

File Pediatric Labeling P.001/003



P e d i a t r i c A I D S F o u n d a t i o n

Hope for Children with AIDS

August 28, 1997

BOARD OF DIRECTORS

- CHAIRPERSON**
 Paul M. Glaser
- Peter Benzian
 Bob Burkett
 Marlene Canter
 Susan DeLaurentis
 Philip A. Pizzo, M.D.
 Susie Zeegen
 Lloyd S. Zelderman
- Elizabeth Glaser
 1947-1994

The Editor
 The Editorial Page
 The Wall Street Journal
 200 Liberty Street
 New York, NY 10281

To the Editor:

The only good-faith explanation for Henry Miller's op-ed on President Clinton's recent proposal on children's pharmaceuticals can be that he has not had a chance to read the regulation. The op-ed contains mistakes on numbers, on current law, on the effect of the proposed regulation, and on the underlying problems. Had he even read the Journal's own coverage of the proposal ("Clinton Wants Drug-Safety Tests for Children," August 13, 1997), he would have had the correct information on all of these points.

First and foremost, let's establish the problem here: Eighty percent of the drugs currently on the market have never been tested for safety for children. Consequently, a parent of a sick child and the pediatrician must choose between administering a drug that may be toxic to children (and there have been tragic examples of this, e.g., some antibiotics) or withholding a drug that has proven effective in adults (and there have been equally tragic examples of this, e.g., the newest AIDS drugs). American children deserve better.

Contrary to Miller's assertions, this will not cost much. The FDA says that the maximum expected cost is \$20 million annually. (Miller misquotes FDA as saying \$200 million; he is mistaken by a factor of ten. The August 13 Journal article had the correct information.) By any reckoning—the number of sick children who stay sick, the number who have unstudied side-effects and adverse reactions, the number of needless hospitalizations, or the eight-ten thousandths of one percent of the revenues of the top ten pharmaceutical companies—this is, as the White House spokesman said, a very, very modest amount.

EXECUTIVE ADVISORY BOARD

- HONORARY CO-CHAIRS**
 President and Mrs. Ronald Reagan
- Mrs. William E. Brock
 Alfred A. Checchi
 Kathryn D. Checchi
 Kitty Dukakis
 Michael D. Elsnor
 Susie Field
 Senator Paula Hawkins
 Elton John
 Michael S. Ovitz
 Steven Spielberg
 Nathan M. Tisch
 Vander Vreeland
 Mrs. Pete Wilson
 Bobbi Ziffin

HEALTH ADVISORY BOARD

- CHAIRPERSON**
 Catherine M. Wilfert, M.D.
Scientific Director, Assistant Chief of Pediatrics
- Mary G. Boland, R.N., M.S.N.
Children's Hospital of New Jersey
- Yvonne J. Bryson, M.D.
UCLA School of Medicine
- Mark Feinberg, M.D., Ph.D.
National Institutes of Health
- Michael S. Gottlieb, M.D.
Shoreline Children's Hospital, California
- Margaret C. Heagarty, M.D.
Columbia University, Children's Hospital
- David D. Ho, M.D.
Asian American AIDS Research Center
- Anna Belle Kaufman, M.F.A., M.A.
Child of Tomorrow
- Daniel V. Landers, M.D.
Stony Brook Hospital
- Michael McCune, M.D., Ph.D.
University of Illinois at Chicago
- James Oleske, M.D., M.P.H.
New Jersey Medical School
- Catherine S. Peckham, M.D.
Institute of Child Health, London
- Philip A. Pizzo, M.D.
Harvard Medical School/Children's Hospital
- Paolo Rossi, M.D.
University of Rome and Ospedale Pediatrico Bambino Gesù
- Rubinstein, M.D.
Mount Sinai College of Medicine
- Gwendolyn B. Scott, M.D.
University of Miami School of Medicine
- E. Richard Stehm, M.D.
UCLA School of Medicine
- Lori Wiener, Ph.D., A.C.S.W.
National Institutes of Health

And, contrary to Miller's assertions, this will not delay new drugs. The proposed regulation is explicit in saying that approvals of drugs for adults will not be withheld. The only action contemplated if a company refuses to test its new drug for safety in children is a court injunction ordering them to do so. All children's advocates oppose the delay of adult drugs as unethical; unlike Miller, however, we go on to argue that delay of children's drugs is unethical, too.

