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Health - Pediatric Drug Testing

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P1 National Security Classified Information [(a)(1) of the PRA]
P2 Relating to the appointment to Federal office [(a)(2) of the PRA]
P3 Release would violate a Federal statute [(a)(3) of the PRA]
P4 Release would disclose trade secrets or confidential commercial or financial information [(a)(4) of the PRA]
P5 Release would disclose confidential advice between the President and his advisors, or between such advisors [a)(5) of the PRA]
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b(1) National security classified information [(b)(1) of the FOIA]
b(2) Release would disclose internal personnel rules and practices of an agency [(b)(2) of the FOIA]
b(3) Release would violate a Federal statute [(b)(3) of the FOIA]
b(4) Release would disclose trade secrets or confidential or financial information [(b)(4) of the FOIA]
b(6) Release would constitute a clearly unwarranted invasion of personal privacy [(b)(6) of the FOIA]
b(7) Release would disclose information compiled for law enforcement purposes [(b)(7) of the FOIA]
b(8) Release would disclose information concerning the regulation of financial institutions [(b)(8) of the FOIA]
b(9) Release would disclose geological or geophysical information concerning wells [(b)(9) of the FOIA]

Health - pediatric labeling

August 12, 1997

PEDIATRIC DOSAGE AND LABELING ANNOUNCEMENT

DATE:	August 13, 1997
LOCATION:	Rose Garden
BRIEFING TIME:	1:15 pm - 1:35 pm
EVENT TIME:	1:45 pm -2:15 pm
FROM:	Bruce Reed

I. PURPOSE

To demonstrate your commitment to children's health issues by announcing a new FDA regulation to improve the safety of pediatric drugs.

II. BACKGROUND

You will be unveiling a new FDA regulation that will require drug manufacturers to study the effects of drugs on children. The regulation will apply both to certain new prescription drugs and to certain drugs currently on the market. Under this regulation, drug manufacturers will be required to complete clinical studies and place information on drug labels to help physicians make informed decisions when prescribing drugs to children.

Although children have distinct needs with regard to doses and potential side-effects of medications, most drugs have not been tested on pediatric populations. Currently, only 42 percent of drugs that have proven highly useful for children are tested on children. As a result, physicians are reluctant to prescribe many drugs to children because they do not want to risk giving an inappropriate dosage. Those physicians that do prescribe drugs without pediatric labels are forced to guess the appropriate dosage.

The FDA has identified ten drugs that are prescribed 5 million times a year to children that have not been adequately tested on children. These include Prozac, Zoloft, Ritalin, and drugs for asthma, allergies, and ear infections. In addition, less than half of the drugs used in the treatment of HIV are being studied on children. The Pediatrics AIDS Foundation has lead the fight for this new regulation on behalf of the 10,000 to 12,000 children with HIV.

Representatives from the Pediatric AIDS Foundation, the National Association of Children's Hospitals, the American Academy of Pediatrics, and other children's health organizations will be in attendance.

III. PARTICIPANTS

Briefing Participants
Secretary Shalala
Bruce Reed
Chis Jennings
Jennifer Klein
Maria Echaveste

Events Participants
Vice President
First Lady
Secretary Shalala
Regan Ralph, mother of 1 ½ year old son with asthma.

Meet and Greet Participants (Following [redacted] Event)
Bill Schultz
Nuke Fredum
Regan Ralph, mother of child with asthma, and family.
Dr. Joseph A. Zanga, Vice President, American Academy of Pediatrics
Susan DeLaurentis, Co-Founder, Pediatrics AIDS Foundation
Francesca DeLaurentis, daughter
Lawrence McAndrews, President and CEO, National Association of Children's Hospitals

IV. PRESS PLAN

Open Press.

V. SEQUENCE OF EVENTS

- You will be announced onto the stage accompanied by stage participants.
- The First Lady makes welcoming remarks and introduces Secretary Shalala.
- Secretary Shalala makes remarks and introduces the Vice President.
- The Vice President makes remarks and introduces Regan Ralph.
- Regan Ralph makes remarks and introduces you.
- You will make remarks and then depart.

VI. REMARKS

Remarks Provided by Lowell Weiss in Speechwriting.

PRESIDENT CLINTON ANNOUNCES NEW MEASURES TO INCREASE AVAILABILITY OF INFORMATION ON SAFE USE OF MEDICATIONS USED TO TREAT CHILDREN
August 13, 1997

Today, President Clinton unveiled a new FDA regulation that will protect children by requiring manufacturers to study the safety and appropriate dosage levels of drugs for pediatric populations. The regulation also requires proper labeling of drugs for use in children. Even though many drugs affect children differently than adults, most drugs have not been tested on pediatric populations. Under this rule, manufacturers of prescription drugs likely to be used by children will be required to complete studies and place information on drug labels to help pediatricians and other health care providers make scientifically-based treatment decisions when prescribing drugs to children.

WHY THIS REGULATION IS NEEDED

Most drugs -- even those commonly used in children -- have not been widely tested on pediatric populations. According to the American Academy of Pediatrics, only a small fraction of drugs and biological products marketed in the United States have had clinical trials performed in pediatric patients. Despite evidence that drugs affect children differently than adults, 80 percent of all drugs marketed in the United States have been labeled for use by infants, children, and adolescents. Forty-two percent of drugs that are widely used in pediatric populations have been tested on children.

- Many drugs commonly given to children under the age of six including Prozac, Zoloft, Ritalin, and drugs for asthma, allergic reactions, and ear infections are inadequately tested and labeled for use in children. These drugs, taken together, are given to over five million children each year.

