Elizabeth Drye - DPC **Box #4**

Folders

FDA Issues

Pediatric Uses
Ephedrine
Other Pharmaceutical Concerns
Home Drug Test Kits
FDA Legislation
POTUS Remarks - Cancer Event
FDA Reform - Medical Devices
Kessler Memo
FDA Reform 1996
FDA Reform - Bills
FDA Reform '97
FDA Clippings (attack of)
FDA Budget
Daschle Access Bill
FDA - Military Waiver

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Sharon Pearley
662-9684

- These talking points version of bill, are on different ~~background~~ but may be useful as background.

The Better Pharmaceuticals for Children Act
(as re-drafted for the Pediatric AIDS Foundation)
offers an additional *6 months of market exclusivity*
to encourage *clinical pediatric studies* or
(in two years) assesses a *pediatric research fee*
to allow NIH to conduct such studies

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Without data, doctors must make decisions on drug treatment for infants and young children based on clinical tests of *adults*.

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Drugs that are safe for adults may cause serious *side-effects in infants and young children*. Dosages and the means of administration which are safe and effective for adults may *not* be safe and effective for children.

Important new drugs are not being tested on infants and young children.

For example in AIDS, the new protease inhibitors, which have been shown to suppress the HIV virus in clinical trials, are being approved with little if any pediatric data.

The absence of pediatric clinical data leaves infants and young children *without a potentially effective* treatment for HIV/AIDS.

Moreover, a delay in pediatric data stymies efforts to reduce HIV/AIDS transmission from mother to fetus through drug treatment.

While AZT during pregnancy reduces the transmission rate by two-thirds (from 25% to 8%), it is not perfect. Many infants might be born infected before trials are conducted on pregnant women to determine if new drugs, like protease inhibitors, could reduce or eliminate transmission of HIV to a fetus.

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Under the Better Pharmaceuticals for Children Act, drug sponsors would get *an additional six months* of market exclusivity for a drug for a serious or life-threatening condition if a manufacturer tests the drug on infants and young children.

The market exclusivity provided by the Better Pharmaceuticals for Children Act will compensate companies for the additional costs of pediatric clinical trials.

Beginning two years from enactment, the bill would also raise pediatric research fees from companies that do not test drugs that are to treat serious or life-threatening conditions in infants and young children.

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E X E C U T I V E O F F I C E O F T H E P R E S I D E N T

29-May-1996 01:59pm

TO: (See Below)

FROM: Elizabeth E. Drye
Domestic Policy Council

SUBJECT: FDA REFORM -- Pediatric studies provision

NEC and the Patent Office are both o.k. with the provision in Sen. Kassebaum's bill that provides an additional 6 months of market exclustivity for drugs for which the Secretary requests -- and the manufacturer completes -- pediatric studies. NEC and the Patent Office agree with us that the provision is not well targeted -- the value of the patent extention may be excessive in some cases. But the Patent Office (Bob Stoll) assured me the provision "does not do violence to the patent system." Further, NEC and Patent Office agreed we do not want FDA to decide on length of patent extension on a case by case basis.

FDA has suggested, and we should support, narrowing the provision so that only drugs with significant pediatric benefits are eligible. I believe the provision's proponents, including the Pediatric AIDS Foundation, would support that.

Given NEC/Patent Office views, FDA/HHS are planning to express the Administation's support for the provision to Senate staff while recommending language to better target the provision as noted above. FDA/HHS will also oppose lengthening the patent extension as some in industry are proposing. Let me know if you have problems with this approach.

At some point we may want to more visibly support the provision, given the VP's commitment to increase pediatric testing for AIDS drugs.

Distribution:

TO: Sally Katzen
TO: Nancy-Ann E. Min
TO: Christopher C. Jennings
TO: Gregory C. Simon
TO: Ira C. Magaziner
TO: Jonathan Winer
TO: Jim R. Esquea
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FAX COVER MEMORANDUM

DATE: 5/13/96

NUMBER OF PAGES, INCLUDING THIS SHEET: 5

TO: Elizabeth Drye

FAX NUMBER: 456-7078

FROM: Tim Westmoreland (via Scott Foster)

COMMENT:

To Elizabeth
From Tim
Re: Pediatric Drugs
May 10, 1996

Attached are the talking points and summary that I have given out on the re-draft that we would propose for the Kassebaum provisions. Please note that neither House nor Senate has yet agreed to these revisions, and that I'm hoping to do a new draft very soon.

Thanks. Call if you need more.

TMW

To Interested Parties
From Tim Westmoreland
Re: Summary of April 9 Draft
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After consultation with public and private experts and solicitation of suggestions, the Secretary is to publish a list of drugs for which pediatric studies are needed.

The Secretary is to request manufacturers to conduct such studies.

If a manufacturer completes these pediatric trials within a year of receiving the request, it receives six months of extended market

exclusivity beyond whatever protections it would normally enjoy.

FDA Reform Provisions Re: Pediatric Studies for New Drug Applications

Background:

For about 80% of drugs, companies have not done studies to assess pharmicokinetics/dosing, safety, or efficacy of pediatric uses. Yet about 80% of drugs are used in kids. FDA does not require manufacturers to do pediatric studies unless the manufacturer is seeking to put pediatric uses on the label. The American Academy of Pediatricians and the Pediatric AIDS Foundation, among other organizations, believe increasing pediatric studies will increase safety, efficacy and availability of drugs for children. FDA is sympathetic. At a meeting he had with FDA and pharmaceutical companies regarding AIDS drugs, the Vice President asked FDA to address this problem. The First Lady has met with the Pediatric AIDS Foundation about the issue and is sympathetic.

Kassebaum Provision:

- To provide a financial incentive for industry to conduct pediatric studies on drugs that benefit children, the bill extends by 6 months the period of market exclusivity for a drug if:
  - (1) the Secretary makes a written request for pediatric studies and
  - (2) the applicant conducts requested studies.
- Required studies can simply be pharmicokinetic studies, but may be clinical trials.

Discussion:

The key issue is how to set the period of exclusivity.

A fixed 6-month extension of exclusivity may be provide a far too generous incentive for pediatric studies, and may unnecessarily drive up drug prices. Based on an OTA study, the value of this exclusion for a successful drug is estimated at $50 million. In contrast, the required clinical studies are expected to cost 750,000 - 1,000,000 per drug.

FDA has suggested as an alternative that the period of exclusivity be "proportional" to the cost of the studies. The Secretary would determine the appropriate exclusivity period. This approach is administratively more complex, and would likely be unacceptable to drug companies, who are pushing for a longer patent extension (1-2 years).

Mary Pendergast

Little information

Rules – had to do 2 more trials for ped use on label

– FDA charged rule – Do pharmikokinetics
– did that in rulemaking
– Fall of 94 (OMB reviewed)

– Focus attn. of companies on
– know that when you come in for end of phase II, phase III.
– Asked every Co. to submit info they have on kids – to see if there's enough information – Rulemaking
– Tell FDA what they know about
– Must submit by end of year

Economic Incentive –

–Mechanics–

–New drugs –

Drug's ~~use~~ approved for a specific use –
– whole
– common for drugs to come out around the same time

Dard's concerns
① Shouldn't be for unimportant use –
– get market exclusivity
② exclusivity period is very valuable –

Efforts – Marion tasked – headed bureau of drugs at FDA – for many drugs used in kids – no incentive to do studies.