His technical arguments against the proposal are also wrong. He suggests that difficulty formulating pediatric drugs (suspending a chemical in a syrup instead of pressing it into a pill) is often a major stumbling block. This is sometimes true, and the proposal makes a specific exception to the rule for this problem. If a company makes a reasonable effort to develop a pediatric formulation and fails, the requirement is waived. (Note that if Miller's formulation argument were the real problem, parents could expect there would be a full range of drugs for tested for older children. There are not; most drugs have not been tested for use even in 10-year-olds, who have no trouble swallowing pills.)

Miller also argues that trials may be difficult if a disease is rare, the patient population geographically diverse, or if study subjects cannot be recruited. True. But the proposed regulation has exceptions for each of these situations. Drug companies are requested to do only what is possible.

Moreover, his suggested alternatives are wrong. First he proposes that the FDA require only that a label say that the drug has not been tested in children, and let parents decide and pressure the companies. That is current law, and it has not worked. Drug companies are already required to display such a disclaimer, the use of untested drugs has continued, and the number of drugs tested for children has not increased and, by some calculations, has declined.

He also suggests that, with the labeling he proposes, the market should be allowed to take its course and will be self-correcting, eventually resulting in companies' testing drugs for children to get the increased sales. For 35 years, medical experts have been calling for these safety data, but with little response. Even in the case of those drugs that have a large pediatric market (e.g., asthma drugs, Ritalin), much remains unstudied and untested. Caveat pediatric emptor doesn't work.

Finally, his argument that FDA regulations like these are responsible for the high price of pharmaceuticals strains credibility. Drug prices are higher than ever, but not because of FDA regulation and, for heaven's sake, not because of a requirement to test drugs for safety in children. Increased pricing is a complex amalgam of patents and the bounties they provide to innovative companies, the increasing need to recover investment early in a drug's patent life, and the new marketing of drugs as an alternative to other services in managed care, as well as insurance, cross-subsidies of Europe, etc.

Miller may have an ax to grind with FDA, but this is the wrong regulation to pick on. When the original food and drug safety laws were passed in this country, they were in response to children's disasters and for the benefit of children. Pediatricians, pharmacists, and parents will be assisted by safety testing for children. It is very long overdue. As Congressman Coffee said in 1934, "Every mother is anxious that the food and medicine given her baby shall be above suspicion.... The purpose of this legislation is to protect the public, to protect the mothers and children." That purpose has gotten lost over the years, and we are delighted that President Clinton has revived it.

Sincerely,



Susan DeLaurentis
Co-founder

File Pediatric Labeling



**INTERNATIONAL
ASSOCIATION OF
PHYSICIANS IN
AIDS CARE**

225 West Washington St.
Suite 2200
Chicago, IL 60606-3418

Telephone: 312.419.7295
FAX: 312.419.7160
EMail: IAPAC@iapac.org
Web site: <http://www.iapac.org>

**ADMINISTRATIVE BOARD
INTERNATIONAL ASSOCIATION
OF PHYSICIANS IN AIDS CARE**

MARIO M. COOPER, ESQ.
NEW YORK, NEW YORK

RABBI ALLEN I. FREEHLING, PH.D., DD.
LOS ANGELES, CALIFORNIA

RODGER MCFARLANE
NEW YORK, NEW YORK

GORDON NARY
CHICAGO, ILLINOIS

MABREY R. WHIGHAM, III
CHICAGO, ILLINOIS

KEN WOLF
FT. LAUDERDALE, FLORIDA

**EDITORIAL BOARD
JOURNAL OF THE
INTERNATIONAL ASSOCIATION
OF PHYSICIANS IN AIDS CARE**

WILLIAM CAMERON, MD, FRCP
OTTAWA, CANADA

BONAVENTURA CLOTET, MD
BARCELONA, SPAIN

DAVID COOPER, MD, DSC
SYDNEY, AUSTRALIA

CHRISTINE KATLAMA, MD
PARIS, FRANCE

JOEP MA LANGE, MD, PHD
AMSTERDAM, NETHERLANDS

JONATHAN M. MANN, MD, MPH
CAMBRIDGE, MASSACHUSETTS

PRAPHAN PHANUPHAK, MD, PHD
BANGKOK, THAILAND

WILLIAM POWDERLY, MD
ST. LOUIS, MISSOURI

C.F. RAMOS-FILHO, MD, MSC
RIO DE JANEIRO, BRAZIL

SCHLOM STASZEWSKI, MD
FRANKFURT, GERMANY

STEFANO VELLA, MD
ROME, ITALY

August 14, 1997

The Hon. William Jefferson Clinton
President of the United States
The White House
1600 Pennsylvania Avenue, NW
Washington, DC 20500

Thank you

Dear Mr. President:

I am writing today on behalf of the International Association of Physicians in AIDS Care (IAPAC) and the 5,500 health care professionals we represent to applaud your executive action yesterday with regard to labeling drugs with pediatric doses. As you so eloquently stated in your remarks, it is unacceptable that less than 50 percent of drugs proven effective in children have been properly tested in children, leading many physicians to rely on guesswork to treat one of our most vulnerable populations.