- Less than half of the drugs used in the treatment of HIV infections carry any safety or effectiveness information for children. Of those that do, the data is often incomplete.

- Safety and effectiveness information is especially sparse for the over seven million children under the age of two.

- The percentage of drugs being tested on children decreased by over one-third between 1996 and 1991.

Drugs are likely to have a different impact on children than on adults. The appropriate use and dosage levels of medication for children and adults is usually different because of disparities in organs, the immune system, and metabolism.

Children who take prescription drugs that have not been tested on pediatric populations are at serious risk for unexpected adverse reactions. Evidence suggests that prescribing drugs that have not been adequately tested on children can be extremely dangerous. One example of the possible harm is the case of "gray baby syndrome" where a number of babies died from chloramphenicol, an antibiotic that their immature livers were unable to accept. Other children had withdrawal symptoms from prolonged administration of fentanyl, a pain killer used as an adjunct to anesthesia in infants and small children. Still others have suffered seizures and cardiac arrest from bupivacaine, a local anaesthetic not adequately tested in pediatric populations.

Some physicians are reluctant to prescribe much needed therapies to children because they have not been tested on pediatric populations. Physicians report that they have denied children important new drugs because, in the absence of adequate testing and labeling, they would have to guess at an appropriate dosage, and they do not want to take that risk. As a result, too many children do not receive the treatment they need and deserve.

SUMMARY OF THE RULE

Pediatric Studies for New Drugs. Under this proposed rule, manufacturers of new drugs would have to do studies on pediatric populations under two circumstances: when the product represents a meaningful therapeutic benefit over existing treatments; or when the product is expected to be widely used on pediatric patients. The FDA anticipates that about twelve new drugs each year would meet this requirement. Manufacturers could receive waivers from the requirement to do a pediatric study under any one of the following circumstances:

(1) The product does not represent meaningful benefits over existing treatments and is not likely to be used on a substantial number of pediatric patients as a whole; or

(2) Necessary studies are impossible or highly impractical-- i.e., the number of patients is too small or geographically diverse; or

(3) There is evidence strongly suggesting that the product would be unsafe or ineffective in pediatric populations.

Pediatric Studies For Existing Drugs. For drugs that are already on the market, the new FDA regulation requires additional testing on the pediatric population only if there is a "compelling need for more information." The criteria used is:

(1) If the product is widely used in pediatric populations and the absence of adequate labeling could pose significant risks to pediatric populations; or

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

President Clinton Continues to Fight to Improve the Health of Our Nation's Children

- **Children and Prescription Drug Testing.** Today's announcement requiring manufacturers to do studies on pediatric populations for new prescription drugs and those currently on the market builds on an impressive array of children's initiatives advocated by President Clinton.

- **Children and Insurance Coverage.** The President fought hard to ensure that the Balanced Budget Act included $24 billion -- the largest investment in children's health care since the passage of Medicaid in 1965 -- to provide meaningful health care coverage to as many as five million of our nation's uninsured children. He also fought to include revenue from a 20 cent tobacco tax which will not only further reduce the number of uninsured children, but it will also serve as a financial barrier to help prevent our children from starting to smoke in the first place.

- **Children and Tobacco.** The President issued guidelines to eliminate easy access to tobacco products and to prohibit companies from advertising tobacco to kids. Each day about three thousand children become regular smokers and 1,000 of them will die from a tobacco-related illness. According to former FDA Commissioner David Kessler, the possibility of a comprehensive, public health oriented settlement with the tobacco industry could not have come about without the President's leadership in this area.

- **Children and Insurance Reform.** By signing the Kassebaum-Kennedy bill into law last year, the President helped millions of American children keep their health care coverage when their parents lose or change jobs.

- **Children and Juvenile Diabetes.** The President fought to include $150 million ($30 million annually for five years) for research to help find the cure for diabetes. Americans with this disease often suffer severe consequences, such as blindness and kidney disease, even when they receive the best treatment and care. The HHS Secretary will have discretion to target the new funds toward the best scientific opportunities. This represents the largest single new investment in Juvenile Diabetes.

- **Children and Immunization.** As the President recently announced, over 90 percent of America's toddlers in 1996 received the most critical doses of each of the routinely recommended vaccines -- surpassing the goal set by the President in 1993.

- **Children and the Environment.** Earlier this year, the President signed an Executive Order to reduce environmental health and safety risks to children by requiring agencies to strengthen policies and improve research to protect children and ensure that new regulations consider special risks to children.

- **Children and Medicaid.** Throughout his Administration, the President has fought to preserve and strengthen the Medicaid program; its coverage of about 20 million children, makes it the largest single insurer of children. The Administration has partnered with states through Medicaid waivers to expand coverage to hundreds of thousands of children.

PEDIATRIC LABELING Qs and As

Q: WHY ARE YOU DOING THIS REGULATION NOW?

A: Despite efforts to increase the number of studies on pediatric populations, still too many children take prescription drugs that have not been tested on children. Over 80 percent of drugs manufactured in the United States have not been tested on children and over 50 percent of drugs that are known to be widely tested in children have not been tested.

As a result, some physicians are reluctant to prescribe much-needed therapies to children. Physicians report that they have denied children important new drugs because, in the absence of adequate testing and labeling, they would have to guess at an appropriate dosage, and they do not want to take that risk.

