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 Drugs

3/20 → meet in 2 wks.

Need evidence of problem?

Kassebaum – 6 mos. of exclusivity for adults + kids → [illegible]
→ windfall in some cases for both kids +
→ patent still up to company
→ generics opposed it – no floor or cmte action

1994 – FDA no double blind clinical tests for kids
→ just do $120,000 [illegible] cost
→ pediatric page on applications
→ data no better than before

Why not do it (firms)? Don't know.
1. Culture – mind set
2. Formulation
3. Small markets + being used already

Firms Never mention liability

1994 reg. says we have the authority to require it
PAF would file a petition b/c believe we must do it

FDA – new drugs: hold in contempt if don't do study – wouldn't come to legal action

– old drugs – compelling use – serious disease, or widely prescribed

Action: proposal, public mtg, final rule

1/29

~~SOTO~~ Pediatric Drugs

1. ~~Date of Q-3~~

2.

~~9,000 indep. students are worse off by nonrefundable~~

-> legacy issue
-> FDA tried several strategies that did not succeed.
~~[illegible]~~ 1994: major change
1. easier to do a pediatric application - no double blind full test
- easier to do trials
- limited to most essential info - simple drug level for right level for kids.
-> limited success
2. Pediatric page in application 3. Asked for ped. info.
-> 1996 - incentive based; led exclusivity for those who do these studies
-> generic drug concerns
-> we do not control
-> drawbacks to this approach - windfall
Spirit: mismatch benefits + cost

∴ can't be ostrich position
obligation to do it for kids if that's how we'll do it

-> Ask HHS to consider action

? -> FDA relies on company to say purposes [who is benefiting]:

1994 Action deadline by Dec 96 ?

1991	1996	
26	53	New molecular entities
15	40	potential ped. use
7	10	pediatric labeling
7	13	approved but required ped. data [Phase IV studies] agreed to do it
1		only 1 followed through

RS – post-1994 data

– approve w/ req of later labeling but w/ label enforcement measures

– consider a presumption that new studies w/ before w/ NDA
⇒ the

→ put out for comment

Kessler cons cancer risks case
→ where is the pediatric plan

Why not do
1. cost
2. new trials
3 liability

Sends to HHS + OMB
→ Late VP mtg w/ next 2 mos.
→ voluntary efforts
→ support req.

Politics
- parents
- pharm - delay + cost but not yield
- Hill ? don't know
~~Hillcrest~~

doing cost check

CLOSE HOLD
NOT FOR DISTRIBUTION 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.

FAREWELL MEETING WITH DAVID KESSLER
February 27, 1997

DATE:	Friday, February 28, 1997
LOCATION:	Diplomatic Room
TIME:	12:00-12:30 p.m.
FROM:	Pauline Abernathy

I. PURPOSE

To say farewell to David Kessler on his last day as FDA commissioner.

II. BACKGROUND

Kessler asked for a few minutes with you. While the purpose of this meeting is to say farewell, the subject of pediatric drug labeling may come up. Kessler sees failure to make significant progress in getting pediatric safety and dosing information on more drugs with pediatric applications as one of his greatest disappointments. In addition, on Tuesday you will be speaking to the Pediatric AIDS Foundation, which supports FDA's issuing a regulation requiring drug companies to provide pediatric safety and dosing information. The Foundation also supports legislation providing financial incentives (patent-like protection) to companies to do this, but would agree that such an approach is less desirable because it is not well targeted. Patent-like protection would provide financial windfalls to some companies who might have provided pediatric data anyway at very little cost.

I have been meeting with FDA and White House staff on this issue. Greg Simon gave Kessler the green light to draft a regulatory proposal with HHS that could then be discussed with the industry. FDA is still working on their proposal, but attached is a description of the problem and their draft proposal. Preliminary FDA estimates suggest their proposal would require new studies for 5-10 drugs each year, costing $200,000 to $5 million per drug.

Kessler just met with Secretary Shalala this week on this issue. Some people within the Administration reportedly would prefer to handle this issue as part of our FDA reform legislative proposal rather than moving forward with a rule. However, it is unclear how quickly or slowly FDA reform will proceed, and pediatric drug labeling could be handled administratively as we have done with tobacco. While drug companies would not support new regulations, it would be difficult for them to oppose publicly a well-designed and targeted rule on this subject.

III. CLOSED PRESS

IV. ATTACHMENTS

-FDA internal description of the issue and their draft proposal.
-Article listing the top 10 drugs prescribed for children without pediatric labeling

THE WHITE HOUSE

WASHINGTON

January 14, 1997

Susan DeLaurentis
Chief Executive Officer and Co-founder
Pediatric AIDS Foundation
1311 Colorado Avenue
Santa Monica, CA 90404

Dear Susan:

Thank you for sending me the information and proposal for Administration action to increase children's access to safe and effective prescription drugs. I continue to be concerned that we make progress on this issue.

As you know, at the Oval Office briefing on AIDS research on December 3, the Vice President expressed his and the President's personal commitment to developing pediatric applications of prevention and treatment therapies. I have asked my staff to review your proposal with our domestic policy team, and I understand White House staff have met with representatives of the Pediatric AIDS Foundation here in Washington. Pauline Abernathy on my staff is working on this issue while Jennifer Klein is on maternity leave, and she would be glad to talk with you or your staff about it.

I also just received your invitation to attend and participate in your awards ceremony on March 4, 1997. I have forwarded a copy of your invitation to my scheduling office for consideration.

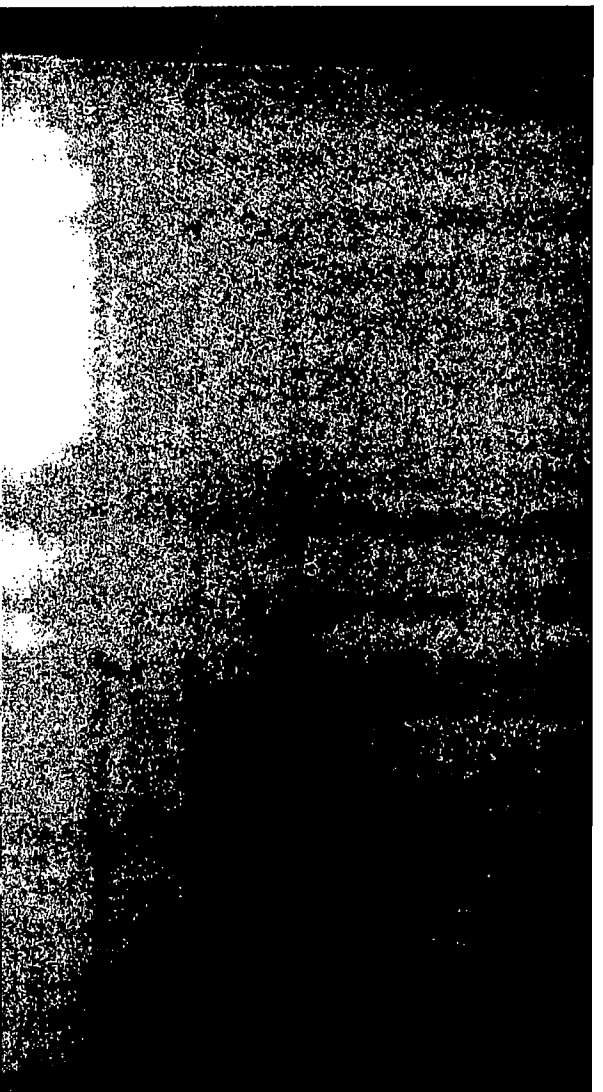
As always, thank you for the important work that you are doing.