Goal is to get studies before drug goes on market.
Maj means clinical trials —

- If you wanted to get drugs tested for kids — original motivation —
- Why we have to build in somebody asking for it; reserving what they can do. —

Hard to draw line at how serious disease is —
Could draw the line on "significant benefit" —

Existing — key feature — reserving decision that they're needed; [redacted] some pushing to expand it further.
-6 months
3-6 months — option —
CO.'s will object to reporting on costs

Re new uses. — Jim working on substitute to take to Jane Williams — would apply to new drug ---

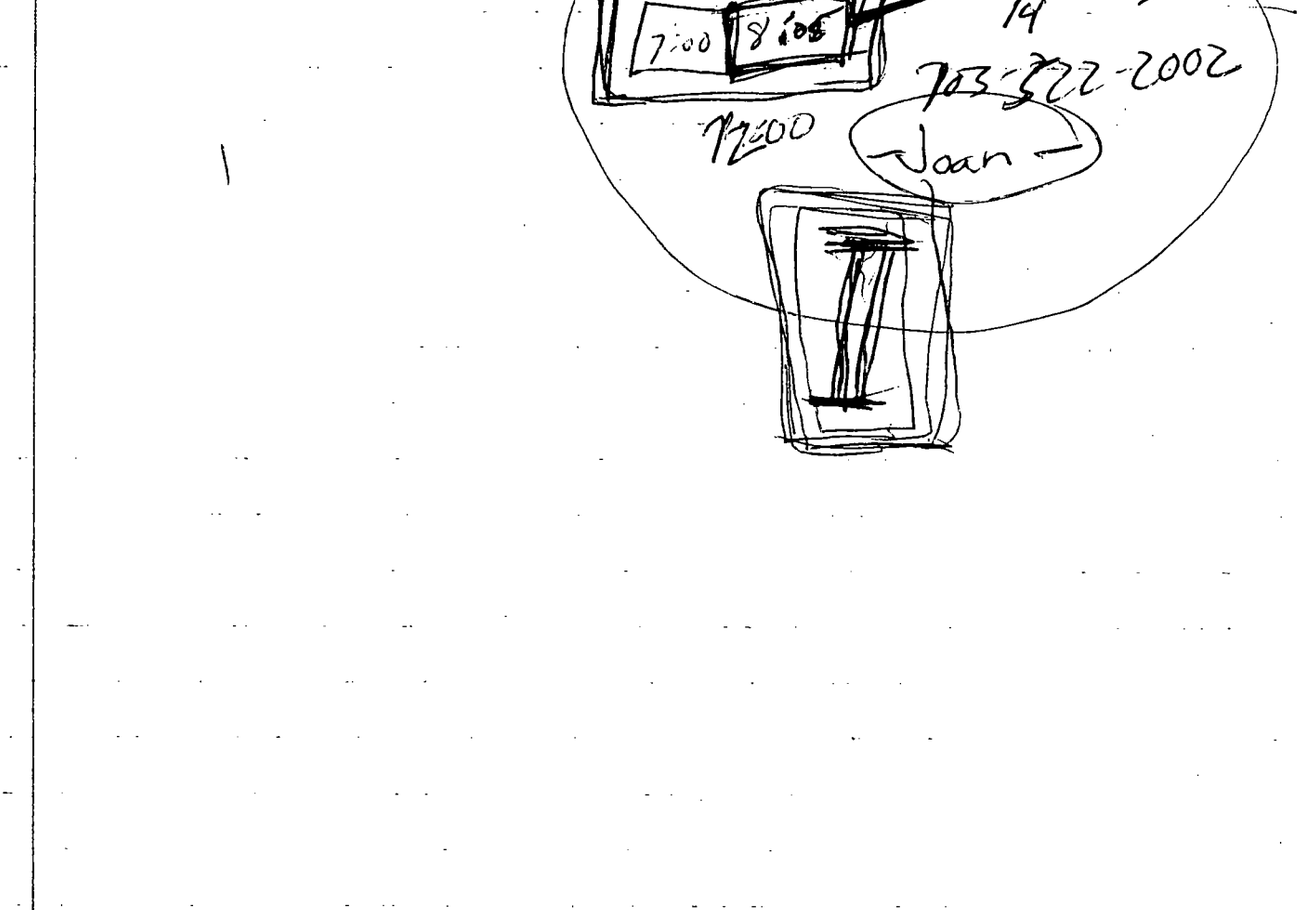
Orphan Drug Act — If you have drug for rare disease — can seek O.D. designation as early as filing of NDA,
or ~~early~~ IND

Jim — For ~~future~~ New — have to seek designation like ruling from FDA —

On Market — win two years

generic drug law — certifies to FDA —
when patent approval expires — FDA makes approval on that day —
— current exclusivity

Core mtg w/ pharm co.'s
- Develop more pediatric indication — one of the 5 uses.
- 6 months — David comfortable.
- Dingell / Kennedy / Waxman —



Jennifer Klein — Foundation
Mrs. Clinton — met w/her

- Pediatric AIDS Foundation wants provision like this

- Bill Corr/Bill Schultz — Kessler —

- 80% of all drugs have no pediatric indications —
- not approved for use in children —

- took 2 years to get pediatric approval on AZT
- none of companies developed meds on protease inhibitors —

- AZT ↓ prenatal transmission to 8%

- protease inhibitors
  - can't use in kids
  - can't use to prevent perinatal } w/out good safety issues
  - ↓ safety, dosing, metabolism —

- SAFETY ISSUE —

Examples — perfectly safe in drugs —

Foundation is so upset because NO one bothered to do trials on kids / preg women — (care risks, e.g. of liver damage). —

- 3-4 years. —
  FDA said they had to do the studies as a condition of approval (phase IV studies)

Preference — FDA says companies have to do peds studies —

- 6 months — less
Trying to get Peds / Induction apps on the same side

- Legislative history - FDCA -
  - everything has prompted by Pediatric legislative disaster

Companies - does they don't want ~~to do them~~

- safety/pharmiko kinetic data is sufficient to get approval. -

Peds. grps asking for ~~less~~
750,000 - 1,000,000

OTA studies exclusivity extension -

- Year of exclusivity estimated to be 100,000,000 yr for successful

$9,000,000

Am Academy Peds
Children's Hospitals
Sm. Children's cancer grps.
Pediatrics AIDS Foundation

MERCK, GLAXO-WELLCOM - BRYSTOL-MYERS, PHARMA, - all of them have technical changes - push to -
Sandos - will defer 6 months.
Has agreed to modify to require more specific - data

but haven't said willingness
Greenwood - interest - to introduce -

(Foundation still opposes general FDA reform bill - both house and senate - AAPeds - concerned w/ off label use).

Opposed - Generic manufacturers - they may swallow it - it swallows

- 7 years period of exclusivity -

Draft: **Better Pharmaceuticals for Children Act**

(April 11, 1996)

Section 1. Short Title

This Act may be cited as the "Better Pharmaceuticals for Children Act".

Section 2. General Rule on Needed Pediatric Drugs

Chapter V of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 351, et. seq.) is amended by inserting after Section 528, the following new subchapter.

"Subchapter C--Drugs for Infants and Young Children

"Sec. 529--Incentives for Pediatric Studies

"(a).-- Additional Period of Market Exclusivity for Conduct of Pediatric Studies on Needed Pediatric Drugs

"If an application for an approval of a drug that is a needed pediatric drug is granted on or after the date of enactment of this section, and such application includes reports of pediatric studies, the Secretary may not

grant another approval for the same product for the same disease or condition for the period of market exclusivity specified in subsection (c).

"(b).-- Assessment of Pediatric Research Fee for Failure to Conduct Pediatric Studies on Needed Pediatric Drugs

"Effective two years after the date of enactment of this section, if an application for an approval of a drug that is a needed pediatric drug does not include reports of pediatric studies, the Secretary shall assess the sponsor of the drug a pediatric research fee, as specified in subsection (d).

"(c)-- Market Exclusivity Period

"The period referred to in subsection (a) shall be

"(1) six months,

"(2) if the Secretary has determined that pediatric formulations are unnecessary or inappropriate for the needed pediatric drug (but the applicant has conducted safety and pharmacokinetic studies), three months, or

"(3) if Secretary has determined that safety and pharmacokinetic studies are unnecessary or inappropriate for the needed pediatric drug (but the applicant has developed a pediatric formulation), three months.

"(d) Pediatric Research Fees.