In some cases, guessing can be extremely dangerous. One example of the possible harm is the case of "gray baby syndrome" where a number of babies died from chloramphenicol, an antibiotic that their immature livers were unable to accept. Other children have had withdrawal symptoms from prolonged administration of fentanyl, a pain killer used as an adjunct to anesthesia in infants and small children. Still others have suffered seizures and cardiac arrest from bupivacaine, a local anaesthetic not adequately tested in pediatric populations.

Q: CAN'T YOU ACHIEVE THE SAME EFFECT THROUGH VOLUNTARY COMPLIANCE?

A: FDA has already implemented reforms to encourage voluntary compliance. However, as 80 percent of drugs manufactured in the United States and over 50 percent of drugs widely used in children still do not have a adequate pediatric labeling, FDA has concluded that this new rule is necessary to ensure that children get the protection they need.

Q: GIVEN THAT THE DRAFT FDA REFORM LEGISLATION, PENDING IN CONGRESS, CONTAINS FINANCIAL INCENTIVES TO ENCOURAGE VOLUNTARY COMPLIANCE, WHY IS THIS RULE NECESSARY?

A: The Congressional approach, while thoughtful and worthy of serious consideration, would not assure that most or all of prescription drugs used by children are tested and labeled appropriately. We believe that the Dodd/Dewine legislation has the potential to complement the regulation the President is unveiling today, but it is not a replacement for it.

Q: DO YOU SUPPORT THE DODD LEGISLATION AS CURRENTLY DRAFTED AS A COMPONENT OF THIS EFFORT?

A: We are reviewing this legislation to determine if it can be designed to compliment and bolster our efforts today. We believe that it has great potential to compliment the legislation but we are not prepared to accept it as currently drafted before we consider all of the ramifications of overlaying the important regulation the President is announcing today.

Q: HAVE CHILDREN BEEN AT RISK IN THE PAST?

A: Yes. In some cases physicians do not prescribe drugs because they determine that it is simply not worth taking the risk of prescribing drugs that have not been tested in children.

In other cases, physicians choose to prescribe treatment, because it is the only means to cure a child's nagging illness or even a life threatening disease. Those physicians are left to make their best guess at the appropriate doses -- rather than rely on the through studies and information that the rest of us take for granted.

In some cases, however, guessing can be devastating. One example of the potential for harm is the case of "gray baby syndrome" where a number of babies died from chloramphenicol, an antibiotic that their immature livers were unable to accept. Other children had withdrawal symptoms from prolonged administration of fentanyl, a pain killer used as an adjunct to anesthesia in infants and small children. Still others have suffered seizures and cardiac arrest from bupivacaine, a local anaesthetic not adequately tested in pediatric populations.

Q: HOW MANY PRODUCTS WILL BE AFFECTED BY THE RULE?

A: FDA anticipates that this will impact about 12 new drugs each year. The agency will also review drugs already on the market to determine which ones should have pediatric studies. FDA will work as quickly as possible to ensure that in a few years the drugs most important to children will have directions for use in kids on their labels.

Q: WHAT KINDS OF DRUGS ARE COMMONLY MISSING THIS PEDIATRIC DATA?

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

Q: WHAT DO DOCTORS DO WHEN THEY DON'T HAVE THIS INFORMATION?

A: In some cases they choose not to prescribe the drugs at all. In other cases, they take their best guess -- without the assistance of information that we rely on for adult medications. Sometime, however, guessing can have dangerous consequences, such as seizures, heart problems, or even death.

Q: WHEN CAN PARENTS EXPECT THAT INFORMATION TO SUPPORT SAFE AND EFFECTIVE USE OF PRODUCTS IN CHILDREN WILL BECOME AVAILABLE?

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

Q: HOW MUCH WILL THIS COST DRUG MANUFACTURERS?

A: FDA estimates that the costs of pediatric studies will be less than 1% of the total costs of developing a drug.

Q: WILL DRUG PRICES INCREASE AS A RESULT OF THIS REGULATION?

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

Q: WILL THIS REQUIREMENT HOLD UP DRUG APPROVALS?

A: Clearly we will provide every incentive to complete the study before the drug is approved. However, the rule explicitly ensures that a drug's entrance into the market is not held up even if all studies on pediatric populations have not yet begun. We will rely on other legal and financial remedies to ensure that companies comply as soon as possible.

Q: WHEN WILL THIS REGULATION GO INTO EFFECT?

A: There is a 90 day period for comment on the proposed rule after which the agency will evaluate and respond to the comments and publish a final rule. The final rule will take effect 3 months after issuance. At that time, for drugs already on the market, FDA, in compelling circumstances, may request that pediatric studies be initiated. Manufacturers of new drug and biologic products, under review at the agency, will have 2 years to comply with the pediatric study requirement. Manufacturers of new products, not yet submitted for review, will have 18 months to comply with the requirement. Drugs already on the marketplace will have 3 months to comply.

Q: WHAT IS THE ENFORCEMENT MECHANISM FDA WILL TAKE TO FORCE COMPANIES TO PROVIDE THIS DATA ON APPROVED DRUGS?

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

File - Health - Pediatric drug testing

Pediatric Drug Labeling Background Materials

CLOSE HOLD

1. Internal FDA fact sheet on the issue and a draft FDA proposal

2. Top 10 drugs used off label on kids (without pediatric safety and dosing information on the label)

3. Information on FDA's 1994 actions which have failed to encourage drug manufacturers to voluntarily provide pediatric information on labels.