The lack of timely and appropriate pediatric clinical trials of combinations of antiretroviral drugs that may prove beneficial for HIV-infected adults have crippled the ability of our physicians to appropriately care for children with HIV disease. Our children deserve more than guesswork about the most effective combinations of antiretroviral drugs necessary for their continued survival with this disease. Our children are entitled to more. Your moral leadership on this issue could save thousands of lives.

Our association represents the majority of physicians providing vital AIDS care to children living with HIV/AIDS. IAPAC's Pediatric AIDS Committee counts on the best and brightest minds in the field. This committee has impressed upon us the importance of prioritizing the needs of children in our national and international advocacy and education initiatives. As a result, the association is working with Committee Chair Mark Kline, MD, associate professor of pediatrics at the Baylor College of Medicine, to advance an ongoing Romanian-American Education and Clinical Research Program that is providing relief to thousands of Romanian children living with this dread disease. Our hope is that this program will eventually become a model for other such pediatric clinical research and treatment initiatives in Eastern Europe.

In this country, IAPAC has outlined an ambitious agenda, including the development of clinical guidelines for the management of pediatric HIV disease and a world congress on pediatric AIDS scheduled for fall of 1998. Additionally, the association is convening an historic meeting between pediatric AIDS experts and leading pharmaceutical industry representatives to jointly address the

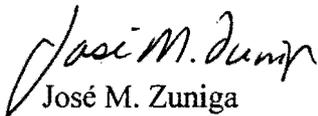
August 14, 1997

Page 2

restructuring and coordination of clinical trials to maximize treatment options for HIV-infected children. As important, we will discuss goals and objectives around the access to care crisis that prevents so many children in this country and abroad from obtaining the drugs they need to stay alive and healthy. Our ultimate goal, and one we will announce at our First International Conference on Healthcare Resource Allocation for HIV/AIDS this November 10-11, is to guarantee every U.S. child access to AIDS drugs regardless of the financial status of their parents or guardians.

Mr. President, you have time and again demonstrated your commitment to children's causes. We applaud your latest action and hope that your administration will join us in our campaign to save the lives of more than 250,000 children each year. Together we must do everything possible to stop the needless pain and hastened deaths that afflict so many of our children.

Sincerely,



José M. Zuniga
Deputy Director

cc Vice President Al Gore, Jr.
Secretary Donna Shalala
Sandra Thurman
Christopher Jennings
Harold Varmus, MD
William Paul, MD
Mark Kline, MD

SUPPORTERS OF THE PRESIDENT'S INITIATIVE ON PEDIATRIC LABELING

PROVIDERS

**American Academy of Pediatrics
American Academy of Family Physicians
American Medical Association
National Association of Children's Hospitals
National Association of Pediatric Nurse Associates and Practitioners, Inc.
American College of Physicians**

CONSUMERS

**American Foundation for AIDS Research
American Lung Association
American Thoracic Society
Pediatric AIDS Foundation
Juvenile Diabetes Foundation International
National Organization for Rare Disorders
Center for Medical Consumers
National Medical Association**

PHARMACY

**National Association of Chain Drug Stores
General Pharmaceutical Industry Association
National Community Pharmacists Association**

OTHER VALIDATORS

**C. Everett Koop, M.D., Sc.D.
Senator Barbara Boxer**

American Medical Association

Physicians dedicated to the health of America



Statement

FOR IMMEDIATE RELEASE

July 13, 1997

AMA CELEBRATES PEDIATRIC LABELING PROPOSAL

Stresses need for clinical research and dosage information specifically for children

Statement attributable to: **Yank D. Coble, MD**
Trustee, American Medical Association

"The American Medical Association today celebrates President Clinton's proposal to make more information on using drugs to treat children available to physicians. We applaud President Clinton for this initiative, and for all his hard work in the area of children's health.

"Currently only about 20% of all prescription drugs marketed in the U.S. are labeled specifically for use by children. As a result, many physicians prescribe drugs for children based on limited research, and without comprehensive information based on clinical trials with children. We hope today's move will dramatically increase the amount of information available, allowing physicians to more confidently treat children using a wider range of prescription medications.

"Although the FDA previously encouraged drug manufacturers to submit pediatric data on new drugs, today's proposal would *require* that data be put on a drug's label so physicians can make treatment decisions based on scientific information aimed specifically at their youngest patients.