"(1) Amount.--The pediatric research fee shall be an amount equal to the total of the following:

"(A) three times the Secretary's estimate of the cost to the Secretary of conducting or supporting pediatric studies of the needed pediatric drug,

"(B) the Secretary's estimate of the administrative costs of conducting or supporting pediatric studies of the needed pediatric drug, and

"(C) the Secretary's estimate of any additional costs the Secretary would incur in conducting or supporting pediatric studyies of the needed pediatric drug.

"(2) Waiver.--The Secretary shall grant a waiver from or a reduction of the pediatric research fee if the Secretary finds that

"(A) such waiver or reduction is necessary to protect the public health, or

"(B) the assessment of the fee would present a significant barrier to innovation because of limited resources available to the sponsor of the needed pediatric drug or other circumstances.

"(3) Unpaid Fees.--An application for an approval submitted by a person subject to fees under this section shall be considered incomplete and shall not be accepted for filing by the Secretary until

all fees owed by such person have been paid.

"(e) Pediatric Studies Research Fund.--The Secretary shall establish a Pediatric Studies Research Fund at the National Institutes of Health. Amounts in the Fund shall be available only to defray the costs of conducting or supporting pediatric studies on needed pediatric drugs whose applicants for approval or holders of approval have elected not to conduct such studies. All fees collected pursuant to subsection (d) shall be credited to the Pediatric Studies Research Fund. Funds shall be available until expended without fiscal year limitation.

"(f) Definitions.--For purpose of this section and of sections 3 and 4 of the Better Pharmaceuticals for Children Act, the term

"(1) 'approval' means, as applicable,

"(A) approval of an application for a drug under section 505,

"(B) if the drug is an antibiotic, a certification under section 507, or

"(C) if the drug is a biological product, a license under section 351 of the Public Health Service Act.

"(2) 'needed pediatric drug' means a drug

"(A) that is intended to be used to treat a serious or life-threatening disease or condition, as defined by the Secretary, that affects infants or young children, regardless of whether the

disease or condition affects another age group, and

"(B) which is not approved for use in infants and young children.

"(3) 'infant' means a child from birth to the age of two. (1yr.) ?

"(4) 'young child' means a child from the age of two through the age of thirteen.

"(5) 'pediatric studies' means clinical investigations that are sufficient to allow the Secretary to approve (or disapprove) the use of the needed pediatric drug in infants or, as appropriate, young children. Such studies must include:

"(A) the development of a pediatric formulation for use by infants (unless the Secretary determines that use by infants is unnecessary or inappropriate),

"(B) the conduct of safety trials and pharmacokinetic analysis in infants (unless the Secretary determines that use by infants is unnecessary or inappropriate), and

"(C) if the Secretary determines appropriate, safety and pharmacokinetic analysis in young children."

"(6) 'pediatric formulation' means a formulation of a needed pediatric drug that is appropriate for use in infants and may include liquid

formulations, aerosol formulations, transdermal formulations, or other appropriate formulations different from those for use in adults.

Section 3.--Special Rule for Drugs that Have Already Been Approved

① NO times
② Sec. requests

(a) Development of List of Needed Pediatric Drugs that Have Been Granted an Approval on or before the Date of Enactment of This Act.--The Secretary shall, after consultation with public and private experts in pediatrics and pediatric specialities, develop a list of needed pediatric drugs that have been granted an approval on or before the date of enactment of this Act. The Secretary shall publish a notice in the Federal Register, inviting manufacturers, experts in pediatrics and pediatric specialties, and the public to submit suggestions for drugs to be included on such list.

(b) Request by Secretary.--The Secretary shall request holders of approvals for needed pediatric drugs on the list developed under (1) to conduct pediatric studies.

(c) Additional Period of Market Exclusivity for Conduct of Pediatric Studies on Needed Pediatric Drugs that Have Been Granted Approval on or before the Date of Enactment--If a holder of an approval of a needed pediatric drug on the list developed under subsection (a) provides to the Secretary reports of pediatric studies within one year of

receiving the Secretary's request under subsection (b), the Secretary may not approve another application for the same product under such sections for the period of market exclusivity specified in section 529(c) of the Federal Food, Drug, and Cosmetic Act.

Section 4.--Special Rule for Drugs that Have Been Submitted for Approval But Not Approved on or before the Date of Enactment

(a) Development of List of Needed Pediatric Drugs that Have Been Submitted for Approval But Not Approved on or before the Date of Enactment--The Secretary shall, after consultation with public and private experts in pediatrics and pediatric specialities and with appropriate consideration of information that is a trade secret, develop a list of needed pediatric drugs that have been submitted for approval but have not yet been granted an approval on or before the date of enactment of this Act. The Secretary shall publish a notice in the Federal Register, inviting manufacturers, experts in pediatrics and pediatric specialties, and the public to submit suggestions for drugs to be included on such list.

(b) Request by Secretary--The Secretary shall request the sponsor of an application for an approval for needed pediatric drugs on the list developed under (1) to conduct pediatric studies.

(c) Additional Period of Market Exclusivity for Conduct of

Pediatric Studies on Needed Pediatric Drugs that Have Been Submitted for Approval But Not Approved on or before the Date of Enactment--If a sponsor of an application of a needed pediatric drug on the list developed under subsection (a) provides to the Secretary reports of pediatric studies within one year of receiving the Secretary's request under subsection (b), the Secretary may not approve another application for the same product under such sections for the period of market exclusivity specified in section 529(c) of the Federal Food, Drug, and Cosmetic Act.

Section 5--Effective Date and Sunset Clause

(a) Except as provided in section 529(b) of the Federal Food, Drug and Cosmetic Act, as added by this Act, the provisions of this Act are effective upon enactment.

(b) Effective three years after the first issuance of the list required in section 3(a), Section 3 is repealed.

(c) Effective five years after the first issuance of the list required in section 4(a), Section 4 is repealed.

To Elizabeth
From Tim
Re: Pediatric Drugs
May 10, 1996

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-Public Service

Lisa Campetti

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TODAY'S DATE: ***May 13, 1996***

THIS FAX IS FOR: Elizabeth Deye

FAX NUMBER: 202 456-7028

FROM: ***PEGGY DOTZEL***

NUMBER OF PAGES INCLUDING FAX COVER:

COMMENTS:

12. STATE AND LOCAL REQUIREMENTS RESPECTING OTC DRUGS (SECTION 608)

AMENDMENT NO. ____ Calendar No. ____

Purpose: To provide for the uniformity of Federal, State, and local requirements respecting nonprescription drugs intended for human use.

IN THE SENATE OF THE UNITED STATES—104th Cong., 2d Sess.

S. 1477

To amend the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act to improve the regulation of food, drugs, devices, and biological products, and for other purposes.

Referred to the Committee on _____
and ordered to be printed

Ordered to lie on the table and to be printed

AMENDMENT intended to be proposed by Mr. GREGG

Viz:

On page 64, between lines 7 and 8, insert the following:

SEC. 608. STATE AND LOCAL REQUIREMENTS RESPECTING NONPRESCRIPTION DRUGS INTENDED FOR HUMAN USE.

Chapter V (21 U.S.C. 351 et seq.) is amended by inserting after section 522 the following new section:

"SEC. 523. STATE AND LOCAL REQUIREMENTS RESPECTING NONPRESCRIPTION DRUGS INTENDED FOR HUMAN USE.

"(a) IN GENERAL.—Except as provided in subsection (b), no State or political subdivision thereof may establish or continue in effect any requirement relating to the regulation of a drug intended for human use that is not subject to the requirements of section 503(b)(1) which is different from or in addition to, ~~or which is otherwise not identical with,~~ a requirement of this Act or the Fair Packaging and Labeling Act, ~~and the administrative implementation thereunder.~~ For purposes of this section, a requirement relating to the regulation of such drug shall be deemed to include any requirement relating to the subject matter in any provision of this Act, the Fair Packaging and Labeling Act, and any requirement relating to the dissemination of information in any manner about such drug, but shall not include any requirement relating to the ~~dispensing of~~ a drug only upon prescription of a practitioner licensed by law to administer such drug.

