductive or developmental toxicity from the use of the investigational drug. The proposal would not apply to clinical studies conducted: (1) Exclusively in healthy volunteers; (2) under special circumstances, such as studies of a single-gender population (e.g., studies evaluating the excretion of a drug in semen or its effects on menstrual function); or (3) in men, as long as a study that does not exclude subjects with reproductive potential has been planned or is being conducted in women. For the purposes of this rulemaking, FDA does not intend the phrase "women with reproductive potential" to include pregnant women. The agency acknowledges the need for more information on the safety and effectiveness of drugs and biological products in pregnant women and is

continuing to explore this complex issue in other forums.

II. Clinical Hold Regulations

A clinical hold is an order, under § 312.42 (21 CFR 312.42), that FDA may issue to a sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation for the development of a new drug, antibiotic drug, or biological product. A clinical hold may apply to one or more of the investigations under an IND. When FDA places a proposed study on clinical hold, subjects in that study may not be given the investigational drug. When FDA places an ongoing study on clinical hold, no new subjects may be recruited to the study and placed on the investigational drug; subjects already in the study should be taken off the therapy involving the investigational drug unless FDA specifically permits continuation of the therapy in the interest of patient safety.

FDA may place a clinical hold on a proposed or ongoing phase 1, phase 2, or phase 3 investigation (§§ 312.42(b)(1) and (b)(2)), a proposed or ongoing treatment IND or treatment protocol (§ 312.42(b)(3)), or any investigation that is not designed to be adequate and well controlled (§ 312.42(b)(4)). Generally, FDA will attempt to discuss and resolve the matter with the sponsor before issuing a clinical hold order unless subjects are exposed to immediate and serious risk (§ 312.42(c)). When the deficiency that prompts a clinical hold is corrected by the sponsor, the investigation generally may resume (§ 312.42(e)).

III. Evolution of FDA Policy Regarding Participation of Women in Clinical Investigations

Although the proposed amendments to the clinical hold regulations address the exclusion from trials for drug products to treat a life-threatening disease of members of either gender who have the disease, the primary intent of the proposed amendments is to ensure that women who have a life-threatening disease are not excluded from clinical trials solely because of their reproductive potential. Since 1977, when FDA first issued guidance on the participation of women in clinical trials, women with reproductive potential often have been excluded from early clinical trials due to the perceived risk or potential risk of reproductive or developmental toxicity. As the following discussion shows, however, views on the participation of women, as well as corresponding FDA guidance and regulations pertaining to clinical trials of investigational drugs, reflect a

"Trends in Federally Sponsored Clinical Trials," *Until the Cure: Caring for Women With HIV*, A. Kurth, editor, pp. 94-103, 1993).

significant evolution of thought during the past two decades within the agency and the scientific community. In addition, during this period considerable public attention has been paid to questions about the participation of women in general in clinical trials. The following background information highlights key FDA statements on the inclusion of women, especially women with reproductive potential, in the clinical drug testing process. Throughout, the phrase "reproductive toxicity" refers to toxicities to reproductive organs, while the term "developmental toxicity" refers to toxicities to potential offspring.

The agency first provided formal guidance on the participation of women with reproductive potential in clinical trials in a 1977 guideline entitled "General Considerations for the Clinical Evaluation of Drugs" (the 1977 guideline). Developed within the protective environment brought on by the thalidomide experience a decade earlier, the 1977 guideline stated that women of childbearing potential should not be included in phase 1 and early phase 2 trials because of the potential for reproductive or developmental toxicity. Women with childbearing potential could be included in later phase 2 and phase 3 studies, as long as animal teratogenicity and the female part of animal fertility studies had been completed and there was some evidence of effectiveness from earlier studies. The 1977 guideline made an exception to this recommendation for early trials involving drug products intended to treat life-threatening diseases, even in the absence of adequate reproduction studies in animals. Despite this exception, however, the exclusion of women of reproductive potential from early trials was in some cases applied to trials for drug products to treat life-threatening diseases.

Since the 1977 guideline was issued, views have evolved about the participation of women in clinical trials. Views also have evolved about informed individuals assuming the risks of investigational products. Recognition has increased in the agency and among the public that patients, especially those with a life-threatening disease, are willing to accept considerable risks to participate in studies that may benefit them. There is increased public recognition of ethical issues such as fairness and an individual patient's ability to participate in decisions that involve personal risk. There is growing understanding that information about population subgroups, e.g., subsets grouped by age, gender, or race, is needed to evaluate the safety and

effectiveness of therapies and to refine labeling, patient selection, and dose selection in those groups. Failure to obtain such information may limit the usefulness of a treatment or expose a segment of the population to risk. These perspectives have influenced FDA policy since the early 1980's.

In the Federal Register of July 22, 1993 (58 FR 39406), FDA issued a "Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs" (the 1993 guideline). That guideline revoked the 1977 guideline's recommendation regarding restrictions on the participation of women with reproductive potential in early clinical trials, including clinical pharmacology studies (e.g., dose tolerance, bioavailability, and mechanism of action studies) and early therapeutic studies. The 1993 guideline left the determination about whether the risks and benefits support the participation of women with reproductive potential to patients, investigators, sponsors, and institutional review boards (IRB's).

Although the 1993 guideline does not require participation of women in any particular trial, it sets forth FDA's general expectations regarding the inclusion of both women and men in drug development, analyses of clinical data by gender, assessment of potential pharmacokinetic differences between genders, and conduct of specific additional studies in women, where indicated. The 1993 guideline is consistent with an earlier guideline, issued in 1988 and entitled, "Guideline for the Format and Content of the Clinical and Statistical Sections of New Drug Applications" published in the Federal Register of October 7, 1988 (53 FR 39524), in which FDA advised that new drug applications (NDA's) should include analyses of data for population subsets, including age, gender, and race, to identify subgroup differences in effectiveness and adverse reactions to investigational drugs. The 1993 guideline notes that participants in clinical studies should, in general, reflect the population that will receive the drug once it is marketed and encourages the participation of women, whether or not they have a serious disease, in early phases of all clinical trials. It points out that including women early is particularly important when a drug is intended for a serious disease and may become available rapidly, for example, through distribution under a treatment IND (§§ 312.34 and 312.35 (21 CFR 312.34 and 312.35)), or marketing under subpart E of part 601 (21 CFR part 601) and consisting of §§ 601.40 through

601.46 or subpart H of part 314 (21 CFR part 314) and consisting of §§ 314.500 through 314.560. (See section IV.A. of this document for a description of these procedures.)