"The AMA has also supported the Better Pharmaceuticals for Children Act, sponsored by Sens. Christopher Dodd and Mike DeWine and Reps. Jim Greenwood and Henry Waxman. This bill, introduced in the 105th Congress, would provide incentives to drug manufacturers who conduct pediatric studies and provide pediatric dosage formulations.

"We look forward to working with the President and Congress on future efforts to insure that America's children have the best health care possible."

#

For more information, please contact:

Brenda L. Craine
AMA Washington
202/789-7447

1101 Vermont Avenue, NW
Washington, DC 20005
202 789-7400



*File
to
Reductive
Labeling*

GEORGETOWN UNIVERSITY LAW CENTER

Federal Legislation Clinic

Dean
Judith C. Areen

Director
Associate Professor of Law
Chai R. Feldblum

Deputy Director
R. Scott Foster

Senior Policy Fellow
Timothy M. Westmoreland

Executive Assistant
Loretta C. Bliss

Federal Legislation Clinic

111 F Street, N.W.

Washington, DC 20001

Phone (202) 662-9595

Fax (202) 662-9682

Visiting Professor
Ralph U. Neas
Supervising Attorneys
David P. Rapallo
Sharon N. Perley

FAX COVER MEMORANDUM

DATE: _____

NUMBER OF PAGES, INCLUDING THIS SHEET: _____

TO: Chris

FAX NUMBER: 456-5557

FROM: Tim

COMMENT: ASAP to Chris.
Thanks.



P e d i a t r i c A I D S F o u n d a t i o n

For immediate release
August 13, 1997

CONTACT: Cheryl Cook
Pediatric AIDS Foundation
310/395 9051
213/703-9011

BOARD OF DIRECTORS

CHAIRPERSON
Paul M. Glaser

Peter Benjian
Bob Burkett
Marlene Canter
Susan DeLaurentis
Philip A. Pizzo, M.D.
Susie Zeegen
Lloyd S. Zeiderman

Elizabeth Glaser
1947-1994

EXECUTIVE ADVISORY BOARD

HONORARY CO-CHAIRS

President and Mrs. Ronald Reagan

Mrs. William E. Brock
Alfred A. Checchi
Kathryn D. Checchi
Kitty Dukakis
Michael D. Eisner
Susie Field
Senator Paula Hawkins
Elton John
Michael S. Ovit
Steven Spielberg
Jonathan M. Tisch
Alexander Vreeland
Mrs. Pete Wilson
Robbi Zilkin

HEALTH ADVISORY BOARD

CHAIRPERSON

Catherine M. Wilfert, M.D.
Stanford University
Pediatric AIDS Consortium

Mary G. Boland, R.N., M.S.N.
Children's Hospital of New Jersey

Yvonne J. Bryson, M.D.
UCLA School of Medicine

Mark Feinberg, M.D., Ph.D.
Biocenter, University of Health

Michael S. Gottlieb, M.D.
Sherman Oaks Hospital, California

Margaret C. Heagarty, M.D.
Columbia University, Harlem Hospital

David D. Ho, M.D.
Aaron Diamond AIDS Research Center

Anna Belle Kaufman, M.F.A., M.A.
Children's Hospital

Daniel V. Landers, M.D.
Markey-Women's Hospital

Michael McCune, M.D., Ph.D.
University of Illinois at Chicago

James Oleske, M.D., M.P.H.
New Jersey State Health Dept.

Catherine S. Peckham, M.D.
University of Colorado Health Science Center

Philip A. Pizzo, M.D.
University of Colorado Health Science Center

Paolo Rossi, M.D.
University of Rome and Karolinska Institute

Arye Rubinstein, M.D.
Albert Einstein College of Medicine

Gwendolyn B. Scott, M.D.
University of Miami School of Medicine

E. Richard Stehm, M.D.
UCLA School of Medicine

Lori Wiener, Ph.D., A.C.S.W.
National Institutes of Health

Bernard Fields, M.D.

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

In its press release dated August 12, 1997, PhRMA commits itself to working with the "Administration and anyone else to advance the goal of better medicine for children." The Pediatric AIDS Foundation (PAF) welcomes that commitment and looks forward to PhRMA's cooperation on this pressing problem.

However, PhRMA goes on in the press release to question the FDA's proposed regulations to require that drugs be tested for safety and dosing for children's use. In asking this question, the press release makes a number of serious errors, omissions, and misleading statements. This is an effort by PAF to correct the record.

Argument in Press Release:

Manufacturers are voluntarily testing drugs for children. "We question whether a government mandate is needed."