With warm regards, I remain

Sincerely yours,

Hillary

Hillary Rodham Clinton



Hope for Children with AIDS

Dear Hillary,

It's my understanding that proposals are under consideration at HHS and not moving.

I know it's complicated, but wouldn't it be great if you could announce something at the Elizabeth Glaser Scientist Awards Ceremony on March 4th?

Love,

Susan

Pediatric AIDS Foundation

[illegible] Colorado Avenue Santa Monica, California 90404

[illegible]-395-9051 Fax 310-395-5149

Hope for Children with AIDS

Pediatric AIDS Foundation

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1947–1994

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Bernard Fields, M.D.

February 20, 1997

First Lady Hillary Rodham Clinton
The White House
Washington, DC 20500

Dear Hillary,

First, thank you very much for agreeing to come to our Elizabeth Glaser Scientist Awards. Everyone is looking forward to seeing you, and we believe it will be a very memorable evening and a fitting tribute to Elizabeth.

Now, however, I am writing about another issue, one about which I have written to you before--pediatric research on pharmaceuticals. After several years of work with HHS, we now understand that proposals to make significant improvement in the way FDA deals with drugs for children are currently under serious consideration at HHS. I am writing to ask that you do all you can to expedite the review and adoption of such proposals and the public commitment of the Administration to them.

Over the past two years, we have been quietly talking with David Kessler and his staff to develop improvements in pediatric drug research. While they were initially skeptical that much could be done, they now seem enthusiastically supportive of new action on pediatric data.

We have made progress. But I feel a sense of urgency to press now for at least three reasons. First, David is leaving and that is a unique loss. As a pediatrician himself, he knows the issue and is an articulate spokesman and defender. Indeed, in a recent magazine interview he said that one of his only unmet goals during his time in government was solving the pediatric data problem.

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

Pediatric AIDS Foundation

Hope for Children with AIDS

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Second, Congress is beginning to develop FDA "reform" bills. Without a clear Administration stance on pediatric data, other approaches will be developed--both by children's advocates and industry--and positions will be taken. This will undoubtedly complicate the Administration's ability to act administratively later.

Finally, kids need it. While a few companies have begun to respond to the universal call for pediatric data, every day a new discovery for adults is announced with no research on children. Children are left out of much biomedical progress. All sick children are "therapeutic orphans."

Whatever you can do to speed up the Administration's internal action and public announcement would be appreciated. What I fear most now is that unintentional delay will jeopardize the progress we've made. Please let me know what we can do to help.

Warm regards,

Love,
Susan

Susan DeLaurentis
Co-founder

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

THE WHITE HOUSE

WASHINGTON

January 14, 1997

Susan DeLaurentis
Chief Executive Officer and Co-founder
Pediatric AIDS Foundation
1311 Colorado Avenue
Santa Monica, CA 90404

Dear Susan:

Thank you for sending me the information and proposal for Administration action to increase children's access to safe and effective prescription drugs. I continue to be concerned that we make progress on this issue.

As you know, at the Oval Office briefing on AIDS research on December 3, the Vice President expressed his and the President's personal commitment to developing pediatric applications of prevention and treatment therapies. I have asked my staff to review your proposal with our domestic policy team, and I understand White House staff have met with representatives of the Pediatric AIDS Foundation here in Washington. Pauline Abernathy on my staff is working on this issue while Jennifer Klein is on maternity leave, and she would be glad to talk with you or your staff about it.

I also just received your invitation to attend and participate in your awards ceremony on March 4, 1997. I have forwarded a copy of your invitation to my scheduling office for consideration.

As always, thank you for the important work that you are doing.

With warm regards, I remain

Sincerely yours,

Hillary

Hillary Rodham Clinton

TO: Hillary Rodham Clinton
FROM: Pauline Abernathy
DATE: January 13, 1997
RE: Letter from Susan DeLaurentis, Pediatric AIDS Foundation

Attached for your signature is a revised response to Susan DeLaurentis, about which we spoke last week. I added an acknowledgement of the attached invitation you just received from her to attend and participate in the Pediatric AIDS Foundation's awards dinner in Washington, D.C. on March 4, 1997.

Other White House staff and I met with lawyers for the Pediatric AIDS Foundation last week to discuss their proposal and possible alternatives, and we will be holding a series of meetings this month to develop quickly recommendations for action.

You asked why the lack of pediatric safety and dosing information has attracted so much attention now. People who have followed this issue closely for some time tell me there are several contributing factors:

- The American Academy of Pediatrics has pressed this issue for decades, but never as aggressively or effectively as the AIDS community has.

- Now that we have made HIV and AIDS therapies available more quickly, making them more readily available for children is the next logical step.

- Adult success with protease inhibitors has increased the pressure for pediatric data. This is because protease inhibitors are quite toxic and therefore many doctors are reluctant to prescribe them for children without pediatric data.

- In 1994, FDA tried to address the issue but allowing pharmaceutical companies to extrapolate drug effectiveness for children from adult clinical trials, permitting them to avoid conducting two sets of expensive clinical trials. Two years later, many experts now believe that it is clear this step was not enough and that additional action is needed to induce the pharmaceutical companies to conduct the much less costly pediatric safety and dosing studies.

Pediatric Corner

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

By L. Miriam Pina, M.D.

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

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

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

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

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

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

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

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

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

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

Office of Policy
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857
Room 14-72
Phone (301) 827-3382
Fax (301) 443-5169

Date: 2/27/97

To: Pauline Abernathy

Fax Number: (202) 456-2878

From:

Ann Witt

Number of Pages (including cover sheet) 4

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NOTE TO PAULINE ABERNATHY:

Attached are two documents that you requested from Jerry Mande concerning pediatric labeling: (1) a preliminary assessment of the economic impact of a pediatric study requirement, and (2) an options paper.