FDA has long recognized the importance of gender data in evaluating the safety and efficacy of a drug. This is reflected in other FDA guidances issued in 1993 ("New Drug Evaluation Guidance Document: Refusal to File" and "Center for Biologics Evaluation and Research (CBER): Refusal to File (RTF) Guidance for Product License Applications (PLA's) and Establishment License Applications (ELA's)" (58 FR 38770, July 20, 1993). These documents state that FDA may refuse to file an application if it contains inadequate evaluation of the safety and/or effectiveness of a drug, biological therapeutic, or vaccine in specific populations, such as in women, intended to use the product.

FDA also recently proposed a rule that would codify expectations regarding presentation in NDA's of safety and effectiveness data by gender as described in the 1993 guideline. Although it would not require the inclusion of women with reproductive potential in clinical investigations, the rule would require the presentation in NDA's of certain data by specific population subgroups, including women, who are likely to receive the drug once it is marketed (60 FR 46794, September 8, 1995).

The 1977 guideline never recommended excluding women with reproductive potential from trials for drugs to treat life-threatening diseases. Moreover, the 1993 guideline recommended that the exclusion of such women be removed from all trials. Nevertheless, a recent limited agency review of clinical trial protocols dealing with antiviral drugs revealed that women with reproductive potential are still being excluded from some protocols of some investigational trials for drug products intended to treat HIV, a life-threatening disease. The agency believes that this violates ethical principles and in some cases could lead to inadequate data on use in women prior to wide availability of the drug. The agency has concluded that women with reproductive potential who have a life-threatening disease should no longer be excluded from investigational clinical trials for drug products to treat that disease because of a risk or potential risk of reproductive or developmental toxicity from use of the investigational drug, as long as patient volunteers are fully informed of the risks, in compliance with informed

consent regulations in part 50 (21 CFR part 50).

IV. Rationale for the Proposed Rule

In the past, women with a life-threatening disease who have reproductive potential often have been excluded from early investigational clinical trials for that disease because of the potential risk of reproductive or developmental toxicity. As a result, although it applies to the exclusion of either gender, the primary goal of this proposed rule is to ensure that women who have a life-threatening disease are not excluded from investigational drug studies for that disease because of their reproductive potential.

In lengthy discussions with representatives of industry and the public during the development of this proposal (Ref. 2), the view was expressed that many early clinical studies involving life-threatening diseases offer the potential for therapeutic benefit. In some cases, for example, participation in an early clinical study is a prerequisite for enrollment in later studies. Based on these discussions, FDA has concluded that all trials involving patients with life-threatening diseases should, for purposes of this proposed rule, be considered to have therapeutic potential and that this proposal would apply to studies in any phase of a clinical investigation that enroll participants with a life-threatening disease.

In developing this proposal, FDA focused on four important factors: (1) FDA is committed to expanding access to and accelerating approval of new therapies for life-threatening diseases; (2) important ethical principles underlie the belief that neither gender should be excluded from early clinical trials involving a life-threatening disease because of their reproductive potential; (3) the mechanisms are in place, or are available, to protect individuals who participate in clinical trials from potential risks; and (4) FDA is committed to expanding the collection of gender-specific data on investigational therapies, especially for those populations who ultimately will be using the therapies. These four factors are discussed in detail in the following sections of this document.

A. Expanding Access and Accelerating Approval

FDA is committed to expanded patient access to potentially beneficial therapies for life-threatening and serious diseases, such as cancer and AIDS, through the IND process. Mechanisms for expanding access include treatment IND's (§§ 312.34 and 312.35), parallel

track protocols (57 FR 13250, April 15, 1992), and other open-label protocols either for groups of patients or for one patient. Tens of thousands of patients have received promising pharmaceuticals under expanded access mechanisms.

In many cases, the risk-benefit assessment for investigational drugs for life-threatening or even serious diseases differs from that for investigational drugs for treating diseases not considered life-threatening or serious. In establishing procedures for the investigation of drugs for life-threatening diseases, FDA has recognized that physicians and patients are generally willing to accept greater risks or side effects from these medical products than they would accept from products that treat less serious diseases (53 FR 41516 at 41518, October 21, 1988).

FDA also is committed to expediting the approval of investigational drugs for treatment of life-threatening and serious diseases. The agency has issued regulations for the expedited development of new therapies intended to treat persons with life-threatening or severely debilitating diseases (subpart E of part 312 (21 CFR part 312) procedures in §§ 312.80 through 312.88), especially where no satisfactory alternative therapies exist. In addition, FDA has issued regulations for the accelerated approval of certain new drugs (subpart H of part 314 procedures in §§ 314.500 through 314.560) and biological products (subpart E of part 601 procedures in §§ 601.40 through 601.46) for serious or life-threatening diseases. For instance, accelerated approval can be based on a surrogate endpoint that reasonably suggests clinical benefit or on evidence of the drug's effect on a clinical endpoint other than survival or irreversible morbidity. On March 29, 1996, President Clinton announced a major initiative undertaken by FDA to make promising new therapies available sooner to American cancer patients with intractable or unresponsive malignancies. Under this initiative, FDA proposes, among other things, to shorten approval times for cancer treatments by recognizing that tumor shrinkage is often an early indication of a treatment's effectiveness and by basing approval of investigational drugs for refractory tumors on evidence of tumor shrinkage.

In view of the agency's commitment to provide expanded access to and accelerated approval of new therapies for life-threatening and serious diseases, this proposed rule is intended to ensure that women with reproductive potential who have a life-threatening disease are not excluded from volunteering for and

being included in clinical investigational trials for drug products intended to treat their disease. Although a risk or potential risk of reproductive or developmental toxicity might exist, FDA recognizes that the potential benefits that may be accrued by these women from participation in a study for their disease may outweigh such risks and that the availability of certain safeguards can reduce these risks. (See section IV.C. of this document for a discussion regarding minimizing risks.)

B. Ethical Principles

In developing this proposal, FDA has carefully considered the evolution of thought within the agency and the scientific community and among the public regarding the participation of women in clinical trials and the related risks or potential risks. The agency also has considered the basic ethical principles that underlie clinical research. Current FDA and Department of Health and Human Services regulations related to informed consent and IRB's are based, in large part, on the three ethical principles relevant to human subject research discussed in the Report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (the Belmont Report) (44 FR 23192, April 18, 1979). These principles include respect for persons, beneficence, and justice.