"(b) EXEMPTION.—Upon application of a State, the Secretary may by regulation, after providing notice and an opportunity for written and oral presentation of views, exempt from the provisions of subsection (a), under such conditions as the Secretary may impose, a proposed re-

quirement relating to the regulation of a drug intended for human use—

"(1) that is justified by compelling local conditions or protects an important public interest that would otherwise be unprotected; and

"(2) that would not cause any drug intended for human use that is not subject to the requirements of section 503(b)(1) to be in violation of any applicable requirement or prohibition under Federal law; and

"(3) that would not unduly burden interstate commerce.".

Diane / Elizabeth –

The idea proposed here is related to one Diane is working on. Could you look into this and get back to me as to whether we should set in motion a policy process? Thanks

Elena

cc Bruce

DATE: 1/12-6

TO: RAHM

Copies for
Me
Elin Drye
Diane Rejas
Bruce Reed

-6423
JOHNSON

ratic Policy Committee
t Senate Office Building
one: (202) 224-3232
ax: (202) 228-3432

MESSAGES: THIS IS THAT "DRUGS FOR KIDS" ISSUE. I ASKED FOR AN ACTION PLAN – AND I ENCLOSE IT. I AM NOT OBSESSED WITH THIS JUST DOING FRIENDS A FAVOR – BUT THE IDEA HAS MERIT...

# of Pages including cover: 4

CALL AT YOUR EARLIEST OPPORTUNITY.

TO: Joel Johnson

FROM: Susan DeLaurentis

DATE: December 5, 1996

RE: **Pediatric Data for Pharmaceuticals**

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

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

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

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

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

Thanks again for everything.

PROPOSED ACTION PLAN

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

- The Executive Order would:

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

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

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

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

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

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

GEORGETOWN UNIVERSITY LAW CENTER

Federal Legislation Clinic

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Associate Professor of Law
Chai R. Feldblum

Deputy Director
R. Scott Foster

Senior Policy Fellow
Timothy M. Westmoreland

Executive Assistant
Loretta C. Moss

Visiting Professor
Ralph G. Neas

Supervising Attorneys
David P. Rapallo
Sharon N. Perley

MEMORANDUM

TO: Elizabeth Drye
White House Domestic Policy Council

FROM: Sharon Perley
Tim Westmoreland
Chai Feldblum

DATE: January 28, 1997

RE: Background Information

The following information is attached for your review:

1. FDA Regulation and Interview with Deputy Director Paula Botstein

The regulation outlines the current FDA approach to pediatric testing and labeling: drug manufacturers are free to omit pediatric data so long as they indicate on the drug's label that pediatric safety has not been established.

Dr. Botstein's interview, conducted several years prior to the issuance of the regulation, notes FDA's concern that children do not have proper access to safe drug usage. Her encouraging statements notwithstanding, nothing has changed to ensure that drugs be proven safe and effective for pediatric use.

2. Statements by Dr. Art Ammann (formerly of the Pediatric AIDS Foundation)

Dr. Ammann's letter to Commissioner Kessler and his testimony before the FDA discuss the urgent need for pediatric data.

3. Statements by the American Academy of Pediatrics (AAP)

The AAP's testimony notes the lack of pediatric data in the majority of approved drugs has led to the creation of "therapeutic orphans." Children are unable to share in

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therapeutic advances to the extent adult patients are, nor are they provided the same protections afforded adults.

The *Pediatrics* article further details the need for pediatric clinical studies.

4. Media Reports

Several news articles are included to demonstrate how the lack of drugs for children with HIV/AIDS has impacted doctors' abilities to treat and families' abilities to cope with the disease.

5. Testimony of mothers at the Delavirdine hearing (FDA Antiviral Drugs Advisory Committee Meeting)

This testimony before the FDA further demonstrates the frustration and lack of hope felt by families who cannot get access to drugs for their children, even though the same drugs are available for the adult population.

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

ADMINISTRATOR
OFFICE OF
INFORMATION AND
REGULATORY AFFAIRS

August 6, 1997

MEMORANDUM FOR ERSKINE BOWLES

THROUGH: Franklin D. Raines

FROM: Sally Katzen

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

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

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

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

PEDIATRIC LABELING FOR DRUGS

BACKGROUND

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

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

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

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

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Pediatric labeling added after approval	1	0	1	0	0	0	2

REGULATORY STRATEGY

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

sufficiently address the problem

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

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

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

Other approaches are needed to supplement any financial incentive. Moreover,

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

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

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

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

Draft
June 13, 1997

PEDIATRIC LABELING FOR DRUGS

BACKGROUND

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

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

These voluntary efforts to increase the amount of pediatric use information on labeling have not resulted in significant gains. The response to the 1994 rule has not been encouraging. Moreover, efforts to date have not increased the number of new drugs entering the marketplace with adequate pediatric labeling. As shown in the chart below, a comparison of new molecular entities (NME's) approved in 1991 through 1996 shows no improvement in the percentage approved with adequate pediatric labeling. While approximately 56% of the drugs approved in 1991 with

potential use in children had some pediatric labeling, 37% of those approved in 1996 with potential use in children had pediatric labeling. The data also suggest that commitments by manufacturers to conduct pediatric studies after approval frequently do not result in pediatric labeling. FDA estimates that pediatric studies are needed for approximately 10-15 products per year that would not otherwise have been studied in children. This figure includes an estimated 10-13 new drugs and biological products and two already marketed products.

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Pediatric labeling added after approval	1	0	1	0	0	0	2

REGULATORY STRATEGY

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The absence of adequate pediatric labeling continues to pose a significant public health issue. New approaches to the problem are needed. Financial incentives may be successful in generating pediatric labeling for some drugs, but there is no assurance that such incentives alone will sufficiently address the problem since they would leave it up to the manufacturer's discretion to conduct the studies. In addition, FDA's experience shows that a significant minority of manufacturers conduct needed pediatric testing without financial incentives. Providing exclusive marketing rights to companies that would have conducted pediatric studies without incentives may impose unnecessary costs on prescription drug consumers, and on governmental and third party payers, in the form of more expensive drugs.

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

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

In the event that a manufacturer failed to carry out a required pediatric study, the drug would not be disapproved or withdrawn, because such an action would deprive adult patients of important therapies. Instead, FDA would have authority to bring an enforcement action against the manufacturer, as it does when there are other violations of FDA's requirements.

June 12, 1997

PEDIATRIC LABELING FOR DRUGS

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June 12, 1997

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June 12, 1997

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U.S. FOOD AND DRUG ADMINISTRATION
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TODAY'S DATE: June 11, 1997

THIS FAX IS FOR: Elizabeth Drye

FAX NUMBER: (202) 456-~~7431~~ 5581

FROM: Bill Schultz

NUMBER OF PAGES W/O FAX COVER: 3

COMMENTS:

DRAFT

PEDIATRIC LABELING FOR DRUGS

BACKGROUND

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Kaiser redraft 6/12

DRAFT

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4 pm Thurs?
Confirm w/ me + E

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.

Jim Brady

pharmacokinetics – ~~3~~ 200,000 ~~300,000~~
– 3-5 million clinical trials

100 million estimate

20-30 per year (15)
50 last year (40)
5-10

therapeutic advance described as significant

Copy 10
Chris Jennings

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%, betamethasone 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
ital (cromolyn odium).	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%)
oloft (sertraline HCl)	Depression.	S&E have not been established in children.	248,000 for children <16 years.	Psychiatrists (72%)
italin tablets and stained-release tablets ethylphenidate HCl) *chedule II drug)*	Treatment of attention deficit disorders and narcolepsy.	S&E have not been established in children <6 years of age.	226,000 to children <6 years old.	Pediatricians (47%) Psychiatrists (26%)
upent Syrup emproterenol lfate).	Bronchodilator for bronchial asthma and for reversible bronchospasms.	Clinical trial experience in children under the age of 6 is limited.	184,000 to children <6 years old.	Pediatricians (59%) Family practitioners (23%)
clomethasone ropionate nasal ays (includes conase AQ and ncenase AQ nasal ays).	Relief of symptoms of seasonal and perennial rhinitis and for the prevention of recurrence of nasal polyps following surgical removal.	S&E in children below the age of 6 have not been established.	174,000 to children <6 years old.	Pediatricians (46%)

95%

HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

P94-21
FOR IMMEDIATE RELEASE
Dec. 13, 1994

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

FDA ANNOUNCES NEW RULES FOR CHILDREN'S MEDICINES

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

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

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

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

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

-MORE-

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

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

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

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

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

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

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

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

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

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

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

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

In the Line for AIDS Drugs, Children Are Last

By LAURIE MCGINLEY
Staff Reporter of THE WALL STREET JOURNAL

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

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

MEDICINE

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

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

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

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."