Please feel free to call me at (301) 827-3385 if you need anything further.

Ann Witt

December 15, 1994
Paula Botstein M.D.

CDER Pediatric Plan [the PeP]

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

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

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

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

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

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

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

Target time: second quarter of 1995.

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

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

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

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

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

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

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

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

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

END of PLAN

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

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

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Is the "Therapeutic Orphan" About to Be Adopted?

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

BACKGROUND

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

INITIATIVES TO SOLVE THE PROBLEM

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

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

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

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

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

DEVELOPING SOLUTIONS

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

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

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

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

SOLUTIONS

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

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

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

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

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

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

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

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Tuberculosis Skin Testing: New Schools of Thought

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

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

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

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

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

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ATTENTION: PLEASE USE OPEN CAPTIONING FOR THE HEARING IMPAIRED.

In 1980, she was named deputy associate commissioner for management and operations and held that post for six years.

In her management roles, Holston has overseen the building of new laboratory facilities and the revision of FDA's ethics programs to conform to the government-wide standards issued by the Office of Government Ethics in 1992. In addition, under her leadership, the consolidation of FDA onto a single campus was brought from concept to implementation.

Holston has received numerous awards during her career at FDA, including the Presidential Rank Award for Meritorious Executives in 1992, the Commissioner's Special Citation in 1985, 1989, 1992 and 1994 and the Department of Health and Human Services Senior Management Citation in 1988.

A native of Cleveland, Ohio, Holston received a bachelor's degree from Barnard College, Columbia University, and a master of public administration from the John F. Kennedy School of Government, Harvard University.

FDA is a Public Health Service agency in HHS.

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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.

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THE WHITE HOUSE

WASHINGTON

March 18, 1997

Sheri Saltzberg, President
David C. Harvey, Executive Director
AIDS Policy Center
918 16th Street, NW Suite 201
Washington, DC 20006

Dear Ms. Saltzberg and Mr. Harvey:

Thank you for your kind words regarding the First Lady's commitment to addressing pediatric AIDS issues and her remarks at the Elizabeth Glaser Scientist Awards ceremony earlier this month. We are, indeed, committed to increasing children's access to safe and effective therapies.

In your March 10th letter, you ask about the First Lady's reference at the awards ceremony to the steps the Administration has already taken to make it easier for companies to tailor drugs for children. The First Lady was referring to the actions the Food and Drug Administration took in 1994, which are described in the enclosed press release. As the First Lady said, unfortunately, despite these steps, too many drugs still have not been tested for children or are not in a form that children can readily take. This is a serious problem that the Administration is committed to addressing.

Your letter also asks about the status of the report requested by Congress on expedited AIDS clinical trials for children and pregnant women and the status of making these drugs available to adolescents. HHS staff inform me that this report will be completed and sent to Congress very shortly.

I hope this information is helpful. Please feel free to call me if I can be of further assistance.

Sincerely,

Pauline Abernathy

Pauline Abernathy
Office of the First Lady

Enclosure

cc: Melanne Verveer
John Podesta

HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

P94-21
FOR IMMEDIATE RELEASE
Dec. 13, 1994

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

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FAX

To: Pauline Abernathy, Office of the Family Lobby

Fax: 456-6244

From: Phil Hay

AIDS Policy Center
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Please call our office for more information about the conference!

AIDS Policy Center
For Children, Youth & Families

March 10, 1997

Hillary Rodham Clinton
The White House
1600 Pennsylvania Avenue, NW
Washington, DC 20036

Dear Mrs. Clinton:

AIDS Policy Center, and the 50,000 affected children, youth and families living with HIV and AIDS that are served by Ryan White CARE Act Title IV care and research projects, were honored to be represented last week at the Elizabeth Glaser Scientist Awards ceremony sponsored by the Pediatric AIDS Foundation. Your remarks, and those of Dr. David Ho, were truly inspiring as we continue to face the many challenges of fighting AIDS in children, youth, and families. We deeply appreciate your commitment to addressing pediatric AIDS issues.

AIDS Policy Center has been very involved with issues related to the testing of new drugs and expedited approval of those drugs for children and pregnant women. The Senate Appropriations Committee requested last fall that the administration develop a report for Congress on the status of expedited AIDS clinical trials for children and pregnant women, and the status of making these drugs available to adolescents. We eagerly await the release of this report which was due to Congress on December 31, 1996 -- but has not yet been completed! Several weeks ago, AIDS Policy Center had an excellent meeting with Vice-President Gore's staff, The White House AIDS Policy Office, and representatives from FDA on this very issue.

During your speech to the Pediatric AIDS Foundation, you mentioned that the Administration has already taken steps to "tailor" the new AIDS drugs for use in children. This is exciting news and we would like to learn more about this development. We respectively request a clarification of this statement so that we may accurately inform the Title IV projects across the country about AIDS drug developments.

We encourage you to continue to address pediatric AIDS issues and invite you to partner directly with us -- AIDS Policy Center for Children, Youth & Families -- as we work to fight AIDS in children, youth, women and families. Thank you for your consideration of our request and for your dedication to AIDS issues.

Sincerely,

Sheri Saltzberg
President

David C. Harvey
Executive Director

918 Sixteenth Street, NW
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Washington, DC 20006
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THE WHITE HOUSE

Office of the Press Secretary

For Immediate Release March 5, 1997

FIRST LADY HILLARY RODHAM CLINTON
REMARKS TO THE PEDIATRIC AIDS FOUNDATION
ELIZABETH GLASER SCIENTIST AWARDS

Thank you for being here for this very important occasion.

I want to thank Suzie and Suzan, and all of you who are part of the board and staff of the Pediatric AIDS Foundation. I want to thank my friend Paul for his extraordinary grace and commitment and willingness to share his feelings and experiences with the rest of us who can only imagine what it is like for him to be worried about whether he will be able to find the drugs that Jake needs.

We are here to honor the life and the living legacy of Elizabeth Glaser. I'm so grateful that Elizabeth's work has been carried on by her devoted friends and husband. It is something that gives all of us a lot of hope because what Elizabeth did when she was with us, was constantly to inspire and provoke and ask those questions that Paul was referring to. I want to congratulate the Elizabeth Glaser Scientists. You are very fortunate to have the opportunity to receive that award, and we are very fortunate that you are using your considerable skills and the passion we heard from each of you on behalf of this cause. None of it would be possible without the generosity and commitment of the supporters of the Pediatric AIDS Foundation. Many of you are here tonight and I want to thank you. Some of you have been supporters of PAF for many many years. Some of you are new to its work, but you are making an extraordinary contribution, not only to this foundation, but through this foundation to work that will literally change and save lives. I hope that when we think of Elizabeth Glaser, we think of how she kept pushing the envelope, and pushing the rest of us. We no longer can hear her voice in person but I hear it often in my head, and any of you who have heard it as well, I hope are still listening. That voice is being heard loudly and clearly.