The principle of respect for persons usually is cited within the context of being certain that individuals are included in clinical research voluntarily after being fully informed. The principle recognizes the ability of autonomous individuals to make their own decisions about participating in clinical research.

The principle of beneficence requires that the risks associated with a clinical research activity be reasonable in the light of expected benefits. Beneficence also requires that the chance for benefits from participation be maximized, and the risk of possible harms be minimized, consistent with sound research design. In weighing risks and benefits, beneficence also recognizes the results of research as a potential benefit, so long as the rights of research participants are protected.

The principle of justice requires that the burdens and benefits of participation in clinical research be equitably distributed across the entire population in the place or region where the clinical research is conducted. In general, racial, ethnic, gender, and economic status should not be used as a basis for excluding participation in clinical research. Furthermore, persons who are eligible for participation in the

clinical research because of their disease or condition should be provided a reasonable opportunity to be included in the research until the research cohort is fully recruited.

An Institute of Medicine committee recently examined the issue of women in health research (Ref. 3). As part of their deliberations, they highlighted the ethical principle of justice and recommended that the scientific community and the institutions that support it ensure that scientific advances in medicine and public health fairly benefit all people, regardless of gender, race, ethnicity, or age. The committee concluded that clinical trials should be conducted consistent with the principle that medical research promotes the health and well-being of both women and men. This proposed rule would help achieve that goal by ensuring that women with a life-threatening disease are not denied the opportunity to contribute to the body of scientific knowledge about their disease and its manifestations in women.

The proposed rule is consistent with the three ethical principles in the Belmont Report and would help to ensure that women with reproductive potential who suffer from a life-threatening disease are no longer excluded from early clinical research.

C. Informed Consent and Other Mechanisms for Protecting People With a Life-Threatening Disease in Early Clinical Trials

A number of mechanisms are in place to protect participants in early clinical trials, including requirements for sound study design, the use of sound research procedures, and the proper use of the informed consent process. In addition to the sponsors, who have the responsibility of designing safe clinical trials, and the investigators, who carry them out, institutional review boards (IRB's) play an important role in ensuring participant safety in clinical trials. It is the responsibility of the involved IRB to determine that specific criteria for the protection of study participants are met before approving research subject to the IND regulations (§ 56.111(a) (21 CFR 56.111(a))). For example, the IRB must determine that risks to study participants are minimized by the use of procedures consistent with sound research design and that risks to study participants are reasonable in relation to anticipated benefits (§ 56.111(a)(1) and (a)(2)). The IRB also is responsible for ensuring that information given to study participants as part of the informed consent process is in accordance with FDA's regulations under part 50 (see § 56.111(a)(4)).

Elements of informed consent require that potential study participants be adequately informed that the study involves research (§ 50.25(a)(1)) and of any foreseeable risks or discomforts (§ 50.25(a)(2)). In addition, prospective study participants must be informed, when appropriate, of certain unforeseeable risks, including potential risks to the embryo or fetus, should a female study participant become pregnant (§ 50.25(b)(1)). As FDA noted in the 1993 guideline, if animal reproductive toxicity studies are complete, the results and an explanation of their significance in humans should be presented as part of the informed consent process (58 FR 39406 at 39411). If these studies are not complete, that fact should be communicated along with any other pertinent information, such as a general assessment of reproductive and fetal toxicity associated with other drugs that have related chemical structures or pharmacological effects. If no relevant information is available, the informed consent should explicitly state that fact and make clear that the potential exists for reproductive risks and/or developmental risks to a fetus. If needed, the IRB should require that a specific period of time lapse between when the potential study participants receive relevant information and when they must decide whether to participate in the study. If in the IRB's judgment, additional information to that required by § 50.25 would add meaningfully to the protection of the rights and welfare of study participants, the IRB may require the imparting of that information to the study participants (21 CFR 56.109(b)).

It is also the responsibility of the IRB to determine that the study is designed in such a way as to minimize the risk of fetal exposure to possibly harmful agents. Developmental toxicity has been linked to maternal exposure to certain drugs. Although a link between paternal drug exposure and developmental toxicity has not been conclusively established, results of some studies suggest that paternal exposure to certain drugs might be associated with developmental toxicity (Ref. 4). In particular, low-level, chronic genotoxic exposures that maintain fertility might lead to fetal developmental abnormalities, particularly when there is exposure of post-stem cell stages of spermatozoal development. Although the agency has not issued formal guidance on this issue, in such cases, it might be prudent to take precautions to prevent impregnation of women by men

participating in such investigational studies.

The risk of fetal exposure can be eliminated by preventing pregnancy (except in those studies designed to test a drug's effect during pregnancy). The risk of fetal exposure also can be minimized by sponsors and IRB's, who can require the use of pregnancy testing to detect unsuspected pregnancy prior to initiation of study treatment or at intervals during the course of drug exposure. When the study design permits, sponsors can minimize potential developmental risks by short-term timing of studies to coincide with the early follicular phase of the menstrual cycle. Thus, in most of these short-term studies, the investigational agent would be eliminated from a woman's body prior to conception, should she inadvertently become pregnant. When the teratogenic effects of a drug are well established, the agency, sponsor, or IRB may require the use of contraception to prevent pregnancy in sexually active individuals of childbearing potential.

Women and men can eliminate the possibility of pregnancy through abstinence and reduce the possibility of pregnancy through the use of contraception for the duration of drug exposure (which may exceed the length of the study). In part because the cooperation of the individual's sexual partner may be needed to ensure that abstinence occurs, or that appropriate contraceptive methods are used, it is important for potential study participants to be provided with an opportunity to discuss their involvement in a clinical trial with their sexual partner prior to deciding whether to participate in the study.

The agency believes that, through the proper use of the informed consent process and the use of other study design mechanisms, risks to participants in early clinical trials can be reduced. When deciding whether to participate in a clinical trial for an investigational drug, potential participants should be able to weigh, in consultation with their spouse or partner, their health care provider, and their researcher, the potential risks of their participation.