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

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

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

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

Argument in Press Release:

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

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

CO-FOUNDERS: Susan DeLaurentis/Elizabeth Glaser/Susie Zeegen
1311 Colorado Avenue, Santa Monica, California 90404

TEL: (310) 395-9051 FAX: (310) 395-5149 E-mail: info@pedAIDS.org

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

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

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

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

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

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

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

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

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

Conclusion

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

Sybil Mathews

P e d i a t r i c A I D S F o u n d a t i o n

August 13, 1997



Hope for Children with AIDS

Honorable William J. Clinton
The President
The White House
1600 Pennsylvania Avenue
Washington, D.C.

Dear Mr. President,

I want to thank you for announcing today a proposed Food and Drug Administration regulation requiring drug manufacturers to perform pediatric studies for new drugs that will be used by children. Thank you for raising this issue to the highest visibility and for taking this step to ensure that children are no longer left behind in the progress of biomedical research.

The Pediatric AIDS Foundation was established to get drugs and research for children with HIV. We have been active on this issue because children with HIV couldn't get the same drugs as their parents. My best friend and fellow co-founder, Elizabeth Glaser, was shocked to find that the drugs that were available to her were not available to her daughter, Ariel.

A decade later, that is still too often the case. Last year, there was great news for adults with AIDS--protease inhibitors offered new hope. But the hope wasn't available to kids for almost a full year later. Only this spring, two of these drugs were finally approved for older children. One was a drug that did its adult trials long before its pediatric trials--the usual story for most AIDS drugs. The other, however, was the drug manufactured by Agouron, a company that did the right thing by developing their drug for children at the same time as for adults.

But still none of these new protease inhibitors have been approved for infants and newborns. This is especially tragic since recent studies show that the most promising time to control and potentially reverse the effects of HIV could be in a newly infected newborn.

Children should not be an afterthought. Progress in research should include both adults and children. And while we have been primarily involved in AIDS, we recognize that this problem affects children with many other illnesses. So the solution should not be disease-specific. It should be for all diseases. It should be children-specific.

Today's announcement will change history. From now on, children will not be automatically left out. From now on, it will be the rule that drugs are tested for children, unless there's a good reason not to.

For that, I am grateful to you. Once again you have demonstrated that this is an Administration that truly cares about children.

Sincerely yours,

Susan DeLaurentis
Susan DeLaurentis
Co-founder

CO FOUNDERS: Susan DeLaurentis/Elizabeth Glaser/Susie Zeegen
1311 Colorado Avenue, Santa Monica, California 90404

BOARD OF DIRECTORS

CHAIRPERSON
Paul M. Glaser

Peter Benzian
Bob Burkett
Marlene Canter
Susan DeLaurentis
Phillip A. Pizzo, M.D.
Susie Zeegen
Lloyd S. Zeiderman

Elizabeth Glaser
1947-1994

EXECUTIVE ADVISORY BOARD

HONORARY CO-CHAIRS
President and Mrs. Ronald Reagan

Mrs. William E. Brock
Alfred A. Checchi
Kathryn D. Checchi
Kitty Oukokis
Michael D. Eisner
Susie Field
Senator Paula Hawkins
Elton John
Michael S. Ontz
Steven Spielberg
Jonathan M. Tisch
Alexander Vreeland
Mrs. Pete Wilson
Bobbi Zifkin

HEALTH ADVISORY BOARD

CHAIRPERSON

Catherine M. Wilfert, M.D.
University of Michigan
Ann Arbor, Michigan

Mary G. Deland, B.N., M.S.N.
Children's Hospital of New York

Yvonne J. Bryner, M.D.
UCLA School of Medicine

Mark Feinberg, M.D., Ph.D.
Harvard Medical School

Michael S. Gottsch, M.D.
University of Michigan

Margaret C. Hopcraft, M.D.
Harvard Medical School

David D. Ho, M.D.
Boston Children's Hospital

Anna Belle Kauffman, M.F.A., M.A.
Harvard Medical School

Daniel V. Lindsley, M.D.
Harvard Medical School

Michael McCune, M.D., Ph.D.
Harvard Medical School

James Olesko, M.D., M.P.H.
Harvard Medical School

Catherine S. Peckham, M.D.
Harvard Medical School

Philip A. Pizzo, M.D.
Harvard Medical School

Paolo Rarsi, M.D.
University of Texas

Arye Rubinstein, M.D.
Albert Einstein College of Medicine

Gwendolyn B. Scott, M.D.
University of Texas

E. Richard Stiehm, M.D.
UCLA School of Medicine

Lori Wisner, Ph.D., A.C.S.W.
Harvard Medical School



N · A · C · H

Statement

Lawrence A. McAndrews

**CHILDREN'S HOSPITALS URGE FEDERAL ACTION
TO STIMULATE MANUFACTURERS' TESTING
OF PHARMACEUTICAL PRODUCTS FOR CHILDREN'S USE**

August 13, 1997

The National Association of Children's Hospitals (N.A.C.H.), representing more than 100 children's hospitals across the country, strongly commends the Clinton administration's recognition of a serious failing of the health care market place -- the absence of adequate market incentives or requirements for testing and labeling of pharmaceutical products for use by children.