Over the last four years, funding for AIDS research, prevention, and care has increased by more than half. Support for AIDS research alone has increased by 42 percent to $1.5 billion and we now have a powerful Office of AIDS Research at the National Institutes of Health. Funding for the Ryan White CARE Act increased by 158 percent, while the AIDS Drug Assistance Programs, which help low-income, uninsured people with HIV and AIDS afford much-needed therapies, have grown three-fold.

Like anything else in life, when you put in considerable effort, you are more likely to see results. And we have seen results from this greater commitment. For the first time since the AIDS epidemic began in 1981, the number of AIDS deaths has dropped substantially all over the United States. The number of reported cases of mothers transmitting the AIDS virus to their babies fell by 27 percent between 1992 and 1995.

That is good news, but there is still so very much to be done. You've already seen and heard from scientists who are on the front line looking for cures, vaccines, doing all they can to understand this disease. We know that daily we are trying to strengthen our prevention and education and treatment efforts here and around the world, and it is especially important as we look at the good news that we have received from the Center for Disease Control here in the United States, not to forget that 90 percent of all AIDS cases occur in other countries, countries that are often without any resources whatsoever to treat the disease, countries where the numbers of those who are infected with HIV are continuing to increase almost geometrically. So we have a lot to do here and abroad to be sure that we are able to provide lifesaving prevention information to women and young people and other groups here in our country and all those elsewhere who are still experiencing very high rates of infection.

We also know that much of the increase in survival rates here in the United States is due to new drug therapies. And we need to make sure that all people, but particularly all children living with HIV- AIDS have access to these life-prolonging treatments. The Administration has already taken steps to make it easier for companies to tailor drugs for children. But, unfortunately, too many therapies still have not been tested on children or are not in a form that children can readily take. We cannot, children like Jake cannot wait forever to resolve this problem.. We won't wait forever. This is a serious problem, and this Administration is committed to addressing it. But it is very important that all of you who care about this Foundation and about children living with HIV and AIDS, make your voices heard.

Our continued success in the fight against AIDS will depend not only on the strength and breadth of the government's commitment to research, prevention, and treatment, but also on strong private sector leadership and support provided by such organizations as the Pediatric AIDS Foundation and the scientists we honor tonight. One of the ways that we can honor Elizabeth is to make sure that we are united in calling for the approval and testing of drugs that children with HIV and AIDS require. If we do that then we will continue to move down the road that Elizabeth started, and we have all fought.

I last saw Elizabeth at a fundraiser two months before she died. Though she was in great physical pain, she had traveled across the country to New York because she never gave up hope that the next research dollar would yield the cure she sought for her son, that the next clinical trial would yield the answer that could allow her to disband the Pediatric AIDS Foundation for good.

Elizabeth's life is a testament to the fact that hope can triumph over despair, that we can all find more meaning in our own lives by helping others. Her spirit is crying out for all of us to do that with respect to those we can reach, touch, and help. So I want to congratulate all of you for helping to bring us to this point this evening, and I hope that not only the scientists who we honor tonight and the other Elizabeth Glaser scientists who are toiling in their labs, working so hard to help defeat this disease, but everyone of us, will think about how we can make the difference in this continuing struggle. When we do so, we not only honor Elizabeth Glaser, but we honor our connection as human beings, and we give each other the greatest gift we can- that we care and that we remain committed to ensure that every person is treated with the dignity and the respect that a person deserves. Thank You.

###

A brave spirit survives, helping AIDS victims

I first met Elizabeth Glaser in the summer of 1992. She spoke to thousands of delegates at the Democratic National Convention and millions of Americans watching at home on TV. Her forceful words about the urgency of the AIDS crisis moved everyone to silence or quiet tears. Like everyone who heard her speak, I was touched by her passion, her courage and her hope.

A blood transfusion during the birth of Elizabeth's daughter, Ariel, in 1981 infected Elizabeth with the AIDS virus. Unknowingly, Elizabeth passed the virus to Ariel through her breast milk and later to her son, Jake, in the womb. Her worst fears came true when she and her husband, Paul, watched helplessly as their daughter succumbed to AIDS at age 7.

Most people would have been paralyzed by so many tragedies. But Elizabeth turned her personal battle into a fight for the life and dignity of every child and every person with AIDS. She refused to be defeated by the prejudice, fear and isolation that greet so many in her situation, but instead worked tirelessly for greater understanding and awareness. With two friends, she began the Pediatric AIDS Foundation to support and encourage research into the prevention and treatment of childhood AIDS. And as a mother hoping to save the life of her son and the lives of other mothers' children, she lobbied congressmen, presidents and presidential candidates, urging them to work harder to find a cure for AIDS.

Since Elizabeth's death in December 1994, I've thought of her often. I've thought of the brave woman with the big smile whom I had the privilege of getting to know not just as an activist but as a fellow mother and friend who was exactly my age. I will always treasure the time we spent together at her home, sipping Diet Coke and talking about our children, our lives and our concerns.

After hearing the good news last week about our progress against AIDS, Elizabeth has been on my mind more than ever. On Friday, the Centers for Disease Control announced that for the first time since the AIDS epi- [illegible] in 1981, the number stantially. Late last year, the CDC also announced that the number of reported cases of mothers transmitting HIV to their babies fell by 27 percent between 1992 and 1995.

There are many reasons for these successes, among them innovative drug therapies and aggressive treatments. Over the last four years, funding for AIDS research, prevention and care has increased by more than half. Funding for health care and other assistance to HIV/AIDS patients has more than doubled, and programs that help low-income, uninsured people with AIDS pay for treatments have grown threefold.

I know that Elizabeth would be encouraged by these efforts. But she would also be reminding us that there is still much more to do. We mustn't let up on our efforts to find a cure and a vaccine. Until we do, we need to get more lifesaving prevention information to women, African-Americans, young people and heterosexuals, groups that are still experiencing high rates of infection. And we need to strengthen our prevention and treatment efforts here and around the world, especially in developing nations, where 90 percent of AIDS cases occur.

But most immediately, we need to make sure that the life-prolonging drug therapies that have already helped so many adults here in America are made more widely available to children and others around the world who are living with HIV and AIDS. Too many of these drug treatments still have not been tested on children or made into a form that children can readily take. And they still have not been distributed worldwide. The cost of these therapies has often made it prohibitive to many families both here and in developing nations, where average citizens can barely afford the price of an aspirin.