D. Expanding the Collection of Gender-Specific Data

As noted previously, the need for gender specific data was the subject of guidances developed by the agency in 1988 and 1993 and was addressed in a proposed rule issued in 1995. Recently, medical and scientific issues related to gender analyses were the subject of an FDA-sponsored workshop on "Gender Studies in Product Development:

Scientific Issues and Approaches" held from November 6 to 7, 1995 (Ref. 5). Workshop participants, including representatives from industry, academia, government agencies, consumer groups, and patient communities, concluded that women should be included in all stages of drug development to fully characterize the safety and efficacy profile of the product. It was noted by numerous participants that use of gender-specific data from early trials may improve the efficiency of phase 3 trials by aiding in the interpretation of expected variations among gender groups.

In the 1993 guideline, FDA acknowledged that although drugs often behave similarly in demographic (age, gender, race) and other (concomitant disease, concomitant drugs) subsets of the population, there are many differences within such subsets, for example, in dose-response, in maximum size of effect, or in the risk of an adverse effect (58 FR 39406 at 39409). To identify such potential differences and to help refine labeling information, patient selection, and dose selection, the agency believes that it is important that those women who are likely to use an investigational agent once it is marketed be included in clinical investigations that may identify potential gender differences. In the case of HIV and AIDS, many of the women who are affected are young women with reproductive potential. Therefore, early participation by these women in clinical trials for such diseases will help ensure that needed gender-specific safety and effectiveness data are available for the women affected by the disease (Ref. 6).

V. Legal Authority

Section 505(i) (21 U.S.C. 355(i)) of the Federal Food, Drug, and Cosmetic Act (the act) confers broad authority upon the Secretary of Health and Human Services (the Secretary) (and by delegation to FDA) to issue regulations governing the clinical investigation of new drugs to protect the rights, safety, and welfare of human subjects (including through informed consent provisions) and otherwise to protect the public health. In addition, section 701 of the act (21 U.S.C. 371) provides that the Secretary has authority to issue regulations for the efficient enforcement of the act (including the drug-related provisions, such as the misbranding and approval provisions of sections 502 (21 U.S.C. 352) and 505 of the act).

The proposed amendment to the clinical hold regulations is intended to protect human subjects against being categorically excluded, based on reproductive potential, from the

opportunity to participate in clinical trials investigating potentially beneficial treatments for a life-threatening disease. In addition, the proposed amendment would enhance public health protection by expanding opportunities to generate data concerning the safety and efficacy of investigational drugs for the treatment of life-threatening diseases.

The agency believes that prohibiting the exclusion of women with reproductive potential who have a life-threatening disease from clinical trials also is consistent with congressional efforts to prevent unwarranted discrimination against women. In the employment context, for example, the Civil Rights Act of 1964, as amended by the Pregnancy Discrimination Act (42 U.S.C. 2000e(k), 2000e-2(e)(1)) and as interpreted by the U.S. Supreme Court in the landmark case of *International Union, United Automobile, Aerospace and Agricultural Implement Workers, UAW v. Johnson Controls, Inc.*, 111 S.Ct. 1196 (1991), prohibits the exclusion of women with childbearing capacity from jobs they are qualified to perform solely because the working conditions of those jobs pose potential risks to exposed fetuses. Although the Court did not consider or hold that the Civil Rights Act applies to clinical drug trials, which are manifestly different in nature and purpose from private employment, FDA believes it is appropriate to consider the Court's opinion when developing policy on the eligibility of women with reproductive potential for participation in clinical trials for a life-threatening disease.

VI. Description of the Proposed Rule

Current § 312.42(b)(1) identifies the grounds for placing a clinical hold on proposed or ongoing phase 1 studies under an IND, and current § 312.42(b)(2) identifies the grounds for placing a clinical hold on proposed or ongoing phase 2 or phase 3 studies. FDA is proposing to amend §§ 312.42(b)(1) and (b)(2) to provide an additional ground for placing a phase 1, phase 2, or phase 3 study under an IND on clinical hold. Under proposed §§ 312.42(b)(1)(v) and (b)(2)(i), FDA may issue a clinical hold on any proposed or ongoing clinical trial for a life-threatening illness or disease that affects both genders if men or women with reproductive potential who have the disease being studied are excluded from eligibility in any phase of clinical investigation because of a risk or potential risk of reproductive toxicity (i.e., toxicity to reproductive organs) or developmental toxicity (i.e., toxicity to potential offspring) from use of the investigational drug. FDA believes that such risks would be outweighed by the

potential benefits that may be accrued by participants in a study for the treatment of their disease and that fully informed potential participants should be able to make their own risk-benefit determination. FDA also believes that, in the case of developmental toxicity, potential risks can be minimized by the prevention of pregnancy through contraception or abstinence.

The clinical hold under proposed §§ 312.42(b)(1)(v) and (b)(2)(i) would not apply to clinical studies conducted: (1) Exclusively in healthy volunteers; (2) under special circumstances, such as studies of a single-gender population (e.g., studies evaluating the excretion of a drug in semen or its effects on menstrual function); or (3) in men, as long as a study that does not exclude subjects with reproductive potential has been planned or is being conducted in women.

The phrase "women with reproductive potential" as used in the proposed rule does not include pregnant women. The proposed rule also would not impose requirements to enroll or recruit a specific number of men or women with reproductive potential.

As is true for clinical holds on any basis, FDA ordinarily would issue a clinical hold only after attempts to convince the sponsor to remove an exclusion had failed (§ 312.42(c)).

Under proposed § 312.42(b)(1)(v), "life-threatening illnesses or diseases" are defined as "diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted." The proposed definition is consistent with the definition of "life-threatening" in the IND regulations governing drugs intended to treat life-threatening illnesses (21 CFR 312.81(a)(1)).

The proposed definition of life-threatening illnesses or diseases is intended to include those fatal diseases where death itself may not be imminent, but where treatment is necessary to prevent premature death. For example, an anti-retroviral drug might be found, on the basis of phase 2 studies, to delay progression from the asymptomatic state to the symptomatic state and then to AIDS when used early after infection with HIV. Although this progression ordinarily would take more than 12 months to occur in most patients, this condition would be within the definition of life-threatening. Other examples of life-threatening illnesses include cancer, certain cardiac arrhythmias, intracranial hemorrhage, or amyotrophic lateral sclerosis.