The proposal for public comment of new regulations mandating testing of pharmaceuticals for pediatric use by the Food and Drug Administration (FDA) reflects the strong, ongoing personal commitment of President Clinton and the First Lady to public policy that helps every family meet its children's needs for health, education, safety, and security. Certainly a serious concern for any parent whose child requires medication is the realization that only about 20 percent of all of the drugs marketed in the United States have been tested and labeled specifically for use by children.

Three weeks ago, in a hearing before the Senate Public Health and Safety Subcommittee, a number of the nation's leading pediatric researchers cited the serious lack of pharmaceutical products tested for children's use as one of the most important challenges facing the pediatric health care community in its efforts to convince the nation of the need for increased investment in research devoted to children's illnesses and conditions.

These researchers included academic leaders from Children's Hospital in Boston and Le Bonheur Children's Medical Center in Memphis. They recognize that the market's failure would not be a problem if children's health care needs were identical to those of adults. But that, of course, is not the case. As both parents and pediatric providers understand all too well, children are not miniature adults. Their health care needs are not appropriately met by providing either adult-sized treatments or even miniature versions of them.

All too often, our children's care givers must rely only on their personal judgment in deciding which drugs and which dosages are best suited for their patients. Because they devote such a large share of their services to children with complex conditions requiring specialized care, children's hospitals are very aware of the limited extent of testing and labeling of pharmaceuticals for children.

N.A.C.H. believes the Administration's new initiative to develop the most appropriate ways to stimulate product testing through regulation can complement the important legislation proposed by Senators Christopher Dodd (D-CT) and Mike DeWine (R-OH) plus Representative Jim Greenwood (R-PA) and Henry Waxman (D-CA) to create market incentives for manufacturers to undertake pediatric studies of new and FDA-approved pharmaceuticals. Their legislation, which has strong bipartisan support, continues the effort begun in 1991 by former Senator Nancy Kassebaum (R-KS) to persuade the Congress of the need to address the lack of pharmaceutical testing for children.

Because they represent only about 30 percent of the nation's population, less than 15 percent of health care spending, and the poorest segment of the population, children do not command the attention of the health care market for investment in research and development (R&D). This is true not just for R&D for children's health care in particular, but for all R&D related to children.

According to the National Science and Technology Council's April 1997 prepublication report on "A National Research Initiative for America's Children for the 21st Century,"

"...(T)he share of total national R&D toward children is less than 1.2 percent. Unlike other areas of research, the Federal Government bears almost total responsibility for children. For example, the private sector provides over 50 percent of health and energy R&D funding and over 90 percent of transportation R&D. In contrast, the Federal Government provides approximately 90 percent of children's R&D."

Clearly, strengthening the federal investment in research devoted to children remains critical. But children's needs will not be fully met if the federal government alone shoulders the responsibility for pediatric research and development. Through a balanced commitment to market incentives and regulation, the federal government can stimulate manufacturers' investment in product testing to meet children's unique health care needs more fully.

Just last week, Congressional and White House commitment to bipartisanship in budget policy helped to launch the most important new federal commitment to strengthening children's health insurance coverage in a generation. We are confident that the same spirit of bipartisanship can lead to effective federal policy combining appropriate incentives and regulations to ensure the necessary testing of pharmaceutical products for pediatric use, which both children and their parents deserve.



August 13, 1997
1:45 p.m. (EST)

Contact: Marjorie Tharp
Gem Benozza
202/347-8600
800/336-5475

**PRESS STATEMENT on
CHILDREN AND DRUG LABELING**

(This statement can be attributed to Joseph R. Zanga, M.D., AAP Vice President)

The American Academy of Pediatrics enthusiastically applauds President Clinton's efforts to ensure that children will no longer be "therapeutic orphans." Thanks to the proposed Food and Drug Administration (FDA) regulations, drug manufacturers will routinely conduct pediatric studies of most new and specific classes of drugs already in the market. The availability of medication approved for infants, children and adolescents just took a much needed step today, and the President is to be commended.