Final

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

JUN 11 1997

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

Dear Senator Jeffords:

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

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

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

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

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

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

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

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

Sincerely,

Donna E. Shalala

Enclosure

S. 830 (Chairman's Substitute)

A. Major Concerns

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

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

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

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

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

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

4. Health Claims For Foods (Sec. 617)

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

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

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

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

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

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

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

8. **Pediatric Labeling**

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

B. Other Significant Concerns

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

C. Currently In The Bill - No Language Provided Yet

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

Corr, Schulte 3/21/97

1984 – Patent Extension for drugs going through FDA. — coming on market with portion of 17 years

– New indication – of drug on market — 3 year patent exclusivity —

Schulte — Not just dosage question —
– hard to get pediatric formulations
– liquid until age 10-11
– Not just 1/20 pharmacokinetics study
– Have to reformulate.

– 1/3 to 1/2 do it anyway —

– Pediatrics AIDS Foundation — have legal obligations

– Said in 94 proposal — Have authority to do it.

Drugs coming on market – if we think it will be used – rebuttable presumption will be used on kids (3/4)

– Civil actions

Injunction — hold in contempt. —

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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.

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."

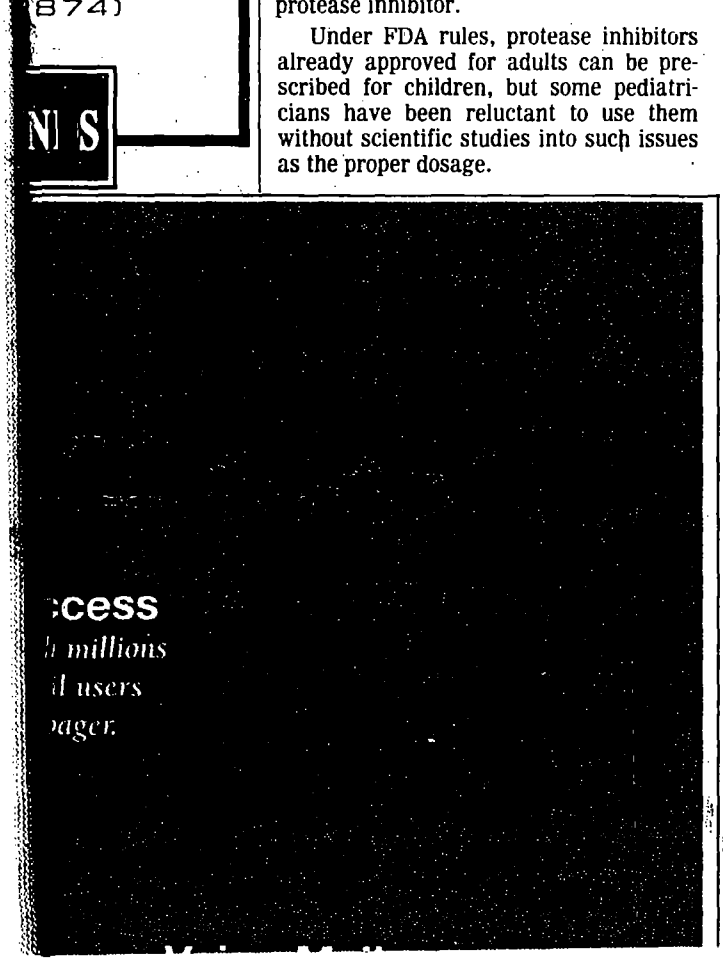
However, clinical data on such critical measures as virus levels in the blood of treated children haven't been disclosed yet. Agouron says that virus-level drops have been equivalent to those in adults, but data on the 52 children treated to date won't be available until later this month.

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** ing. Abbott said it expects to soon amend



Apple Plans PC Using Systems From Mac, Nex

By Lee Gomes
Staff Reporter of The Wall Street Journ

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signed 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.

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

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At a Macintosh trade show in San Francisco yesterday, Apple said that for the next several years it plans to pursue a "dual operating system" strategy that will offer machines with both its existing Macintosh operating system and its new Next-based system. Company officials would not be more specific about how long the dual-system offer will continue.

Meanwhile, Apple's stock plummeted as investors reacted to Apple's announcement Friday that the company will post an operating loss as wide as $150 million for the fiscal first quarter ended Dec. 27. In Nasdaq Stock Market trading yesterday, Apple shares fell $3.875, or 18%, to $17.875, near its 52-week low of $16.

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Even when it begins selling machines with the new operating system, Apple will continue to make available its current operating system, known as System 7, Ms. Hancock said. System 7 should remain available for several years, she said.

Industry analysts said Apple's new strategy is designed to make sure the company doesn't lose customers or software developers while it moves toward its new operating system. Some customers

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~~CONFIDENTIAL~~

TO: Elizabeth Drye
White House Domestic Policy Council

FROM: Sharon Perley
Tim Westmoreland
Chai Feldblum

DATE: January 28, 1996

RE: **Pediatric studies for pharmaceuticals**

As you know, the Federal Legislation Clinic, on behalf of its client, the Pediatric AIDS Foundation (PAF), has been looking into whether FDA has the authority to require pediatric studies for pharmaceuticals. Extensive research has led us to conclude that not only does the Food, Drug, and Cosmetic Act (FDCA) *authorize* the FDA to require pediatric studies, the statute actually *mandates* the FDA to require such studies prior to its approval of a new drug application. Our legal arguments are set forth below.

The need for pediatric studies for pharmaceuticals cannot be overstated. We have attached, under separate cover, background materials explaining the problem. While a number of these materials highlight the lack of pediatric studies (and, hence, the lack of approval for pediatric use) for AIDS drugs, the problem is much greater than just AIDS. 80% of all drugs marketed in the United States -- including those commonly prescribed for pediatric patients -- have not been proven safe and effective for use by children. Doctors must choose between guessing what dosage of a nonapproved drug is safe for their pediatric patients or depriving children of needed remedies. As FDA itself has found:

> Most prescription drug products . . . lack adequate information about their use in pediatric populations. . . . [W]ithout adequate information, practitioners may be reluctant to prescribe certain drugs for their pediatric patients, or may prescribe them inappropriately, choosing dosages, for instance, that are arbitrarily based on the child's age, body weight, or body surface area without specific information as to whether this is appropriate. As a result, pediatric patients may be exposed to an

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increased risk of adverse reactions, or decreased effectiveness of the drugs prescribed, or may be denied access to valuable therapeutic agents.

59 Fed Reg. 54240, 64240 (1994).

To its credit, FDA has tried to rectify these problems by promulgating regulations encouraging the development of pediatric data. In 1979, FDA issued the first regulations concerning pediatric studies. (Prior to that time, there were no requirements whatsoever concening pediatric clinical studies or pediatric labeling.) The regulation stated that *if* there were clinical studies supporting pediatric use of a drug, that information was to be described on the drug's label. The regulation was intended to encourage manufacturers to provide pediatric data; it did not, however, require that pediatric data actually be submitted.

In 1994, recognizing that its first attempts had failed, FDA promulgated a new regulation. The regulation (and the accompanying interpretive guidance) *encourage* manufacturers to conduct pediatric studies, but again do not require such studies. Instead, the regulation merely requires that drugs not proven safe and effective for pediatric use bear the warning: "safety and effectiveness in pediatric patients . . . have not been established."