The exclusion of subjects with reproductive potential addressed by this proposed rule not only includes explicit

exclusion but also de facto exclusion. For example, a de facto exclusion might result from setting study entry criteria that require sterilization and would have the effect of precluding enrollment of participants with reproductive potential. De facto exclusions also might result from setting criteria that are inherently difficult for subjects to meet, such as weight, or other physical requirements that generally differ between women and men.

VII. Environmental Impact

The agency has determined under 21 CFR 25.30(h) 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. Paperwork Reduction Act of 1995

This proposed rule does not contain any information collection provisions that would be subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-3520).

IX. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601-612). 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 Regulatory Flexibility Act requires agencies to analyze regulatory options if the proposed rule is expected to have a significant impact on a substantial number of small entities.

The Unfunded Mandates Reform Act (Pub. L. 104-4) requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in an annual expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation). This proposed rule does not impose any mandates on State, local, or tribal governments, or the private sector that will result in an annual expenditure of \$100,000,000 or more. The data for the impacts analysis were developed by FDA's Economics Staff, Office of Management and Systems, Office of Planning and Evaluation, and their full

report is on file at the Dockets Management Branch (address above).

A. Costs

Implementation of this proposed rule could impart additional direct costs to the industry in one area—the cost associated with testing for pregnancy in women with reproductive potential who volunteer to participate in clinical trials that would have previously excluded them.

As fully described in its detailed study (Ref. 7), FDA estimated the direct cost in the following manner. Using an FDA protocol database, the agency estimated the number of clinical trials for drug products for life-threatening diseases from which women with reproductive potential are being excluded. The agency then determined the total number of subjects recruited for those clinical trials. Using published information, the agency estimated the relative incidence among women with reproductive potential for the specific life-threatening diseases compared to the incidence in the general population. Using the estimates of relative incidence among women with reproductive potential for the specific disease, it was estimated how many women would be participating in clinical trials for the specific disease, were they not being excluded. Finally, using the approximate length of each phase of clinical trials (phases 1, 2, and 3), the agency calculated the number of pregnancy tests that would be necessary to test for pregnancy in this volunteering population subset.

FDA conducted its analysis using data extracted from the majority of the clinical trial protocols submitted to four review divisions in the Center for Drug Evaluation and Research (CDER) during a 20-month period between August 1, 1993, and March 31, 1995: Cardio-Renal; Anti-Viral; Medical Imaging, Surgical and Dental; and the former Pilot Drug Evaluation. The protocol data base includes information on the phase of the studies (whether they are phase 1, 2, or 3), the planned size of the trials, and the indications for which the therapies are being studied. Data from this data base were analyzed to estimate how many protocols were submitted to these four FDA divisions involving life-threatening illnesses that excluded women with reproductive potential. Forty-three protocols involving life-threatening illnesses and excluding women with reproductive potential were identified as having been submitted to FDA during this 20-month period.

Projecting the number of submissions from the four review divisions across the entire agency required additional analysis because it could not be assumed that all review divisions receive protocols for life-threatening diseases at the same rate. To adjust for the difference from division to division, the agency calculated the number of NDA approvals that were granted in each division for drugs to treat life-threatening and severely debilitating illnesses under the accelerated approval procedures of subpart E of part 312. Using the results of this analysis and the annualized numbers from the four analyzed review divisions, it was possible to calculate approximately how many protocols for life-threatening diseases that exclude women are submitted to individual review divisions each year. It was projected that approximately 62 protocols are submitted to FDA per year for life-threatening diseases that exclude women with reproductive potential.

Next it was assumed that, once they are no longer excluded, women with reproductive potential would enter clinical trials in proportion to the relative incidence of the disease occurrence in that population at diagnosis. Using published data on the relative incidence among women with reproductive potential at diagnosis of AIDS, HIV, and coronary heart disease and the number of protocols submitted to the four divisions projected across the entire agency and annualized, the agency estimated how many women (ages 13 to 49 years) are excluded per year from phase 1, phase 2, and phase 3 clinical studies in the United States. The results showed that approximately 90 women with reproductive potential are excluded from phase 1 studies, 266 from phase 2 studies, and 40 from phase 3 studies annually in the United States.

If one assumes further that phase 1 studies last approximately 2 weeks, phase 2 studies approximately 3 months, and phase 3 studies about a year, the costs for pregnancy testing can be assessed. During phase 1 studies, approximately 1 pregnancy test would be required for each woman with reproductive potential entering the study; during phase 2 studies, approximately 3 tests would be required; and, during phase 3 studies, approximately 12 tests would be required. At a cost of \$30 per test, the annual cost to industry is estimated to be at most about \$41,000. This estimate is summarized in Table 1.

TABLE 1.—ESTIMATED ANNUAL COSTS OF TESTING FOR PREGNANCY IN WOMEN WITH REPRODUCTIVE POTENTIAL IN U.S. CLINICAL TRIALS FOR THERAPIES FOR LIFE-THREATENING ILLNESSES

Study Phase	Tests Required per Woman	Estimated Number of Women Annually	Cost per Test	Annual Costs
1	1	90	\$30	\$2,700
2	3	266	\$30	\$23,940
3	12	40	\$30	\$14,400
Totals		396		\$41,040

The largest cost encountered in the 43 analyzed protocols was a phase 2 trial from which an estimated 45 women with reproductive potential were excluded. The cost of pregnancy testing for this trial, if women with reproductive potential had been included, would have been about \$4,050. Of the 43 protocols analyzed, 6 had estimated costs of pregnancy testing exceeding \$1,000.

The agency is aware of industry's concerns about the liability exposure associated with the inclusion of women with reproductive potential in clinical trials, particularly prior to completion of animal reproductive studies. FDA believes, however, that the inclusion in investigational studies of women with reproductive potential who have a life-threatening disease and who have given informed consent is not likely to lead to increased liability. Informed consent means that a study participant has agreed to participate despite recognition and appreciation of known or potential risks, an agreement that should minimize the legal risks associated with drug development. Careful use of study design and informed consent is likely to minimize exposure to liability (Refs. 8 and 9). There is, of course, no way to guarantee this, but there have been few instances of liability assessed against drug manufacturers for the conduct of clinical trials.

As already stated, if a deficiency exists in a clinical investigation that may be grounds for the imposition of a clinical hold, FDA will generally attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order (§ 312.42(c)). An IND would be placed on clinical hold for specifically excluding women with reproductive potential only as a last resort. Only for those few protocols could there be an increase in cost, due primarily to a delay in starting the clinical trials.