4. Wall Street Journal article on the issue.

Health – Pediatric Drug Labeling

PROPOSAL TO ADDRESS THE LACK OF PEDIATRIC LABELING FOR DRUGS

BACKGROUND

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

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

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

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

PROPOSAL

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

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

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

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

Pediatric Corner

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

By L. Miriam Pina, M.D.

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

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

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

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

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

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

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

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

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

Table data published with permission, © IMS America, Ltd., 1994.

·95%

HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

P94-21
FOR IMMEDIATE RELEASE
Dec. 13, 1994

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

FDA ANNOUNCES NEW RULES FOR CHILDREN'S MEDICINES

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

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

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

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

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

-MORE-

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

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

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

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

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

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

other available data. If so, they have to submit an application for supplemental labeling within two years.

Finally, the new regulation clarifies that the agency has the authority to request specific pediatric use information. For example, FDA may decide to request pediatric use data for a drug that is widely used, represents a safety hazard or is therapeutically important in the pediatric population. The rule, however, does not limit the manner in which a practitioner may prescribe an approved drug.

The additional measures will include the establishment of a special pediatric subcommittee that will track the implementation of the new regulations and draft policies and guidance documents to ensure that the possibility of pediatric testing and use are explored during the development of new drugs.

The agency also will work closely with the Pediatric Pharmacology Research Units that are funded by the National Institute of Child Health and Human Development to conduct pediatric studies on selected therapies. Finally, FDA will work with sponsors on investigational new drug applications and on new marketing applications to ensure that necessary pediatric data are included for products that have a potentially widespread use in children.

FDA is one of the Public Health Service agencies within HHS.

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

In the Line for AIDS Drugs, Children Are Last

By Laurie McGinley
Staff Reporter of The Wall Street Journal

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

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

MEDICINE

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

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

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

Mostly Out of Reach

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

*Protease inhibitors

Sources: Pediatric AIDS Foundation; Food and Drug Administration

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

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

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

How did this happen?

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

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

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

Please Turn to Page B9, Column 1

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

Continued From Page B1

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

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

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

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

Elena –

FDA estimates its draft proposal would affect 5-10 drugs per year at a cost of $200,000 - $5 m per drug.

– Pauline

Fib-Health - Pediatric drug Testing

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DRAFT

IMPACT OF PEDIATRIC STUDY REQUIREMENT

FDA has made a very preliminary assessment of the impact of the proposed pediatric study requirement. This assessment is based on the assumption that the requirement would apply to drugs classified as "new molecular entities" and biological products that either (a) represent a significant therapeutic advance or (b) would be prescribed to children more than 100,000 times per year.

- FDA estimates that it approves 5-10 drugs and biological products per year that would require new studies under this rule that would not otherwise have been conducted.

  (In making this estimate, FDA analyzed product approvals between 1991 and 1995, looking at 4 factors: (1) the number of products approved with potential use in children; (2) the number of products that the manufacturers voluntarily studied in children; (3) based on (1) and (2), the number of products that were not studied in children, but should have been; (4) of the latter category, the number that represented a significant therapeutic advance or that were prescribed to children more than 100,000/year.)

- The cost of conducting studies that adequately assess pediatric safety and effectiveness could vary from approximately $200,000 for a pharmacokinetic comparison of adults and children to $3-5,000,000 for a full-scale clinical trial.

  - The cost of a study is calculated based on a rough estimate of $5,000 per subject enrolled in the study. Pharmacokinetic studies require very few patients (40-50, in most cases), while controlled clinical trials may require several hundred patients.

- It is difficult to estimate in advance which kinds of studies will be needed for specific future drugs. The total cost to manufacturers per year is therefore likely to be between $2,000,000 and $25,000,000.

Health - Pediatric Drug Labeling

Health-pediatric drugs

PEDIATRIC LABELING FOR DRUGS

BACKGROUND

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

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

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

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

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

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

REGULATORY STRATEGY

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

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

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

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

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

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

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

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

THE PRESIDENT HAS SEEN
12-1-97

PROPOSAL TO TEST DRUGS IN CHILDREN MEETS RESISTANCE

ETHICAL CONCERNS RAISED

Citing Cost and Safety Issues, Makers of Medicines Fight Plan Offered by Clinton

By ROBERT PEAR

WASHINGTON, Nov. 27 — Fierce disputes have erupted over a proposal by President Clinton that would require drug companies to test their products in children before putting new medicines on the market.

Mr. Clinton says such studies will improve health care for children by helping doctors assess the safety and determine the proper doses of drugs that are used to treat children.

But drug companies say the President's proposal will needlessly put thousands of children at risk. And these companies contend that the Government has no legal authority to make them conduct such studies.

When Mr. Clinton announced his proposal on Aug. 13, it seemed politically irresistible. But it is proving much more complicated than expected, and Federal officials now acknowledge that the testing of drugs in children raises ethical questions not found in clinical trials with adults.

Since many important drugs are not tested in children, Mr. Clinton said, doctors must often guess at the appropriate doses, and youngsters may be deprived of "the very best treatment available."

Doctors have generally supported the proposal. Dr. Susan P. Etheridge, a pediatric cardiologist at the University of Utah, said it could be "the biggest step forward for drug treatment of children in three decades."

Lawrence A. McAndrews, president of the National Association of Children's Hospitals, said, "Only about 20 percent of drugs marketed in the United States have been tested and labeled specifically for children."

Under the President's proposal, drug makers would have to test their products in children if the drugs were used, or were likely to be used, in "a substantial number of pediatric patients" or if they offered "a meaningful therapeutic benefit over existing treatments" for children.