Unfortunately, the agency's efforts to encourage the development of pediatric data have not been successful. Despite the FDA's urging, PAF's numerous conversations with pharmaceutical manufacturers, and the exhaustive efforts of many others, only 4 of the 28 new drugs approved by the FDA in 1995 contained pediatric data. More importantly, there is no evidence this trend is likely to change any time soon.

Accordingly, we believe the only way to solve the problem is by having the FDA issue a regulation *requiring* pediatric studies. (Although, of course, we would gladly discuss any other ideas you might have.) The attached sets forth what we believe to be the best legal arguments supporting FDA's authority to issue such a regulation.

We are heartened by the White House's interest in this matter and urge you to continue your good work. If we can be of any further assistance, please do not hesitate to contact us.

LEGAL ARGUMENTS

I. Section 505 of the FDCA Requires That Drugs be Proven Safe and Effective For *All* Foreseeable Users, Not Only Adults

a. The plain language, purpose, and legislative history of the statute demonstrate Congress' intent that drugs be proven safe and effective for all foreseeable users

Section 505(b)(1) of the FDCA mandates that new drugs be proven "safe for use and . . . effective in use." 21 U.S.C. § 355(b)(1)(1994). The burden is on the sponsor of a new drug application, who must submit "reports of investigations," -- *i.e.*, clinical studies -- demonstrating the drug's safety and efficacy. *Id.* The statute contains no limiting or qualifying language. It does not say "safe and effective for use in the adult population only," or "safe and effective for use by adult, but not pediatric, users." A plain reading of the statute thus requires that drugs be proven safe and effective for *all* foreseeable users, adults *and* children.

This reading of the statute is supported by the statute's purpose. The FDCA, first enacted in 1938, was designed to protect the public health -- to ensure that drugs are safe for use prior to their being marketed in the United States. Congress was particularly concerned with protecting the health and safety of children. Indeed, Congress ultimately passed the Act, various versions of which had been considered since 1933, in direct response to the tragic death of 107 persons, the majority of whom were children.[1]

Congressional intent to protect child health is plainly demonstrated in the Act's legislative history, which is replete with references to children and their well-being. Earlier versions of the bill had focussed on forbidding adulterated and misbranded drugs, rather than on requiring an express showing of "safety."[2] In reporting one of these earlier versions out of the Senate Commerce Committee, Senator Copeland, one of the bill's key sponsors, explained:

> It is a matter of great concern to every man what he shall put into his stomach. Every mother is anxious that the food and medicine given to her baby shall be above suspicion. The welfare of every man, woman, and child is involved in the quality and preparation of the foods and drugs sold in America. . . .

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1 *See, e.g.*, Cavers, "The Food, Drug, and Cosmetic Act of 1938: Its Legislative History and Its Substantive Provisions," 6 *Law & Contemp. Prob.* 2 (1939); CHARLES O. JACKSON, FOOD AND DRUG LEGISLATION IN THE NEW DEAL 161-68 (1970); HENRY G. GRABOWSKI & JOHN M. VERNON, THE REGULATION OF PHARMACEUTICALS: BALANCING THE BENEFITS AND RISKS 2 (1983).

2 *See, e.g.*, S. 2800, 73d Cong., 2d Sess. (1934); S. 5, 74th Cong., 2d Sess. (1936).

> I ask you to bear in mind that the purpose of this legislation is not primarily to control industry. Its purpose is to protect the public, to protect the mothers and the children, to protect the consumers. . . .
>
> [This bill] is in the public interest. Enacted into law, it will add to the safety of the American family, and I hope serve to save many a life. Mother, father, and babies -- men, women, and children -- all will be better guarded in health and pocketbook than ever before in American history.[3]

Similarly, in 1936, Congressman Coffee, another sponsor of the legislation, cited the need to protect children as he argued in support of the bill:

> Strychnine is another highly toxic drug the presence of which does not have to be declared under the present law [the Pure Food and Drugs Act of 1906]. In one 5-year period 75 children, most of them under 5 years of age, died in New York State alone of strychnine poisoning. . . . Laxative and tonic pills containing strychnine were responsible for the majority of these deaths and are the foremost cause of fatal poisoning among young children. Parents assume such preparations to be innocuous. They have no way of knowing that the chocolate or sugar coating of these pills, so attractive to children, covers sufficient strychnine that six or eight tablets accidentally eaten may constitute a lethal dose of poison for a small child.[4]

In 1937, the legislation still had not been enacted, and 107 persons died as a result of ingesting a drug known as "Elixir Sulfanilamide." Most of the victims were children. The Senate requested an investigation by the Secretary of Agriculture, who concluded legislation was needed to protect the public from potentially toxic drugs.[5]

The legislation was finally passed in 1938. The final version contained specific language requiring new drugs to be adequately tested for safety prior to their being marketed. As the House Committee on Interstate and Foreign Commerce Report explained:

> [Section 505(a) is intended] to prevent the premature marketing of new drugs not properly tested for safety. One recent outstanding instance of the hazards this

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3 78 Cong. Rec. 567-73 (1934).

4 81 Cong. Rec. 7312 (1937).

5 *Secretary of Agriculture, A Report on Elixir Sulfanilamide-Massengill*, S. Doc. No. 124, 75th Cong., 2d Sess., 9 (1937) (responding to S. Res. 194, 75th Cong., 1st Sess. (1937)).

provision is intended to safeguard against was the introduction of an untested elixir sulfanilamide, which claimed nearly 100 lives.[6]

The most extensive amendments to the FDCA were enacted in 1962, in which Congress further tightened the safety requirements for testing new prescription drugs and added the requirement that manufacturers prove their products effective -- as well as safe -- before FDA would grant approval. As with the 1938 enactment, the 1962 amendments were precipitated by a tragic event affecting children -- in this instance, newborns.

The "thalidomide babies," as these newborns came to be known, were born with physical deformities resulting from maternal ingestion of the sedative thalidomide during pregnancy. The infants' fate is referenced throughout the legislative history accompanying the 1962 amendments. Even a cursory review of this history demonstrates Congress' concern with the health and well-being of American children.

Indeed, in addressing Congress on the need to amend the FDCA, President Kennedy admonished:

> It is time to give American men, women, and children the same protection we have been giving hogs, sheep, and cattle since 1913 under an act forbidding the marketing of worthless serums and other drugs for the treatment of these animals.[7]

Testimony before the House Committee on Interstate and Foreign Commerce specifically focused on the need to protect children:

> All of us who give drugs to our children or loved ones do so with faith in the doctor who prescribed them, the druggist who compounded the prescription and the industry that manufactured the basic ingredients. . . .
>
> All of us can imagine, I am sure, the uncertainty in the mind of a mother with a sick child. She wants her child to recover; she wants to be sure of the drug she is administering. She needs, and I submit she should have, that confidence and it is within the power of this Congress to give her that peace of mind.[8]

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6 H.R. Rep. No. 75-2139, at 9 (1938).

7 President of the United States, *Message to the Committee of the Whole House on the State of the Union, Consumers' Protection and Interest Program*, H.R. Doc. No. 364, 87th Cong., 2d Sess. (1962).

8 *Drug Industry Act of 1962: Hearings on H.R. 11581 and H.R. 11582 Before the House Comm. on Interstate and Foreign Commerce,* 87th Cong., 2d Sess., 456 (1962) (statement of Andrew J.