The agency believes that the societal benefits more than outweigh the potential minimal additional costs because a considerable patient population (women with reproductive potential who have a life-threatening

disease) could receive a potentially beneficial new therapy.

B Small Entities

The protocol analysis identified protocols sponsored by small businesses. The largest additional pregnancy testing cost incurred by a small business in the reviewed protocols under the proposed rule was \$990. Projected across all CDER/CBER review divisions and annualized, we expect no more than nine protocol submissions per year from small businesses that might incur additional costs under the proposed rule. Few small firms are likely to be affected in any given year and most of these would incur no significant additional costs. Therefore, under the Regulatory Flexibility Act, the Commissioner of Food and Drugs certifies that this rule will not have a significant effect on a substantial number of small entities.

X. Request for Comments

Interested persons may, on or before December 23, 1997, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

XI. References

Copies of the following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. McGovern, T., "Proposal to Eliminate Obstacles Facing Women in the Drug Development Process: A Recommendation to the National Task Force on AIDS Drug Development," HIV Law Project of the AIDS Service Center, June 30, 1994.

2. Transcript of the meeting of the National Task Force on AIDS Drug Development, October 28, 1994 (see discussion on pp. 25 to 70).

3. Mastroianni, A. C., R. Faden, and D. Federman, editors, *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Vol. 1, National Academy Press, Washington, pp. 75-83, 1994.

4. DeLap, R. J., J. L. Fourcroy, and G. A. Fleming, "Fetal Harm Due to Paternal Drug Exposure: A Potential Issue in Drug Development," *Drug Information Journal*, 30:359-364, 1996.

5. Transcript of the FDA workshop "Gender Studies in Product Development: Scientific Issues and Approaches," November 6-7, 1995.

6. Sherman, L. A., R. Temple, and R. B. Merkatz, "Women in Clinical Trials: An FDA Perspective," *Science*, 269:793-795, 1995.

7. Food and Drug Administration, Office of Management and Systems, Office of Planning and Evaluation, *Impacts of Not Excluding Women with Reproductive Potential Who Have Life-threatening Illnesses from Clinical Trials*, January 10, 1997.

8. Flannery, E., and S. N. Greenberg, "Liability Exposure for Exclusion and Inclusion of Women as Subjects in Clinical Studies," in *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Vol. 2, edited by A. C. Mastroianni, R. Faden, and D. Federman, National Academy Press, Washington, pp. 96-97, 1994.

9. Clayton, E. W., "Liability Exposure When Offspring Are Injured Because of Their Parents' Participation in Clinical Trials," in *Women and Health Research: Ethical and Legal Issues of Including Women in Clinical Studies*, Vol. 2, edited by A. C. Mastroianni, R. Faden, and D. Federman, National Academy Press, Washington, pp. 108-109, 1994.

List of Subjects in 21 CFR Part 312

Drugs, Exports, Imports, Investigations, Labeling, Medical research, Reporting and recordkeeping requirements, Safety.

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, it is proposed that 21 CFR part 312 be amended as follows:

PART 312—INVESTIGATIONAL NEW DRUG APPLICATION

1. The authority citation for 21 CFR part 312 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug,

and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371); sec. 351 of the Public Health Service Act (42 U.S.C. 262).

2. Section 312.42 is amended by adding new paragraph (b)(1)(v) and by revising paragraph (b)(2)(i) to read as follows:

§ 312.42 Clinical holds and requests for modification.

* * * * *

(b) * * *

(1) * * *

(v) The IND is for the study of an investigational drug intended to treat a life-threatening illness or disease that affects both genders, and men or women with reproductive potential who have the disease being studied are excluded from eligibility in any phase of clinical investigation because of a risk or potential risk of reproductive (i.e., toxicities to reproductive organs) or developmental (i.e., toxicities to potential offspring) toxicity from use of the investigational drug. The phrase "women with reproductive potential" does not include pregnant women. For purposes of this paragraph, "life-threatening illnesses or diseases" are defined as "diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted." The clinical hold would not apply under this paragraph to clinical studies conducted:

(A) Under special circumstances, such as studies of a single-gender population (e.g., studies evaluating the excretion of a drug in semen or the effects on menstrual function); or

(B) In men, as long as a study that does not exclude subjects with reproductive potential has been planned or is being conducted in women.

(2) * * *

(i) Any of the conditions in paragraphs (b)(1)(i) through (b)(1)(v) of this section apply; or

* * * * *

Dated: September 16, 1997.

Michael A. Friedman,

Lead Deputy Commissioner for the Food and Drug Administration.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 97-25268 Filed 9-23-97; 8:45 am]

BILLING CODE 4160-01-F

HHS NEWS

U.S. Department of Health and Human Services

P97-33

FOR IMMEDIATE RELEASE

September 26, 1997

FOOD AND DRUG ADMINISTRATION

Media Press: (301) 827-6242

Broadcast Media: (301) 827-3434

Consumer Hotline: (800) 532-4440

FDA WARNS CONSUMERS ABOUT TWO UNAPPROVED HOME-USE TEST KITS

FDA is advising consumers and pharmacists about two unapproved, fraudulently marketed home-use test kits distributed by Lei-Home Access Care, a division of Jin-Greene Biotechnology, Inc. in Sunnyvale, Calif. One test kit is advertised on the internet as the "Personal HIV Test Kit" and is labeled the "Lei-Home Access HIV Test." The other test kit is labeled as an "In-home Hepatitis A Test Kit." Results from any unapproved tests for home use are unreliable.

The human immunodeficiency virus (HIV) is the virus that causes the disease AIDS. The hepatitis A virus, usually a food-borne illness, causes a mild, rarely serious, liver disease.

FDA is recommending that pharmacists remove any of these unapproved test kits from their stores.

Currently, the only approved HIV home collection system being marketed in the United States is the Home Access HIV-1 Test System (also called the Home Access Express HIV-1 Test System), manufactured by the Home Access Health Corporation, Hoffman Estates, Ill. With this home system, the user mails a dried blood sample obtained from a finger prick to a laboratory for analysis. Confidential, highly accurate test results are obtained by telephone, with a trained counselor available. FDA has not approved a hepatitis A home test kit.

FDA is advising consumers who purchased the "Lei-Home Access HIV Test" or the "In-Home Hepatitis A Test Kit" to consult with a health professional about other available approved tests that detect antibodies to the HIV virus and the hepatitis A virus.