The Pediatric AIDS Foundation is Elizabeth Glaser's living legacy. It is a testament to her will and her indomitable spirit. Her spirit lives on in the breakthroughs of the scientists who have conducted and will conduct research in her name. Most importantly, it lives on in every child with HIV or AIDS who is enjoying a happy and healthy childhood today be-

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.

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; Jonca Bull, M.D., Division of Anti-Inflammatory, Analgesic and Ophthalmologic Drug Products; Cazimiro Martin, Division of Over the Counter Drug Products; Frank Rosa, recently retired from the Division of Pharmacovigilance and Epidemiology; and Charles Maynard, Division of Pharmacovigilance and Epidemiology. The December *Pike* lists representatives from each of the Center's review divisions who can assist you with Pediatric Rule issues. The working group plans on publishing in-patient data in a future issue.

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

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

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

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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
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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-

ATTENTION: PLEASE USE OPEN CAPTIONING FOR THE HEARING IMPAIRED.

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.

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

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Mostly Out of Reach

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

*Protease inhibitors

Sources: Pediatric AIDS Foundation; Food and Drug Administration

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

Continued From Page B1

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

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

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

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

12/96
From Pediatric AIDS Foundation

PROPOSED ACTION PLAN

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

- The Executive Order would:

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

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

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

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

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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.

12/96
Pediatric AIDS Foundation

PEDIATRIC STUDIES IN PHARMACEUTICALS URGENTLY NEEDED

THE PROBLEM

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

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

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

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

The problem seems to be getting worse.

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

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

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

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

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

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

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

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

THE PROPOSAL

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

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

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

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

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

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

EXPECTED RESPONSE

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

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

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

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

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

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

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

Press interest will be high.

DRAFT

OPTIONS FOR ADDRESSING LACK OF PEDIATRIC LABELING

1. **Require manufacturers of all drugs and biological products to conduct pediatric studies**

PRO:
- Would provide maximum gain in pediatric labeling

CONS:
- Very costly (would cover over 150 products per year)
- Would sweep in many drugs that are rarely used in children or that provide little therapeutic benefit
- Inefficient use of FDA resources needed to review studies
- Strong opposition from pharmaceutical industry on grounds of cost, liability concerns, impracticality of conducting studies in children, and slow-down in FDA review of new products

2. **Require manufacturers of innovative drugs that are therapeutically significant or widely used in children to conduct pediatric studies**

PROS:
- Would provide substantial gain in pediatric labeling for products of greatest significance to children
- Far less costly than option #1 to both industry and FDA resources (would cover about 5-10 products per year)
- Support from pediatric community

CONS:
- Opposition from pharmaceutical industry
- For a small number of products, cost of studies may outweigh return to company

3. **Provide financial incentives to industry to perform pediatric studies in the form of monopoly rights (patent extensions or statutory protection from generic competition)**

PROS:
- Support of pharmaceutical industry

- Depending on language of statute, could provide substantial gain in pediatric labeling
- Would ensure that companies recoup costs of pediatric studies

CONS:
- Would require new legislation
- Legislation supported by industry in last session would have provided monopoly rights for conducting pediatric studies regardless of whether study resulted in improved labeling information
- Exclusion of competition means significantly higher drug costs to consumers and to government

4. **Comprehensive approach, including required studies, financial incentives, other support from the Department of Health and Human Services, e.g., financial or other support for pediatric studies**

PROS:
- Would provide substantial gains in pediatric labeling
- Likely to bring broader support than options 1-3

CONS:
- Much of approach beyond FDA's authority
- Would require new legislation to provide financial incentives
- Higher cost to government and consumers than option 2

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.

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; Jonca 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%, ›etamethasone 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 ›dium).	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%)
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italin 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%)
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HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration
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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-

ATTENTION: PLEASE USE OPEN CAPTIONING FOR THE HEARING IMPAIRED.

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.

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

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

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

How did this happen?

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

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

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

Please Turn to Page B9, Column 1

Mostly Out of Reach

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

*Protease inhibitors

Sources: Pediatric AIDS Foundation; Food and Drug Administration

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

Continued From Page B1

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

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

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

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

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

Tim [Lunch w/ Waxman
Pediatric AIDS
Trusted Friends

Westmoreland –
FDA – pediatric
drugs
Cos. required to test

PHOTOCOPY
HRC HANDWRITING

TO: Hillary Rodham Clinton
FROM: Pauline Abernathy
DATE: December 30, 1996
RE: Letter from Susan DeLaurentis, Pediatric AIDS Foundation

Attached are a letter and packet of materials from the Susan DeLaurentis of the Pediatric AIDS Foundation and a draft interim response from you. Also attached is Susan's Christmas card to you in case you want to add a note about it.

Her letter recommends that the Administration issue an executive order directing the FDA to require drug companies to submit pediatric safety data, and if appropriate pediatric efficacy data, for drugs for which children are foreseeable users. I have sent copies of their proposal to the appropriate staff in the Vice President's office and at the DPC for further discussion when people return after the holidays.

The public-private collaborative on HIV research continues to work on this issue, and the FDA has been informally pushing pharmaceutical companies to submit pediatric data with certain new drug applications.

I will keep you apprised.

cc: Melanne Verveer

Pauline,

Before I send this letter,
Can you explain to me what
the problems are with changing
the regulations as Susan suggests.
Please call me. Thanks,
love

THE WHITE HOUSE

WASHINGTON

January 6, 1997

Susan DeLaurentis
Chief Executive Officer and Co-founder
Pediatric AIDS Foundation
1311 Colorado Avenue
Santa Monica, CA 90404

PHOTOCOPY
HRC HANDWRITING

Dear Susan:

Thank you for sending me the information and proposal for Administration action to increase children's access to safe and effective prescription drugs. I continue to be concerned that we make progress on this issue.

As you know, at the Oval Office briefing on AIDS research on December 3, the Vice President expressed his and the President's personal commitment to developing pediatric applications of prevention and treatment therapies. I understand the public-private Forum for Collaborative HIV Research continues to work on this issue and to look at additional steps to increase the number of anti-HIV therapies with pediatric indications.

I have asked my staff to review your proposal with our domestic policy team. Pauline Abernathy on my staff is working on this issue while Jennifer Klein is on maternity leave, and she would be glad to talk with you or Tim Westmoreland.

As always, thank you for the important work that you are doing.