Dr. Michael A. Friedman, Deputy Commissioner of the Food and Drug Administration, said, "Many drugs labeled only for adult use are, in fact, widely used in pediatric patients" for the same illnesses.

Indeed, doctors say, drugs are routinely prescribed for children even when the labels carry a disclaimer

Continued on Page 28

Continued From Page 1

saying, "Safety and effectiveness in pediatric patients have not been established."

Mr. Clinton's proposal would authorize the Food and Drug Administration to seek court orders requiring drug companies to study how their products affect children. Violators would be subject to fines and other penalties.

In proposing the requirements, the F.D.A. said, "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."

Alan F. Holmer, president of the Pharmaceutical Research and Manufacturers of America, a lobby for drug companies, said Mr. Clinton's proposals were well-intentioned but could harm children because they would require testing of new chemical compounds in children before the drugs' safety in adults had been adequately studied.

The proposals would impose "new risks on children who might be recruited for clinical trials," Mr. Holmer said. Companies worry that children injured in drug tests might file lawsuits years later, after they grow up, even though parents gave consent for the tests. The tests raise the ethical question of how researchers can obtain informed consent from children as they do from adults.

Drug makers including Merck, Glaxo Wellcome, Novartis and Wyeth-Ayerst said they shared Mr. Clinton's goal of discovering better medicines for children but found the details of his proposal extremely impractical and burdensome.

Mr. Holmer said that a prescription drug should ordinarily not be tested in children until scientists had clear evidence that it was safe and effective for adults. Requiring that drugs be studied simultaneously in children and adults could delay the approval of life-saving medications for adults, he said. Drug company executives said that Mr. Clinton, in his zeal to protect children, was exceeding his authority under Federal law. The job of the F.D.A., they said, is to review drugs for the uses proposed by manufacturers.

The Clinton Administration assumed that the new drug trials would cost an average of $5,000 to $9,000 for each child included in a study. Overall, it said, the proposed rule would impose costs of $13 million to $21 million a year on the drug industry.

But drug companies said the costs would be much higher. Mr. Holmer said the proposal would set "a dangerous precedent," diverting money and other resources away from "drug research that is more beneficial to the general public."

Janne Wissel, vice president of the Alza Corporation, a maker of drug-delivery technology in Palo Alto, Calif., said, "The cost of performing pediatric studies, especially for small companies, may be prohibitive."

Young children often have difficulty swallowing pills, tablets and capsules. So drug companies often need to devise liquid, chewable or injectable forms of their products. Companies say it may cost millions of dollars to develop a formulation specifically for children.

In the absence of such products, parents make their own arrangements, cutting up tablets, crushing them with a mortar and pestle or mixing them with liquid so children can swallow them. But, Dr. Etheridge said, that is "not the most accurate way" to measure out drugs.

Drug companies said that under Mr. Clinton's proposal they would have to conduct separate tests in newborn infants, young children and teen-agers, because children of different ages often reacted differently, requiring different amounts of drug per pound of body weight.

Chris Jennings, a White House aide, said the drug companies' objections were not surprising. "We tried it their way, and it didn't seem to work particularly well," he said, noting prior efforts by the Government to encourage voluntary testing of drugs in children.

Dr. Joseph R. Zanga, president of the American Academy of Pediatrics, supported Mr. Clinton's proposal. Many drugs go on the market with little or no information about their effects on children, he said, so the Government must use its authority to require drug makers to conduct pediatric studies.

But Dr. Bonnie J. Goldmann, vice president of the research laboratories at Merck & Company, said that financial and other incentives would be far more effective than threats of punishment in encouraging studies of drugs for children.

The New York Times

Health - pediatric labeling

Q&As
December 1, 1997

PEDIATRIC LABELING

Q. Are you concerned about the ethical and health care concerns raised by drug manufacturers regarding the Administration's regulation requiring companies to test their products in children before marketing them?

A. Absolutely not. Our regulation ensures that physicians and other health care professionals have the information they need to most appropriately prescribe needed medications to our nation's children. Today, countless thousands of children are prescribed medications in the absence of this information. This is why national representatives of pediatricians and children's hospitals are so supportive of this regulation. It borders on the unethical not to take these steps.

Follow-up question: There does seem to be a disagreement between the industry and health providers on this issue; aren't you concerned even if just one child is needlessly exposed to clinical trials that might be harmful?

A: What the *New York Times* article did not mention is that the Food and Drug Administration (FDA) Commissioner will have the authority to waive testing requirements if he or she determines they are ethically or medically unsound.

MEDICARE COMMISSION

Q. Why are you not announcing your appointments to the Medicare Commission today --the date the Balanced Budget Agreement law explicitly calls on the Congress and the Administration to make its selections?

A. After consulting with the Congress, we have decided that it would be preferable to announce the Commission appointees along with the Chair. We have not finalized our discussions on the Chair and, by mutual agreement, have decided to delay the final announcement of appointees until that time.

Follow-up question: When do you anticipate this process concluding? Why is this taking so long?

It is our hope and expectation that we will reach closure on the chair in the very near future. We are committed to getting the work of the Commission underway as soon as possible.

Health - pediatric labeling

THE WHITE HOUSE

WASHINGTON

August 12, 1997

PEDIATRIC DOSAGE AND LABELING ANNOUNCEMENT

DATE:	August 13, 1997
LOCATION:	Rose Garden
BRIEFING TIME:	1:15 pm - 1:35 pm
EVENT TIME:	1:45 pm -2:15 pm
FROM:	Bruce Reed

I. PURPOSE

To demonstrate your commitment to children's health issues by announcing a new FDA regulation to improve the safety of pediatric drugs.