ATTENTION TV BROADCASTERS: Please use open caption for the hearing impaired.

FDA HOME PAGE

Unpasteurized Cider and Juice Can Contain Bacteria That Make Children and Some Other People Sick

People in the
following
high-risk
groups should
drink *only*
pasteurized
cider and juice:

- Children
- Older adults
- People with weakened immune systems, such as those with HIV, AIDS, or cancer.

Some kinds of juice and cider have not been pasteurized and may contain harmful bacteria. Unpasteurized juice and cider may not be labeled with a statement saying they are unpasteurized and warning of the risk of unpasteurized juice.

Frozen concentrate, shelf-stable juice in hermetically sealed containers, and canned juice are processed to eliminate harmful bacteria. Fresh unpasteurized juices normally are found in the groceries' refrigerated sections. Unpasteurized apple cider may also be found at cider mills and farm markets.

Parents of children in day-care centers and schools that serve cider and juice may want to ask if the products are pasteurized. Children on field trips to apple cider mills or farm markets should not drink unpasteurized cider.

If you or someone in your family is in one of the high-risk groups and you cannot determine if a juice product has been processed to destroy harmful bacteria, either don't use the product or bring it to a boil to kill any possible harmful bacteria.

For other food safety information, go to
<http://vm.cfsan.fda.gov/list.html>



FDA TALK PAPER

*Food and Drug Administration
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, MD 20857*

FDA Talk Papers are prepared by the Press Office to guide FDA personnel in responding with consistency and accuracy to questions from the public on subjects of current interest. Talk Papers are subject to change as more information becomes available.

T97-49	Ivy Fleischer Kupec:	301-827-6242
Sept. 29, 1997	Broadcast Media:	301-827-3434
	Consumer Inquiries:	800-532-4440

FDA APPROVES FIRST COMBINATION DRUG FOR AIDS

On Friday, Sept. 26, FDA approved a combination of AZT (zidovudine) and 3TC (lamivudine) for treating AIDS and HIV infection. Combining these two drugs, which are commonly prescribed with one another, into one tablet could decrease the number of pills people with HIV have to take daily. The following can be used to answer questions:

Combivir, as the new drug is called, given twice a day provides an alternative regimen to 150 mg 3TC twice a day plus AZT 600 mg per day in divided doses. This drug form reduces pill intake for these two drugs to two per day instead of up to eight.

AZT and 3TC are members of the nucleoside analogue class of drug compounds, and both interfere with the replication of HIV, the virus that causes AIDS. These drugs are frequently part of the "drug cocktails" used to attack the virus in people with HIV.

Adverse events continue to be those associated with nucleoside analogue drugs: nausea, diarrhea, anemia, low white blood cells, pancreatitis and neuropathy.

AZT has been available for people with AIDS since 1987; 3TC was approved in 1995 for use in combination with AZT.

All three drugs are manufactured and marketed by Glaxo Wellcome of Research Triangle, N.C.

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FDA HOME PAGE

Liposomal daunorubicin is not recommended in patients with less than advanced HIV-related Kaposi's sarcoma

A recent report [1] described results of a small randomized crossover study that compared liposomal daunorubicin with observation in patients with early Kaposi's sarcoma. Liposomal daunorubicin appeared to delay disease progression by about 8 weeks. Data from this and other studies of liposomal daunorubicin were submitted to the US Food and Drug Administration (FDA) and presented at a public meeting of the FDA Oncologic Drugs Advisory Committee on 8 June 1995. These data included information on survival and the rate of opportunistic infections in this study that were not included in the published report, but are pertinent to the interpretation of the study results.

As described in the report, patients in the study had early Kaposi's sarcoma (< 20 mucocutaneous lesions; no visceral disease) and were randomized to two groups, one to receive liposomal daunorubicin for six cycles (12 weeks) followed by observation off treatment for 12 weeks, the other to be observed off treatment for 12 weeks or until progression occurred, then crossed over to receive six cycles (12 weeks) of liposomal daunorubicin. The study was intended to determine whether liposomal daunorubicin delayed progression of Kaposi's sarcoma, as indicated by the rate of appearance of new lesions or increase in size of existing lesions. According to the study protocol,

accrual of 40 patients (20 per arm) was planned, but the study was terminated after accrual of 29 patients.

The study showed as reported that liposomal daunorubicin has biological activity against early AIDS-related Kaposi's sarcoma. As reported, patients randomized to receive initial treatment with liposomal daunorubicin had a significantly prolonged time to progression (≥ 90 days) compared with patients who were initially observed (31 days) and later crossed over to receive this treatment (log-rank and Wilcoxon tests, $P = 0.0001$).

The crossover nature of the study limits inferences about long-term outcomes (i.e., survival and occurrence of opportunistic infections), because they occur, for the most part, well after the study at a time when both groups have received the experimental treatments. An effective therapy could, however, lead to a delay in such outcomes in the group treated first. Data on these long-term outcomes were not included in the published report, but were presented at the 1995 FDA Advisory Committee meeting. These data do not suggest a benefit of early treatment on these long-term outcomes.

The median survival for patients initially treated with liposomal daunorubicin was 359 days, compared with a

Correspondence 1413

median survival of 586 days for patients who initially received no treatment, a nominally significance difference (log-rank, $P = 0.16$; Wilcoxon, $P = 0.02$). The median time to the first opportunistic infection following study entry was also shorter in the patients who received initial liposomal daunorubicin treatment, 145 versus 371 days in patients who initially received no treatment (log-rank, $P = 0.068$; Wilcoxon, $P = 0.038$).

As the only treatment difference between the two groups in this crossover study was a delay in liposomal daunorubicin of at most 84 days, it is not easy to see how a difference of more than 84 days could result from treatment. The 32-week difference in survival and time to first opportunistic infection thus appears at least partly due to chance. The direction of the result should remind us, however, that administration of immunosuppressive cytotoxic drugs to patients with HIV might decrease resistance to infection and shorten survival. It may be reasonable to accept this risk in

advanced Kaposi's sarcoma that is interfering with patients' lives, but available data do not support use of liposomal daunorubicin at earlier stages.

The indications and usage section of the FDA-approved prescribing information for DaunoXome (liposomal daunorubicin) includes the statement, 'DaunoXome is not recommended in patients with less than advanced HIV-related Kaposi's sarcoma'.