Several members of Congress, including former Sen. Nancy Kassebaum (R-Kan.), have long recognized the need to actively pursue this goal. We believe the proposed regulations will complement AAP-backed legislation introduced in the 105th Congress. The Better Pharmaceuticals for Children Act, sponsored by Sens. Christopher Dodd (D-Conn.) and Mike DeWine (R-Ohio), and Reps. Jim Greenwood (R-Pa.) and Henry Waxman (D-Calif.), will solidify the establishment of a drug development system that meets the unique needs of children.

Proper drug studies must be done to ensure that children receive optimal treatment. The wrong drug, or even too much or too little of the right drug, does no good and may do harm. Currently, only 20 percent of all drugs marketed in the United States have been labeled for use by infants, children and adolescents. As a result, pediatricians must prescribe drugs based on information from limited medical studies, rather than more comprehensive clinical trials in children. Adults have had the benefits of testing and labeling for over half a century. For children, we label the food they eat and the television shows they watch. However, when it comes to prescribing children's medicine, information about how much and how often to give it to them is sorely lacking. For example, asthma is the leading cause of hospitalization of children in the United States, and commonly affects children younger than age 5. Despite that, there is only one asthma drug labeled for use in children under the age of 6.

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

###

The American Academy of Pediatrics is an organization of 53,000 primary care pediatricians, pediatric medical subspecialists, and pediatric surgical specialists dedicated to the health, safety, and well-being of infants, children, adolescents and young adults.

File Ped Labeling
Stephania

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 200, 312, 314, and 601

[Docket No. 97N-0165]

RIN 0910-AB20

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

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

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

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

FOR FURTHER INFORMATION CONTACT:

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

301-827-5321.

SUPPLEMENTARY INFORMATION:

I. Introduction

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

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

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

Many of the drugs and biological products most widely used in pediatric patients carry disclaimers stating that safety and effectiveness in pediatric patients have not been established (Refs. 2 and 3). Based on 1994 data from IMS America, Ltd., a research firm that provides data on prescription drug usage, FDA compiled a list of the 10 drugs that were most widely

prescribed for pediatric patients, on an outpatient basis, despite inadequate pediatric labeling. In each case, the label lacked any use information for the age group prescribed to, or the information was inadequate. The drugs were: Albuterol inhalation solution for nebulization for treatment of asthma (prescribed 1,626,000 times to pediatric patients under 12); Phenergan for treatment of allergic reactions (prescribed 663,000 times to pediatric patients under 2); ampicillin injections for treatment of infection (prescribed 639,000 times to pediatric patients under 12); Auralgan otic solution for treatment of ear pain (prescribed 600,000 times to pediatric patients under 16); Lotrisone cream for treatment of topical infections (prescribed 325,000 times to pediatric patients under 12); Prozac for treatment of depression and obsessive compulsive disorder (prescribed 349,000 times to pediatric patients under 16, including 3,000 times to infants under 1); Intal for treatment of asthma (solution prescribed 109,000 to pediatric patients under 2; aerosol prescribed 399,000 times to pediatric patients under 5); Zoloft for treatment of depression (prescribed 248,000 to pediatric patients under 16); Ritalin for treatment of attention deficit disorders and narcolepsy (prescribed 226,000 times to pediatric patients under 6); Alupent for treatment of asthma (184,000 times to pediatric patients under 6). These 10 drugs were thus prescribed over 5 million times in 1 year for pediatric patients in age groups for which the label carried a disclaimer or lacked adequate use information (Ref. 2).

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

Inadequate pediatric labeling thus exposes children to the risk of unexpected adverse reactions or lack of optimal treatment. Even after a drug has been used in pediatric patients for

some time, and there has been substantial clinical experience with the drug, directions for safe and effective use in pediatric patients are not provided on the label.

Children were once viewed as a population entirely distinct from adults, in whom safety and effectiveness of new drugs had to be established entirely independently. It has become increasingly clear, however, that children may be considered a demographic subpopulation with many similarities to the adult population. In most cases, drugs and biological products behave similarly in demographic subgroups, including age and gender subgroups, even though there may be variations because of differences in, for example, pharmacokinetics. As FDA has already stated in a FEDERAL REGISTER document, where the disease and the drug's effects are similar in adults and children, adequate and well-controlled trials may not be needed in children to establish pediatric use information (59 FR 64240, December 13, 1994) (hereinafter referred to as the 1994 rule).