II. BACKGROUND

You will be unveiling a new FDA regulation that will require drug manufacturers to study the effects of drugs on children. The regulation will apply both to certain new prescription drugs and to certain drugs currently on the market. Under this regulation, drug manufacturers will be required to complete clinical studies and place information on drug labels to help physicians make informed decisions when prescribing drugs to children.

Although children have distinct needs with regard to doses and potential side-effects of medications, most drugs have not been tested on pediatric populations. Currently, only 42 percent of drugs that have proven highly useful for children are tested on children. As a result, physicians are reluctant to prescribe many drugs to children because they do not want to risk giving an inappropriate dosage. Those physicians that do prescribe drugs without pediatric labels are forced to guess the appropriate dosage.

The FDA has identified ten drugs that are prescribed 5 million times a year to children that have not been adequately tested on children. These include Prozac, Zoloft, Ritalin, and drugs for asthma, allergies, and ear infections. In addition, less than half of the drugs used in the treatment of HIV are being studied on children. The Pediatrics AIDS Foundation has lead the fight for this new regulation on behalf of the 10,000 to 12,000 children with HIV.

Representatives from the Pediatric AIDS Foundation, the National Association of Children's Hospitals, the American Academy of Pediatrics, and other children's health organizations will be in attendance.

III. PARTICIPANTS

Briefing Participants
Secretary Shalala
Bruce Reed
Chis Jennings
Jennifer Klein
Maria Echaveste

Events Participants
Vice President
First Lady
Secretary Shalala
Regan Ralph, mother of 1 ½ year old son with asthma.

Meet and Greet Participants (Prior to Event)
Regan Ralph, mother of child with asthma, and family.
Dr. Joseph A. Zanga, Vice President, American Academy of Pediatrics
Susan DeLaurentis, Co-Founder, Pediatrics AIDS Foundation
Francesca DeLaurentis, daughter
Lawrence McAndrews, President and CEO, National Association of Children's Hospitals

IV. PRESS PLAN

Open Press.

V. SEQUENCE OF EVENTS

- You will be announced onto the stage accompanied by stage participants.
- The First Lady makes welcoming remarks and introduces Secretary Shalala.
- Secretary Shalala makes remarks and introduces the Vice President.
- The Vice President makes remarks and introduces Regan Ralph.
- Regan Ralph makes remarks and introduces you.
- You will make remarks and then depart.

VI. REMARKS

Remarks Provided by Lowell Weiss in Speechwriting.

Health-pediatric labeling

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF MANAGEMENT AND BUDGET
WASHINGTON, D.C. 20503

ADMINISTRATOR
OFFICE OF
INFORMATION AND
REGULATORY AFFAIRS

August 6, 1997

MEMORANDUM FOR ERSKINE BOWLES

THROUGH: Franklin D. Raines

FROM: Sally Katzen

SUBJECT: Heads-up on FDA Proposed Rule on Pediatric Labeling

We are about to conclude review of an FDA proposed rule that would require companies to study the effects on children of new and currently available drugs and biological products. Because some of these products are not adequately tested for use in children, their labels often fail to provide directions for their safe and effective use in children, and the absence of adequate pediatric labeling has resulted in children receiving inappropriate doses of drugs or experiencing unexpected adverse effects. In other instances, the absence of adequate pediatric labeling has led some physicians to refuse to prescribe otherwise helpful drugs because they have not undergone pediatric testing.

This proposed rule is the subject of a Presidential event tentatively scheduled for August 11th. The rule is expected to receive very positive support from the public. Many drug companies will refrain from criticizing the rule, but there will be some companies that may express concerns. Perhaps the most touchy aspect is the issuance of the rule while the FDA reform legislation is in a fairly active state on the Hill. If you have any questions or comments, please let me know.

cc: Maria Echaveste
Rahm Emanuel
Thurgood Marshall, Jr.
Don Gips
John Hilley
Ann Lewis
Sylvia Mathews
Bruce Reed
Chris Jennings
Elena Kagan
Victoria Radd
Barry Toiv
Michael Waldman
Josh Gotbaum
Larry Haas

Health - Pediatric Drugs

SCHEDULE REQUEST PROPOSAL
7/1/97

_____ ACCEPT _____ REGRET _____ PENDING

TO: Stephanie Streett
Deputy Assistant to the President &
Director of Scheduling

FROM: Melanne Verveer
Bruce Reed
Don Gips

REQUEST: To announce new regulations that requires drug companies to improve pediatric labeling information for parents.

PURPOSE: The President and the First Lady (and possibly the Vice President) would announce new HHS/FDA regulatory action that we are taking to ensure that drug companies test their products specifically on children who may need different doses and have different reactions and to ensure that parents are aware of this information. Children's groups such as the National Association of Children's Hospitals and The American Academy of Pediatrics will validate the need for such an action.

BACKGROUND: Children suffer from most of the same diseases as adults, however, most drugs have not been tested to understand their unique impact on children. The absence of pediatric labeling poses serious a serious risk of inappropriate doses and unexpected adverse effects in children. It also my lead to failure to provide children with optimal treatment in cases where physicians are reluctant to prescribe potentially toxic drugs to children before they have undergone pediatric testing. For example, a recent study by the Pediatric AIDS Foundation found that fewer than 10 percent of children with AIDS were receiving protease inhibitors, the newest and most promising of AIDS drugs.