*R. M. White, Medical Officer, Division of Oncology Drug Products
FDA, Center for Drug Evaluation and Research, HFD-150,
Rockville, Maryland, USA.*

Reference

- 1 Uthayakumar S, Bower M, Money-Kyrle J, et al.: Randomized cross-over comparison of liposomal daunorubicin versus observation for early Kaposi's sarcoma. *AIDS* 1996, 10:515-519.

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7 Number of Pages (including coversheet) Date: June 11, 1997

FAX TO: *Sandy Thurman*

FAX NO: *202-632-1096*

FROM: **Donald Pohl**

Message: Health Advisory for Protease Inhibitors

Dear Health Care Professional Letter, dated June 11, 1997

FDA Talk Paper, T97-23, dated June 11, 1997

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857**FDA PUBLIC HEALTH ADVISORY**

Subject: REPORTS OF DIABETES AND HYPERGLYCEMIA IN PATIENTS RECEIVING PROTEASE INHIBITORS FOR THE TREATMENT OF HUMAN IMMUNODEFICIENCY VIRUS (HIV)

Dear Health Care Professional:

The Food and Drug Administration would like to call to your attention recent post marketing reports of new onset diabetes mellitus, hyperglycemia or exacerbation of existing diabetes mellitus occurring in HIV-infected patients receiving protease inhibitor therapy. At the present time there exists no conclusive evidence establishing a definite causal relationship between protease inhibitor therapy and the incidence of diabetes and hyperglycemia. Based on present reporting, we believe the occurrence of this event is relatively infrequent. As such, patients for whom these products are indicated should not discontinue therapy without consulting their health care professional. However, given the potential seriousness of this complication, we believe that patients and health care professionals should be notified of this information.

SUMMARY OF REPORTS

- As of May 12, 1997, there have been 83 cases reported to FDA of diabetes mellitus or hyperglycemia in HIV-infected patients who were receiving anti-retroviral protease inhibitor therapy; 27 of the 83 cases were reported to require hospitalization. Fourteen patients were known to be diabetic at baseline; for these patients, there was a loss of glucose control. The average time of onset was approximately 76 days after initiating protease inhibitor therapy, but occurred as early as four days after starting therapy. Five cases of diabetic ketoacidosis occurred, including patients who were not reported to be diabetic at baseline; however, the baseline status of these patients is not well characterized.
- Some patients required either initiation or dose adjustments of insulin or oral hypoglycemic agents for the treatment of these events. On an average, fifty percent of patients discontinued their protease inhibitor therapy as a result of this acute adverse event. Hyperglycemia persisted in some patients after protease inhibitor therapy was withdrawn including patients not known to be diabetic at baseline; however a causal relationship between protease inhibitor therapy and these events has not been established.
- Many of these reports occurred in patients with confounding medical conditions, some of which required therapy with agents that have been associated with the development of diabetes mellitus or hyperglycemia.
- Diabetes and hyperglycemia have been reported to varying degrees for Crixivan® (indinavir), Invirase® (saquinavir), Norvir® (ritonavir) and Viracept® (nelfinavir).

FDA will continue close monitoring for additional events. We encourage all health care professionals to report any cases of diabetes or hyperglycemia, or any other serious toxicity associated with the use of protease inhibitors, to the FDA's MEDWATCH program at 1-800-FDA-1088/fax 1-800-FDA-0178; or to the respective pharmaceutical manufacturers:

Crixivan® (indinavir), Merck Research Laboratories, 1-800-672-6372
Invirase® (saquinavir), Hoffman-La Roche, 1-800-526-6367
Norvir® (ritonavir), Abbott Laboratories, 1-800-633-9110
Viracept® (nelfinavir), Agouron Pharmaceuticals, 1-888-847-2237

Sincerely yours,

Murray M. Lumpkin, M.D.
Deputy Center Director (Review Management)
Center for Drug Evaluation and Research

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TALK PAPER

FOOD AND DRUG ADMINISTRATION
U.S. Department of Health and Human Services
Public Health Service 5600 Fishers Lane Rockville, Maryland 20857

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Ivy Fleischer Kupec: 301-443-3285
Broadcast Media: 301-827-3434
Consumer Hotline: 800-532-4440

HEALTH ADVISORY FOR NEWEST CLASS OF AIDS DRUGS

FDA today warned physicians that protease inhibitors may contribute to increases in blood sugar and even diabetes in HIV patients and recommended close monitoring of their glucose levels. In a letter to doctors, FDA noted that it had received 83 reported cases of new or exacerbated diabetes mellitus and hyperglycemia (increased blood sugar levels) in HIV-infected patients taking any one of these newest class of AIDS drugs. However, none of this data definitively demonstrates that the drugs caused the condition.

While diabetes is a very serious condition, the agency believes these events occur relatively infrequently in patients taking these drugs and does not recommend that patients forego protease inhibitor therapy. Indeed, many patients who developed diabetes while on protease inhibitors were able to control the diabetes through insulin or other more modest agents. Based on present information, the agency continues to believe the benefits

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of these drugs to patients suffering from HIV infection outweigh the various risks of taking these drugs.

Of the 83 patients, 27 were reported to require hospitalization, including six life-threatening cases. Five cases resulted in ketoacidosis, a serious diabetes-related condition that is characterized by a fruity mouth odor, nausea, vomiting, dehydration, weight loss, confusion, and, if untreated, coma or death.

All four approved protease inhibitors (saquinavir, indinavir, ritonavir and nelfinavir) will soon carry revised labeling that delineates this potential side effect. While many patients who discontinued protease inhibitor therapy saw a reduction in their symptoms, a clear causal relationship between the drugs and the onset of hyperglycemia or diabetes has not been established. Many of these reports occurred in patients with confounding medical conditions, some of which required therapy with agents that have been associated with the development of diabetes mellitus or hyperglycemia.

HIV patients on protease inhibitor therapy should know the warning signs of hyperglycemia and diabetes: increased thirst and hunger, unexplained weight loss, increased urination, fatigue and dry, itchy skin. In the 83 reported cases, these symptoms occurred, on average, in approximately 76 days from starting

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protease inhibitor therapy, but the agency is aware of cases
where symptoms appeared as early as four days after starting this
therapy.

FDA will continue close monitoring for additional events.
The agency encourages all health care professionals to report any
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