Senator Humphrey specifically expounded on the importance of protecting child health:

> Genuine miracle drugs have contributed immeasurably to maternal and child health, but adverse effects are often suspected and must now be thoroughly explored, and suitable safeguards taken.[9]

And both Senator Humphrey and Senator Kefauver introduced articles from scientific journals expressing concern about the effects drugs can have on young children, particularly infants.[10]

Plain language and legislative history notwithstanding, FDA has interpreted the statute as requiring that drugs need be proven safe and effective only for use by adults. While testing in adults may have been sufficient when the FDCA was first enacted and the medical community treated children as if they were metabolically indistinguishable from adults, it is now clear children are not "little adults." Children metabolize drugs differently; drugs proven safe and effective for use in adults may in fact be harmful to children. To meet the statute's mandate, FDA must require the submission of pediatric studies prior to its approval of a new drug application.

b. FDA must issue regulations to satisfy its statutory mandate

FDA should amend its Investigational New Drug Application ("IND") and New Drug Application ("NDA") regulations, so as to require that drugs be proven safe and effective for use by children. The regulations should require pediatric pharmacokinetic data, pediatric pharmacodynamic data, and pediatric safety data. The regulations may, however, allow a manufacturer to extrapolate efficacy data from adequate and well-controlled studies in adults, if appropriate.[11] FDA should make clear that when children are foreseeable users of a drug, it will not approve an NDA for that drug unless the manufacturer supplies data sufficient to support a pediatric indication or pediatric use statement (including warnings against use, when

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Biemiller, Director, Department of Legislation, AFL-CIO).

9 108 Cong. Rec. at 15687 (1962).

10 *Interagency Coordination in Drug Research and Regulation, Hearings Before the Subcomm. on Reorganization and Int'l Organizations of the Senate Comm. on Gov't Operations,* 87th Cong., 2d Sess. 45-46 (1962) (Senator Humphrey submitting *Effect of Drugs Upon the Fetus and Infants, J. of Pediatrics.*, Oct. 1961, at 678) (also reprinted at 108 Cong. Rec. 15658 (1962)); 108 Cong. Rec. 17384 (1962) (Senator Kefauver submitting Somers, G.F., *Latronic Diseases of the Newborn, The Lancet*).

11 *Cf.* 21 C.F.R. 201.57(f)(9) (1996) (allowing the extrapolation of adult efficacy data to demonstrate effectiveness in children).

appropriate).[12] Often, to obtain proper pharmacokinetic, pharmacodynamic, and dosing data, manufacturers will have to conduct clinical studies in disparate age groups within the pediatric population -- *e.g.*, neonate, infants, children and adolescents. FDA should require such studies when necessary.

We recognize these regulations will provide FDA with a very strong stick, the exercise of which could theoretically delay the approval of drugs for adults. But so long as drug manufacturers comply with FDA's regulations, the approval of drugs for adults need not be delayed. Pediatric Phase 1 studies, which require only small numbers of children, would generally be started concurrently with, but no later than upon the successful completion of, Phase 1 studies in adults. Any needed Phase 2 pediatric studies would be commenced at the conclusion of Phase 1 pediatric studies. Phase 1 and, if needed, Phase 2 pediatric studies would, therefore, be completed long before adult Phase 3 (efficacy) studies are completed and ready for submission to FDA.

In other words, we are not seeking (nor would we ever seek) that FDA delay the approval of drugs proven safe and effective for use by adults. *To the contrary, we ask FDA to change the paradigm.* We ask FDA to operate pursuant to its statutory mandate and require pediatric clinical studies, and we ask pharmaceutical manufacturers to comply with the regulations FDA promulgates. Only if a manufacturer refuses to comply with these regulations should a new drug application be denied.

II. The Labeling Requirements of the FDCA Provide Separate (And Perhaps More Flexible) Statutory Authority For Requiring Pediatric Studies

In addition to requiring that drugs be safe and effective, the FDCA requires that drugs not be misbranded. 21 U.S.C. § 331(a) (1994). The FDCA defines a drug as being misbranded if, *inter alia*, its labeling is "misleading in any particular," its labeling does not have "adequate directions for use," or its labeling does not bear "adequate warnings against use by children where [the drug's] use may be dangerous to health." *Id.* at §§ 352(a), (f). These labeling requirements *separately* mandate FDA to require pediatric studies when children are foreseeable users of the drug.

a. A drug is misbranded if it fails to reveal the consequences of pediatric use

Section 502(a) provides that a drug is misbranded if its labeling is "false or misleading in any particular." *Id.* at § 352(a). In determining whether a drug's labeling is misleading, FDA must consider not only representations made on the labeling, but the extent to which the labeling fails to reveal "material facts." *Id.* at § 321(n). Material facts include consequences that may

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12 In addition, FDA should revise its current pediatric use labeling regulation. *See infra* (discussing how and why FDA's pediatric use labeling regulation should be revised).

result from use of the drug under labeled conditions of use, as well as those under "customary or usual" conditions of use. *Id.* As FDA itself has noted, "customary or usual" conditions of use include off-label uses, including off-label uses by children.[13]

Accordingly, when children are foreseeable users of the drug -- *i.e.*, when the manufacturer or FDA knows, or has reason to know, that the drug will be prescribed off-label to children -- the drug is misbranded if its labeling fails to reveal information concerning appropriate pediatric use. Such information must include that which can only be derived from pediatric studies, such as pediatric indications, if any; appropriate pediatric dosage information; specific hazards associated with use of the drug in any subsets of the pediatric population; differences between pediatric and adult responses to the drug; and other information related to the safe and effective use of the drug by children. *Cf.* 21 C.F.R. § 201.57(f)(9)(ii) & (iii) (1996).

The statement "safety and effectiveness in pediatric patients have not been established" is insufficient when children are foreseeable users of the drug. Such a statement fails to reveal *material facts* concerning the consequences -- be they positive or negative -- resulting from use of the drug by children. *See* 21 U.S.C. § 321(n) (1994).

Even an explicit warning, such as "Danger: Do Not Prescribe to Children" would be misleading unless supported by data demonstrating actual harm, for, if the drug actually would be beneficial to children, a warning against pediatric use would be directly misleading. And if, conversely, the drug actually would be harmful to children, a standard, unsupported warning against pediatric use would still be misleading, because parents and physicians would know that neither the manufacturer nor FDA had the data to support the warning. In the absence of *any* data, physicians would, as they do now, prescribe these drugs off-label when there are no available alternative therapies.[14]

b. A drug is misbranded if it fails to bear adequate directions for pediatric use

Section 502(f)(1) of the FDCA provides that a drug is misbranded if it fails to bear "adequate directions for use." 21 U.S.C. § 352(f)(1) (1994). The regulations explain that "adequate directions for use" mean directions under which the layman can use a drug safely --

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13 59 Fed. Reg. 64240, 64243 (1994).

14 Indeed, in instances in which a child's life or health is at stake, it is questionable whether any unsupported warning can ever be "adequate." Desperate parents and doctors will take any potentially useful action they can, unless they *know* such action is dangerous. FDA cannot be cognizant of this desperation, be aware of the ease and frequency of off-label use (indeed, its promotion by manufacturers), and pretend that warnings without data will be rigidly adhered to. Unless FDA is prepared to revisit its unwillingness to regulate off-label uses, unsupported warnings should be considered to be intrinsically misleading.

under both the conditions for use intended by the manufacturer and the "*conditions, purposes, or uses for which the drug is commonly used.*" 21 C.F.R. § 201.5(a) (1996) (emphasis added). Indeed,

> if a manufacturer knows, or has knowledge of facts that would give him notice, that a drug . . . is to be used for conditions, purposes, or uses other than the ones for which he offers it, *he is required to provide adequate labeling for such a drug which accords with such other uses to which the article is to be put.*

Id. at § 201.128 (1996) (emphasis added).[15]

Accordingly, if a manufacturer knows or should know a drug is to be used by children, he or she is required to provide adequate labeling for pediatric use. The statement "safety and effectiveness in pediatric patients have not been established" is again insufficient. When a manufacturer knows a drug is to be used by children, existing FDA regulations require that he or she provide adequate information -- as derived from clinical pediatric studies -- concerning pediatric use of the drug.

c. A drug is misbranded if it does not contain adequate warnings against use by children when appropriate

Finally, Section 502(f)(2) provides that a drug is misbranded if it fails to bear adequate warnings against use by children where such use may be dangerous to a child's health. 21 U.S.C. § 352(f)(2) (1994). There is no way a pharmaceutical manufacturer can know whether a drug may be harmful to children -- and, if it is, under what circumstances -- unless pediatric safety studies have been conducted. Again, statements such as "Danger: Do Not Prescribe to Children" are not adequate unless supported by specific data, for, in the absence of such data, pediatricians will continue to prescribe the drug off-label.[16] Accordingly, when children are foreseeable users of a drug, manufacturers must conduct studies to determine whether use of the drug may be dangerous to a child's health, as well as to determine what dosage or methods or duration of administration may be unsafe in the pediatric population, or subsets of the population. *Cf.* 59 Fed. Reg. 64240, 64243.