With warm regards, I remain

Sincerely yours,

Hillary

Hillary Rodham Clinton

UARY 9, 1997

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First Protease Inhibitor Drug Designed For HIV-Infected Children Is Due Soon

By RHONDA L. RUNDLE
Staff Reporter of THE WALL STREET JOURNAL

The first protease inhibitor drug designed especially for HIV-infected children is becoming available through a government-approved giveaway program that drug maker **Agouron Pharmaceuticals** Inc. will announce today.

The drug, Viracept, is a member of the protease inhibitor family that, when used in combination with some older drugs, has made the AIDS virus undetectable in the blood of some adults. Small preliminary studies among children under the age of 13 suggest that Viracept has comparable benefits in youngsters, Agouron said.

Pediatricians and parents of infected children are increasingly frustrated that protease inhibitors have been available to only a handful of children enrolled in clinical trials, despite the inhibitors' proven powers. Critics have accused drug makers of being slow to act because children make up only a small proportion of infected individuals.

Some Pediatricians Reluctant

Viracept is awaiting approval by the U.S. Food and Drug Administration following Agouron's request last month to market the drug both as a tablet for adults and a pediatric powder for children. Protease inhibitors made by three other companies are being sold now, but none is approved for pediatric use. Agouron, based in San Diego, is the first company to seek approval for a pediatric formulation of a protease inhibitor.

Under FDA rules, protease inhibitors already approved for adults can be prescribed for children, but some pediatricians have been reluctant to use them without scientific studies into such issues as the proper dosage.

People in an advanced stage of AIDS who have exhausted treatments with the approved protease inhibitors have been receiving Viracept since September under an "expanded access" program. Now Agouron plans to also give the drug free of charge to infected children aged two to 13. Both programs will end as soon as the drug is approved for sale, but Agouron says patients in the program won't be cut off if they don't have insurance or funds to pay for the drug.

There were about 7,300 children under age 13 with AIDS in the U.S. as of June 1996, according to the U.S. Centers for Disease Control. There are as many as 20,000 HIV-infected children nationwide, according to the Pediatric AIDS Foundation in Santa Monica, Calif.

The giveaway program is "great news" because "I have a waiting list," said Andrew Wiznia, director of the pediatric HIV program at Bronx Lebanon Hospital in New York. Dr. Wiznia has treated 12 children with Viracept during the past three months. "This is a real good drug, it may be a great drug, we don't know. It seems to be well tolerated by children taking it," and "only occasionally do kids say 'yukky,' " he said.

Parents with children in the study were "ecstatic," Dr. Wiznia said. "We've had parents come in and say it was like a lightbulb went on in the child. Within one or two weeks of starting therapy, some children are showing dramatic changes, going from apathetic to interactive."

However, clinical data on such critical measures as virus levels in the blood of treated children haven't been disclosed yet. Agouron says that virus-level drops have been equivalent to those in adults, but data on the 52 children treated to date won't be available until later this month.

Child Gains Weight

One mother said her six-year-old daughter has gained three or four pounds and is more active since starting Viracept treatment in September. "Raven eats a tremendous amount of food now and her energy level has improved a lot," said her mother, Michelle Lopez. The girl has switched to Viracept tablets, cut in two for easier swallowing, because she didn't like the taste of the powder.

The pediatric formulation of Viracept is a sandy, white powder that can be scooped out of the bottle and mixed with milk, formula or soft foods such as pudding. Agouron said parents and doctors seeking information about the giveaway program can call 1-800-621-7111.

Some other drug makers have had trouble formulating their protease inhibitors into effective medications that children can take. **Abbott Laboratories**, whose Norvir drug was approved for adult use last March, appears to be ahead of the other two companies with protease inhibitors on the market, **Merck & Co.** and **Roche Holding**. Abbott said it expects to soon amend its label for Norvir to include children.

Apple Plans PC Using Systems From Mac, Nex

By LEE GOMES
Staff Reporter of THE WALL STREET JOUR

Apple Computer Inc. sought to reass customers and software developers t the company has no plans to jettison current operating system as it moves ward a new system based on its re **Next Software** Inc. acquisition.

At a Macintosh trade show in Francisco yesterday, Apple said that the next several years it plans to purs "dual operating system" strategy that offer machines with both its existing M intosh operating system and its new N based system. Company officials would be more specific about how long the d system offer will continue.

Meanwhile, Apple's stock plumm as investors reacted to Apple's annou ment Friday that the company will pos operating loss as wide as $150 million the fiscal first quarter ended Dec. 27 Nasdaq Stock Market trading yester Apple shares fell $3.875, or 18%, to $17. near its 52-week low of $16.

Pall Cast Over Trade Show

Apple officials have blamed the lar than-expected quarterly loss on weak sales of its Performa home compu during the holiday season. Apple also hinted that more layoffs are likely, rai questions about whether the Cuper Calif., company has turned the corne its turnaround effort. Apple's PC s continue to suffer from competition f **Microsoft** Corp. and **Intel** Corp. Whe reports its first-quarter results later month, Apple will have posted more $900 million in red ink over five quarte $11.8 billion in sales.

Last week's surprise announcer cast a pall on the annual MacWorld t show, which is so large a gathering of fans that it regularly ties up traffic a San Francisco. Nonetheless, Apple cials used the gathering to fill in son the technical details of how they pla using the software from Next, w Apple purchased last month for ar $400 million, as the basis for a new M tosh operating system

Ellen Hancock, Apple's chief tec ogy officer, said the new operating tem – code named "Rhapsody" – wil some pieces of Next's system and o developed in-house. She told a grou Apple customers that while many exi Mac programs will run on the new op ing system, software developers wr new programs for Rhapsody will ne use different techniques and tools they do with the current Macintosh.

Even when it begins selling mac with the new operating system, Appl continue to make available its cu operating system, known as System 7 Hancock said. System 7 should re available for several years, she said.

Industry analysts said Apple's strategy is designed to make sure company doesn't lose customers or

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CUS FUNDS

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By Rhonda L. Rundle
Staff Reporter of The Wall Street Journal

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THE WHITE HOUSE
OFFICE OF THE VICE PRESIDENT

FOR IMMEDIATE RELEASE CONTACT: 202-456-7035
WEDNESDAY, February 21, 1996

Vice President Gore Says Meeting With Pharmaceutical Firms, AIDS Researchers, An Important Step in Fight Against Disease

WASHINGTON -- Highlighting his and President Clinton's commitment to AIDS drug development, Vice President Gore met Tuesday (2/20) with pharmaceutical company representatives and leading government researchers. He said the private and public sectors should accelerate their joint effort to find and develop as quickly as possible AIDS vaccines, therapeutics, and microbicides.

Attending the meeting were representatives of 11 pharmaceutical companies and leading AIDS researchers and officials from the National Institutes of Health, the Department of Defense, and the Food and Drug Administration. They discussed ways to accelerate the development of AIDS vaccines, therapeutics, and microbicides.