PREVIOUS PARTICIPATION:	None
DATE AND TIME:	July
DURATION:	1 hour
LOCATION:	Flexible
OUTLINE OF EVENTS:	The event would include providers, children's groups, and children.
REMARKS REQUIRED:	Prepared by speech writing.
FIRST LADY'S ATTENDANCE:	Yes
VICE PRESIDENT'S ATTENDANCE:	Not required
SECOND LADY'S ATTENDANCE:	Not required
RECOMMENDED BY:	Melanne Verveer, Bruce Reed, Ron Klain, Chris Jennings, Nancy-Ann Min
CONTACT:	Jennifer Klein, 456-2599

Health — pediatric drug labeling

Elizabeth Drye
06/11/97 08:03:08 PM

Record Type: Record

To: Elena Kagan/OPD/EOP

cc: Jennifer L. Klein/OPD/EOP, Christopher C. Jennings/OPD/EOP
Subject: Here's my ped. labeling issue

I think we should force closure with Katzen tomorrow on what signals WH should send on Senator Dodd's pediatric labeling incentive (patent extension) proposal. Last night HHS sent a 2 1/2 pager over for clearance that gently pointed out the drawbacks of Dodd's approach, and stated our intention to do regulation (you have HHS's version of this document; this is the piece FDA wants to get to Ped AIDS Foundation and Amer. Academey of Pediatrics as backgrounder and proof we're planning to do reg). Katzen modified p. 2 to state that "other approaches are needed to supplement any financial incentive," implicitly embracing Dodd's piece.

I see no reason to send any signal now that we want to do the incentive as well as regulation. It's a poorly-targeted windfall for companies at the expense of consumers and gov't health care payors and will do little to promote pediatric studies. Sally should reject it on efficiency grounds alone, given her idealogical bent, so I assume she wants to embrace it as a gesture to Dodd. Not sure that has any benefit at this point (Dodd reportedly said today he is supporting Jeffords bill), and HHS doesn't seem to think it's necesarry given the cleared draft they sent over.

Bottom line, we shouldn't casually send a signal that we want to do both an incentive and reg approach. I suggest we (you?) talk to her, ask her why she made the change, push her on substance, and ask her to withdraw her edits of HHS's backgrounder.

Schultz thinks we need to get the 2 /12-pager out tomorrow. Is there any way you can take up this narrow issue with Sally and get closure tomorrow? If you'd like me to talk to her directly with your backing I'd be happy to. FYI Toby shares my concern and will talk to Gips about it.

Health-pediatric AIDS drugs

Elizabeth Drye
05/29/97 03:18:25 PM

Record Type: Record

To: Elena Kagan/OPD/EOP

cc:
Subject: pediatric labeling

Any progress? Elena -- my understanding is that Sally asked for an FDA briefing on the issue. Is that /did that happen(ing)? Do you need me to staff? Chris tells me Sally is on board (yeh!). Feeling the need for me or Jen to get back to Ped. AIDS Foundation on this given that they are holding back at our request -- let me know how I can be helpful.

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DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
001. email	Cornelius_C to distribution list at 10:03:00. Subject: Manifest. (1 page)	05/22/1997	P6/b(6), b(7)(C), b(7)(E), b(7)(F)

COLLECTION:
Clinton Presidential Records
Domestic Policy Council
Elena Kagan
OA/Box Number: 14363

FOLDER TITLE:
Health - Pediatric Drug Testing

2009-1006-F
ab809

RESTRICTION CODES

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

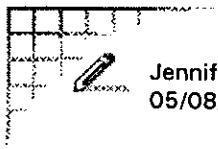
P1 National Security Classified Information [(a)(1) of the PRA]
P2 Relating to the appointment to Federal office [(a)(2) of the PRA]
P3 Release would violate a Federal statute [(a)(3) of the PRA]
P4 Release would disclose trade secrets or confidential commercial or financial information [(a)(4) of the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

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

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

b(1) National security classified information [(b)(1) of the FOIA]
b(2) Release would disclose internal personnel rules and practices of an agency [(b)(2) of the FOIA]
b(3) Release would violate a Federal statute [(b)(3) of the FOIA]
b(4) Release would disclose trade secrets or confidential or financial information [(b)(4) of the FOIA]
b(6) Release would constitute a clearly unwarranted invasion of personal privacy [(b)(6) of the FOIA]
b(7) Release would disclose information compiled for law enforcement purposes [(b)(7) of the FOIA]
b(8) Release would disclose information concerning the regulation of financial institutions [(b)(8) of the FOIA]
b(9) Release would disclose geological or geophysical information concerning wells [(b)(9) of the FOIA]

Health - pediatric drugs



Jennifer L. Klein
05/08/97 04:17:16 PM

Record Type: Record

To: Elena Kagan/OPD/EOP

cc:
Subject: Pediatric AIDS

I think its time to bug Bill Corr again. Rich Tarpelin was supposed to talk to Dodd to temper him before the press conference on the DeWine-Dodd bill and didn't. According to Tim Westmoreland of the Pediatric AIDS Foundation, DeWine was fine and Dodd wasn't (went on and on about how we should do this through the market, not by regulation). So, now it will be even harder for us to do this by regulation. Grrrr!!!!

Call me if any of this rambling doesn't make sense.

4/18 Pediatric Drug Labeling

Hum moved along. Bliley / Shalala reached ag on process — mum discs w/ ind to Hill.