Although use of a drug in children is no longer considered a new indication (with the exception of specific "pediatric indications"), the development of additional information in pediatric patients is needed to provide appropriate dosing recommendations. Correct pediatric dosing cannot necessarily be extrapolated from adult dosing information using an equivalence based either on weight milligrams per kilogram (mg/kg) or body surface area (mg/square meter (m^2)). Potentially significant differences in pharmacokinetics may alter a drug's effect in pediatric patients. The effects of growth and maturation of various organs, maturation of the immune system, alterations in metabolism throughout infancy and childhood, changes in body proportions, and other developmental changes may result in significant differences in the doses needed by pediatric patients and adults. For example, studies have shown that fentanyl, a potent

opioid, widely used in anesthetic management of infants and small children but not labeled for use in pediatric patients under 2 years of age, demonstrates differences in clearance between the neonatal period and 2 or more months of age due to improving hepatic blood flow and hepatic microsomal maturation (Ref. 4). Comparable doses in adults and neonates (calculated on a microgram (μg)/kg basis) produce twofold to threefold higher plasma concentrations in neonates (Ref. 5). Pharmacokinetic differences of this kind demonstrate the importance of studying the pharmacokinetics of a drug in pediatric patients of different ages before they are widely exposed to it. Inadequate dosing information may expose pediatric patients to dangerously high doses or to ineffective treatment. The absence of pediatric testing may thus result in less than optimal treatment for many pediatric patients.

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

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

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

II. FDA Initiatives to Improve Pediatric Use Information

FDA has taken a number of steps in recent years to address inadequate pediatric drug testing and inadequate pediatric use information in drug labeling. Perhaps the most significant step was the issuance of the 1994 rule requiring drug manufacturers to survey existing data and determine whether those data are sufficient to support additional pediatric use information in the drug's labeling (59 FR 64240). Under the 1994 rule, if a manufacturer determines that existing data permit modification of the label's pediatric use information, the manufacturer must submit a supplemental new drug application (NDA) to FDA seeking approval of the labeling change. The rule explicitly recognizes that controlled clinical studies to support pediatric use information need not have been carried out in pediatric patients where the course of the disease and the effects of the drug are sufficiently similar in children and adults to permit extrapolation from the adult effectiveness data to pediatric patients. In these cases, controlled clinical studies in adults together with pharmacokinetic and adverse reaction data in pediatric patients may be sufficient to establish pediatric safety and effectiveness.

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

FDA's Center for Drug Evaluation and Research (CDER) and Center for Biologics Evaluation (CBER) and Research have implemented a "Pediatric Plan" designed to focus attention on and encourage voluntary development of pediatric data both during the drug development process and after marketing. At specified points during the investigation of a new drug or biological product, FDA staff discuss with the sponsor the data needed to support pediatric labeling and encourage them to conduct needed studies. CDER and CBER have also begun to implement a program in which, after review of an NDA, biologics license application (BLA), or supplemental application, the FDA reviewer fills out a "pediatric page." The pediatric page does not itself impose any requirements, but describes the adequacy of product labeling for

pediatric patients and plans for further pediatric studies. If pediatric labeling is found to be inadequate, the pediatric page states whether additional pediatric studies are needed. If pediatric studies are needed, the pediatric page states whether the applicant has agreed to conduct the necessary studies and, if necessary, to develop a pediatric formulation. FDA is also developing a draft guidance document on pediatric pharmacokinetics.

In addition, FDA has taken steps to improve pediatric use information for marketed drugs under the pediatric plan. CDER has identified the 10 drugs most used in pediatric populations for which there is no pediatric use information or for which the pediatric use information is inadequate given the pattern of use in pediatric patients. The manufacturers of these drugs have been notified of the widespread use of their drugs in the pediatric population and asked to respond to the 1994 rule. CBER is currently identifying the biological products most frequently used in pediatric patients without labeling information. FDA has developed guidance to manufacturers on the content and format for pediatric use supplements under the 1994 rule and is tracking pediatric use supplements and commitments.

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

Although the actions taken by FDA to date have produced some gains in pediatric labeling, they have not yet substantially increased the number of drugs and biological products for which there is adequate pediatric use information. The percentage of new products entering the marketplace that contain adequate pediatric safety and effectiveness information has not shown consistent improvement in the last decade. An informal survey conducted by the American Academy of Pediatrics in 1990 found that of all new molecular entities (NME's) approved between 1984 and 1990, 20 percent had information on pediatric use. Not all NME's

have usefulness in pediatric patients, however. For example, for NME's approved in the years 1991-1996, 53 percent were regarded by FDA as having potential usefulness in pediatric patients. Presumably, if only the NME's with usefulness in pediatric patients had been considered in the survey, the percentage with pediatric labeling would have been somewhat higher, and as high as 42 percent. 7?

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

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

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

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

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

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 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 an 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, (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

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

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 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