"This meeting was an important step in strengthening the government-industry partnership that is essential to finding and developing effective treatments -- and ultimately a cure -- for AIDS," Vice President Gore said. "We are committed to marshalling our best minds and resources in the fight against AIDS."

At the December 6, 1995, White House Conference on HIV and AIDS, President Clinton asked Vice President Gore to convene this meeting to "identify all the ways in which we might accelerate the development of vaccines, therapeutics, and microbicides that can protect people from HIV and the infections it causes." The meeting reflects President Clinton's commitment to bring the AIDS epidemic to an end.

In his three years in office, President Clinton has increased funding for AIDS research by 26 percent, expedited AIDS drug approval, and strengthened the Office of AIDS Research at the National Institutes of Health.

At the conclusion of the two-hour meeting, Vice President Gore announced the following steps:

The Administration will join with pharmaceutical manufacturers, health insurance companies and other third-party payers, and patient advocacy organizations to develop

a collaborative system of clinical trials of AIDS drugs that have been approved by the FDA under expedited procedures to determine the best uses and the long-term effectiveness of those drugs.

The Administration will work with international organizations -- such as the World Bank -- to increase investment in AIDS vaccine development and trials worldwide.

The Administration will help facilitate the development of microbicides to enable women to protect themselves from HIV infection.

The Vice President will facilitate ongoing discussions between the government and the pharmaceutical industry to identify promising areas of AIDS research that the government can support in order to stimulate private sector investment in the next generation of AIDS vaccines, therapeutics, and microbicides.

The Food and Drug Administration will pursue additional measures to increase the number of anti-HIV therapeutics with pediatric indications.

Participants in Vice President Gore's Meeting
with Pharmaceutical Companies and AIDS Researchers
2/20/96

The following pharmaceutical company representatives participated in the February 20 meeting on AIDS drug development with Vice President Gore:

Anne-Marie Corrier
President, Chief Executive Officer
BIOSYN

Manuel Navia, PhD
Vice President, Senior Scientist
Vertex Pharmaceuticals Inc.

Michael Riordan
President, Chairman
Gilead Sciences

Joseph Pittelli
Senior Vice President for Clinical Research
Wyeth-Ayerst Research

George Morrow
Group Vice President, Commercial Operations
Glaxo Wellcome, Inc.

Dan Hoth
Senior Vice President, Chief Operating Officer

Cell Genesys, Inc.

Peter Johnson
President, Chief Executive Officer
Agouron Pharmaceuticals, Inc.

Patrick Zenner
President, Chief Executive Officer
Hoffman-La Roche

Rajen Dalal
Vice President for Corporate Planning and Business Development
Chiron Corporation

David Pizzuti
Vice President for Anti-Infective Development and Medical Affairs
Abbott Laboratories

Eve Slater
Senior Vice President for Clinical and Regulatory Development
Merck

##

To Pauline Abernathy
From Tim Westmoreland
Re: Pediatric Drugs
January 7, 1997

I hope that Jennifer Klein has told you that I will be contacting you. If not, this note will seem a little odd.

For almost two years now, I have been working with the Pediatric AIDS Foundation (PAF, the group founded by the late Elizabeth Glaser, now headed by Susan DeLaurentis) to try to improve the pediatric research on pharmaceuticals. In this case, we are talking about all drugs, not just AIDS drugs (since FDA estimates that 80% of all drugs now on the market have no pediatric data), although AIDS drugs are a particular problem that is particularly visible.

In addition to a nearly (but not quite) successful legislative initiative with Senator Kassebaum and Congressman Greenwood last session, we have been working with FDA to see if there is some regulatory action that might be taken to correct the problem. While initially skeptical that there was much they could do except use the bullypulpit with the industry, they now have become very supportive. I think that you will find that David Kessler, Bill Schultz (his deputy), and their lawyers are interested.

It is also my understanding that friends of the PAF have met with Mrs. Clinton personally about this topic and that she expressed interest.

In very brief (if you'd like, I'll send you the background memo on this), we have argued that the Food, Drug and Cosmetic Act does not allow the Commissioner to approve a drug without pediatric data. The Act says "safe and effective," not "safe and effective for adults only." Supporting this argument, the legislative history is replete with references to kids. There are other arguments (about labeling and misbranding drugs that kids will use).

I am writing now because I understand that there is to be a meeting tomorrow (Wednesday) with Greg Simon, et. al., and a group called the AIDS Policy Center for Children, Youth, and Families, represented by David Harvey. I am concerned that the work we have done with the FDA and the White House not be discussed at this meeting. I would caution you that, good cause that he represents, David sometimes discusses issues with others after meetings that should best be kept for another day. I would hate for the pharmaceutical industry types to hear about this before the FDA or the White House is prepared to act.

Toby Donnenfield (sp?) has invited the Pediatric AIDS Foundation to attend this meeting also, although I am in London until the end of the month. Others could certainly attend in my place, but I am inclined to agree with Toby's suggestion that this meeting proceed and that we plan a second one.

I am writing now to ask your help. If you attend this meeting tomorrow, will you try to ensure that the PAF proposals are not discussed as such and that nothing gets to the industry people? I have sent a message to Chris Jennings as well, although he will not be attending.

In addition, I hope I can call on your assistance when I return. If you need anything from me, including background materials, please let me know. You can also call my office (at Georgetown Law School) and ask for my teaching assistant, Sharon Perley, who knows this issue and its politics inside and

out (202-662-9595). You can also call me if you'd like (011-44-171-235-8932).

Thanks for your time and assistance.

Sincerely,

Tim Westmoreland

12/20

THE WHITE HOUSE

WASHINGTON

Jane Sandville – AIDS

- yes for it but not at expense of holding back for adults
- FDA pushing pediatric AIDS indications
- advisory council
- no stick still
- "safety dosing": hard to find kids + expensive
- ethical concerns w/ parents having kids tested before approved
- formulation – liquid + flavor
- World AIDS day statement

12-20

THE WHITE HOUSE
WASHINGTON

Greg Simon —
Collaborative effort
public - private
→ trials
→ pediatric AIDS
meeting w/ VP.
→ moving forward
→ public - private
looking at it -

Melanne Verveer

Meale – we need to help as we can

Call Patsy Phil Lee / Bill Lowe

Hope for Children with AIDS

Dear Melanne,

Enclosed are copies of materials I sent to the First Lady today. I wanted you to be aware of them, too.