Goal: Moderate Drug reform + PDUFA

No devices or food — keep off-label issue off.

Feel good abt limits.

Senate wait apace — in fact Jeffords wants to do a bill.

Puts us in awk pos — everyone puts in favorite provisions.

Bill says by next week, FDA may be finished — ready to send to dept.

Members are holding off introducing legislation

PA: Yes, but only so long — need something from us.

Rich thinks — have to be careful. Want to dig a bit deeper.

Exec w/ Jeffords.

Hill could — [redacted] a week if we want.

Health - Pediatric drug labelling

Elizabeth Drye
04/18/97 04:44:40 PM

Record Type: Record

To: Pauline M. Abernathy/OPD/EOP

cc: Elena Kagan/OPD/EOP, Jennifer L. Klein/OPD/EOP, Christopher C. Jennings/OPD/EOP
Subject: Re: Pediatric drug labeling

Also, Don Gips has a meeting w/Sally next Friday, per Toby, and could help out here.

Pauline M. Abernathy
03/11/97 03:50:48 PM

Record Type: Record

To: Elena Kagan/OPD/EOP

cc: Elizabeth Drye/OPD/EOP, Christopher C. Jennings/OPD/EOP
Subject: pediatric labeling

Can we sit down with you on Thursday or Friday to discuss pediatric drug labeling? We would then invite Bill Corr to come over and brief you, along with Eric G and OVP staff, on the substantive issue and HHS's plans.

If this is agreeable, what time makes sense to meet with you on Thursday or Friday?

Thanks.

Health - pediatric drug

Pauline M. Abernathy

03/02/97 07:07:23 PM

Record Type: Record

To: Elena Kagan/OPD/EOP

cc:

Subject: pediatric drug labeling

HRC is speaking to the Pediatric AIDS Foundation on Tuesday night, and they clearly want her to say something about pediatric drug labeling, the issue I mentioned in my email to you about issues and event ideas. I am sure I can work out some language with HHS, FDA, and OVP for HRC to get us through Tuesday. But after Tuesday would you like the DPC to take this issue on? Kessler met with Shalala on this issue late last week. Apart from the policy question of how best to achieve the shared goal of having pediatric labeling on more drugs, the strategic question is whether to move on this issue administratively and separately from FDA reform. Some people reportedly believe that it would make it more difficult to win passage of a good FDA reform bill.

I will try work out some language for HRC along the lines of "the Administration is committed to ensuring we make more progress on this issue," (which has been said before) and if possible something about time frames for action.

Health-Pediatric Drug Letter

TO: Joel Johnson

FROM: Susan DeLaurentis

DATE: December 5, 1996

RE: **Pediatric Data for Pharmaceuticals**

Thank you for your willingness to pass along our proposal to the appropriate White House staff for such matters. As you have requested, I will briefly describe here the "best case scenario" from our view. We have been discussing this issue (i.e., the need for pediatric data) with David Kessler, Bill Schultz (his deputy), and their lawyers over the past year, and I think you will find them supportive as well. Everyone has put a lot of time into this and it has been productive.

The following scenario presents the President with the most visibility on what we believe will be a very popular, "Christmas-present-to-all-children" initiative. If this seems right to the White House, we can -- and must -- begin work immediately. (It would be particularly helpful if there were a White House staff contact for us. With most of our issues we would go directly to the AIDS staff, but this is obviously broader than AIDS alone.)

We propose that some time during the week of December 16, the President issue an Executive Order, directing the FDA to take immediate regulatory action to ensure that all drugs be proven safe and effective for use by children prior to their approval by the FDA. We propose that the President sign the Order in the Oval Office, with children, parents, and pediatricians present. We would ask that the President dedicate this action to Elizabeth Glaser and her work to improve child health, and that the Pediatric AIDS Foundation be included in the event.

A proposed action plan detailing the steps that need to be taken, including what should be included in the President's Executive Order and accompanying statement, is attached to this memo. We would be happy to help in effectuating this plan in any way possible -- from drafting the Executive Order, to generating support in the media, to making physicians, parents, and advocates available for comment. Just let us know what we can do.

We are very excited about this proposal, and appreciate your attempt to steer us toward the appropriate decision makers.

Thanks again for everything.

PROPOSED ACTION PLAN

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

- The Executive Order would:

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

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

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

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

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

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

Kris M Balderston
03/07/97 06:49:17 PM

Record Type: Record

To: Patricia F. Lewis/WHO/EOP

cc: Elena Kagan/OPD/EOP, Nicole R. Rabner/WHO/EOP
Subject: Re: Early Learning Conference

Just a few Q's re the regionals

1- do we have a determination fr the counsel on whether this is an official event
2- what's the update on the financing sponsorship
3- the regions are interested -- we have a few co-sponsorship q's
4- next Mtg?

File
03 Conf.

3/12 Ped Drug Labeling -

No pediatric uses on label < vs. Eur. uses are on label
bec no testing on kids (which is a req)

1994 - Proposal - pharmacokinetic study / instead of this
get label this way.
Not much bkt this way

HHS / FDA - considering - moving to req. of ped testing
req phs studies on
most innov drugs -
providing access to
kids.

Alter - patent extension
incentive

help kids a lot
help a lot of kids
defer until after approval
for adults

First lady said publicly - can't wait forever.

Is your face active re the FDA Reform ??
to req proposal will count as bad fait.
HHS says as
keep this in. sweetener to FDA reform.

Kessler wanted to.
Dunn opposed.