Hope you are doing well –

Love,
Susan DeLaurentis

Pediatric AIDS Foundation
1311 Colorado Avenue, Santa Monica, California 90404
310-395-9051 Fax 310-395-5149

Write Interim Response

[Jane Saneville
non-political]

→ Dec 3 → brief

→ Public Remarks
Transcript

→ Asked VP. to look
into — Toby.

working VP office

- write memo to flotus
- send w/ draft respons.
  JE + PA ~~to~~ work ~~w/ VPs.~~ [illegible]
  I have asked ~~office~~ others
- send Greg + Toby
  attachments

Pediatric AIDS Foundation

Hope for Children with AIDS

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December 12, 1996

First Lady Hillary Rodham Clinton
c/o Pam Cicepti
The White House
Washington, D.C. 20500

Dear Hillary,

There's an issue we have been working on for some time and I want to ask for your help.

As we have tried to get HIV drugs to children, we were astonished to learn that 80% of all pharmaceuticals now on the market have not been tested for safety and effectiveness in children. The Food, Drug, and Cosmetic Act requires that drugs be "safe and effective," not "safe and effective for adults only."

We believe the best way to resolve this is to have the President issue an Executive Order directing the FDA to require that drugs that can be used for children be proven safe and effective for them before they are approved for adults.

We have had contact with Hill leadership and have made some forays into the White House to get reaction to this idea. It would have been wonderful to make this a holiday gift to all of America's children, but it seems that time is running out. Most important is that it happen as soon as possible.

Would you consider interceding on our behalf to make this happen? There is a sense of urgency to accomplish this before David Kessler leaves the FDA. We have been discussing this with Dr. Kessler and the lawyers at the FDA and feel you will find them supportive. We have also been in discussions for over a year with Jennifer Klein who has been supportive as well. I am including memos we have prepared with background information and a proposed action plan.

There has been a great deal of momentum building in support of this including a recent Wall Street Journal article. The FDA has been encouraging drug companies to provide pediatric data but it just won't save lives until the regulations are changed to require it.

Thank you for your help.

Warmest regards,

Susan DeLaurentis
Co-founder

CO-FOUNDERS: Susan DeLaurentis, Elizabeth Glaser, Susan Zeegen
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THE WHITE HOUSE

Office of the Press Secretary

For Immediate Release December 3, 1996

REMARKS BY THE PRESIDENT
AT BEGINNING OF BRIEFING ON AIDS RESEARCH

The Oval Office

11:45 A.M. EST

THE PRESIDENT: This is World Aids Awareness Week -- and you also know I'm a little hoarse. I'm very excited about the progress we've made in the last four years. I'm determined to keep pressing until we have a vaccine and ultimately a cure.

And I'd like to ask the Vice President to sort of take over for me with the opening remarks, and then we'll hear from Secretary Shalala. We have some of our nation's top health officials, our top public health officials here. I thank them for coming, for their work, and I'd like to ask the Vice President to speak.

VICE PRESIDENT GORE: Thank you very much, Mr. President.

As you can tell, the President needs to conserve his vocal cords a little bit. He's had quite a lot to say about this topic of AIDS over the last four years, especially internally with this tremendous team that Secretary Shalala has pulled together and led on the President's behalf. And this is one of several briefings that the President has had periodically on the progress our country is making against HIV/AIDS.

And the experts here will provide some statistics to back these assertions, but let me just briefly, on behalf of the President, note that this administration has presided over a 40 percent increase in NIH-supported AIDS research, a 158 percent increase in Ryan White AIDS Treatment grants, a 24 percent increase in CDC-HIV prevention activities, a 96 percent increase for HUD's housing opportunities for people with AIDS program. He has greatly strengthened the office of AIDS research at NIH and, as a result of public health service guidelines recommending the use of AZT by HIV-positive pregnant women and their newborns, there has been a very encouraging 17 percent drop in the number of infants with perinatally

acquired HIV infections -- those are the last statistics available from '94 to '95 -- also responding rapidly to FDA approval of a new class of AIDS therapies called protease inhibitors, with increases in funding for state AIDS drug assistance programs.

We have eased Social Security disability rules to speed approval of eligibility. And, of course, the President created the Office of National AIDS Policy at the White House and the Presidential Advisory Council on HIV/AIDS.

Last year, at the White House Conference on HIV and AIDS, the President asked me to preside over an effort to look for ways to overcome obstacles in developing new therapeutics, vaccines,

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and microbacides to combat HIV and AIDS. And we have achieved a great deal since last year. Working with this team here today, we convene meetings that led to the establishment of the Forum for Collaborative HIV Research. And I'm proud that the participants in this forum -- AIDS clinicians, researchers, drug companies, insurance

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companies, and patient advocacy groups -- have all expressed their belief that this has become an unprecedented and productive forum for discussing the future of HIV research.

These new scientific advancements in HIV and AIDS treatment -- optimism and hope in the AIDS community for people with AIDS and their families. So this is a very positive report this year. And many our now feeling that there is cause for more optimism in the near future.

Through collaborative efforts like this new forum, and the cooperative efforts of the government and private sector researchers, we'll continue the fight for better and more affordable prevention strategies, vaccines, and microbacides. We will not forget the children. The President is personally committed to focusing this research effort on the crying need to develop pediatric applications of these prevention and treatment strategies and products. And we've all talked a great deal about how to do that.

Working with our team assembled here and with our partners in research, we will continue to knock down every barrier to the development of successful therapeutics, vaccines, and microbacides until we knock down the last barrier of all -- the HIV virus itself.

Now, on behalf of the President, I want to turn this over to Secretary Donna Shalala to expand on the administration's efforts to defeat this terrible disease.

SECRETARY SHALALA: Thank you very much, Mr. Vice President.

Mr. President, before I start I'd like to present you with this card. It's actually a thank-you card from the leaders of public health in the United States. It was presented to me yesterday, and it says: Dear Mr. President, essentially, thank you, thank you, thank you for everything that you have been able to do. And they all signed it. It's in honor of World AIDS Day, which, of course, was yesterday.

Thank you. Let me begin by first thanking Patsy Fleming. I know she's announced that she is not going to continue with us for the second term, and she has done a tremendous job for you and for the American people.

THE PRESIDENT: She sure has.

SECRETARY SHALALA: She has actually been our coach. I think all of us would say that Patsy has coached us. She has spent her career on the AIDS issue, and she spent a lot of time coaching us to make sure that we had a very focused strategy for this administration.

The Vice President has outlined some of the successes in

the increase in funds for AIDS. I'd actually like to start with a chart back there, but I'm not sure I'm going to get to it.

Q Mr, President, can you tell us how you feel about James Carville's effort to mount an offensive on your behalf?

THE PRESIDENT: I can't comment.

Q You're not going to talk to him about it?

Q How's the Cabinet going?

Q Any decisions, sir?

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