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15 Interestingly, FDA cited 21 C.F.R. 201.128 in the guidance accompanying its pediatric use labeling regulation. In the guidance, however, FDA said that the manufacturer *may* be required, rather than *shall* be required, to provide adequate labeling for pediatric use. 59 Fed. Reg. 64240, 64243 (1994). This interpretation in the guidance directly contravenes the language of the regulation.

16 *See supra.*

d. FDA must issue new regulations to satisfy its statutory mandate

The FDCA's labeling requirements -- and FDA's own regulatory interpretations -- provide separate authority for requiring pediatric studies. In the absence of such studies, drugs for which children are foreseeable users will be misbranded.

Accordingly, FDA should revise its pediatric use labeling regulation, 21 C.F.R. § 201.57(f)(9) (1996). It should revoke subparagraphs (v) and (vi), which currently permit manufacturers to include in their labeling the statement "safety and effectiveness in pediatric patients have not been established." Instead, it should require that the label fulfill the requirements of subparagraphs (ii) and (iii) for all drugs for which children are foreseeable users.[17]

FDA should also revise its NDA regulations to make clear it will reject an NDA if the drug's label does not comply with these requirements. *See* 21 U.S.C. § 355(d)(7) (1994) (the Secretary shall issue an order refusing an NDA if, "based on a fair evaluation of all material facts, [the drug's] labeling is false or misleading in any particular"). In addition, FDA should promulgate regulations requiring manufacturers of already-approved drugs, where it is established that the drug is being prescribed off-label to children, to revise its labeling in accordance with the new pediatric use labeling requirements. FDA should make clear that if manufacturers do not comply with the new labeling regulations, it will withdraw the approval of the drug's NDA pursuant to Section 505(e).[18]

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17 In other words, the label must (a) describe any specific pediatric indications and any specific limitations on the indication; (b) provide appropriate pediatric dosage information; and (c) describe any need for specific monitoring, specific hazards associated with use of the drug in any subsets of the pediatric population, differences between pediatric and adult responses to the drug, and other information related to the safe and effective pediatric use of the drug. *See* 21 C.F.R. 201.57(f)(9)(ii), (iii) (1996).

18 *See* 21 U.S.C. § 355(e) (1994):

> . . . The Secretary may also, after due notice and opportunity for hearing to the applicant, withdraw the approval of an application submitted under subsection (b) or (j) with respect to any drug under this section if the Secretary finds . . . that on the basis of new information before him, evaluated together with the evidence before him when the application was approved, the labeling of such drug, based on a fair evaluation of all material facts, is false or misleading in any particular and was not corrected within a reasonable time after receipt of written notice from the Secretary specifying the matter complained of. . . .

Of course, FDA should give manufacturers sufficient time to conduct pediatric studies before it withdraws approval.

FYI

THE WALL STREET JOURNAL

Friday, B1 col. 3 Nov. 15, 1996

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 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.

MEDICINE

"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.

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

Source: Pediatric AIDS Foundation, Food and Drug Administration

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

Please Turn to Page B17, Column 3

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

Continued From Page B1

much earlier stage," says Philip Pizzo, a leading AIDS researcher who is physician in chief and chairman of the department of 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."

Daily News Oct. 21, 1996 P. 8

Docs urge drugs for AIDS kids

By JOE NICHOLSON
Daily News Staff Writer

Children with AIDS are dying unnecessarily because they can't get the life-saving medicines that are restoring adults to robust health, medical experts charge.

Doctors and advocates for children with HIV said drug companies are moving too slowly to test and approve protease inhibitors for children.

"It's just immoral," said Arthur Ammann, research director at the Pediatric AIDS Foundation, a national group based in California.

"Here's a group of infected individuals — children — who are being denied therapy," he said. "The disease progresses more quickly in children, and yet they are not benefiting from all these advances."

Protease inhibitors have produced remarkable results in adults — in most cases reducing the HIV virus in a patient's blood to the point where it is undetectable. Many adult patients who were close to death suddenly were restored to health.

Manufacturers of the new drugs, however, have not sought approval for their use for children. Critics said that's because they have been focused on the big profits in the larger adult market.

The adult protease inhibitors can be prescribed for children by any physician, but many doctors balk because they don't want to risk it on their young patients without further testing. On a more practical level, the adult drugs are in pill form and most children cannot ingest them.

"I'm personally anxious to see these drugs available for young children," said Elaine Abrams, director of the pediatric HIV program Harlem Hospital Center.

Only one of Harlem's 114 child patients receives the drugs, Abrams said. The single case was an older teenager who could be treated as an adult.

Nationally, only 66 of 965 AIDS-infected children were being treated with the new drugs, according to a survey by Ammann's foundation.

"To be blunt, people are just turning their backs on these kids," Ammann said.

U.S Food and Drug Administration officials deplore the delay, but say they have no power to order companies to speed up the drug testing process.

"There is no regulatory power to compel the pharmaceutical companies to do pediatric trials," said Samuel Maldonado, who chairs an FDA working group on the effects of pediatric drugs.

Maldonado said the agency has asked drug manufacturers to speed efforts to get the drugs approved for children.

The companies said they are trying but have been delayed by difficulty converting pills into a liquid or powder form for infants.

Some drug companies also say they have qualms about subjecting children to the risks of testing such a powerful drug.

But Maldonado said, "A lot of this is market driven."

"I'm not saying cynically that all these people care about is profit, but they have their limits," he said.

Stephen Spector, chairman of the federal program for testing AIDS drugs on children, said the drug companies are known to lag in testing drugs for children. But, he said, "HIV is a potentially lethal disease in children as well as adults, so children should not be excluded in early testing."

Hoffman-LaRoche, the first drug company to get approval for protease inhibitors, said difficulty converting pills to powder form delayed pediatric testing.

Sandra Pallaja of Hoffman-LaRoche called the lag in pediatric approval "an important problem," and said pediatric testing would begin in January.

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<Show: MORNING EDITION>
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BOB EDWARDS, HOST: This is MORNING EDITION. I'm Bob Edwards.

In the past 12 months, a new class of anti-AIDS drugs has produced remarkable recoveries in adults with the disease. People who once faced imminent death are now looking forward to longer and healthier lives.

But for children with AIDS, the future is far less certain. In part two of a series on AIDS, NPR's Vicky Que reports that there are many questions about whether these drugs are safe and effective in young people.

VICKY QUE, NPR REPORTER: It's afternoon in New York. School's out and Lisette Rivera (ph), a registered nurse with the St. Mary's Hospital home care program, is making her rounds in the Bronx.

SOUND OF KNOCKING

LISETTE RIVERA, REGISTERED NURSE, ST. MARY'S HOSPITAL HOME CARE PROGRAM: It's Lisette.

SOUND OF DOOR OPENING

QUE: At this stop, nurse Rivera is visiting Sara, a pint-sized 13-year-old with rosy cheeks and a zest for life, despite the fact that she's infected with the AIDS virus. After Sara's older sister, her legal guardian, ushers us into the living room, Rivera begins to examine the girl.

RIVERA: Let me take Sara's blood pressure, which usually runs about 90 over 60. That's her normal.

QUE: Dressed in a school uniform and tights, Sara looks like your average teenager. But to stay healthy and suppress the virus that has racked her body since she was born, Sara must take more than a dozen pills every day, combinations of antibiotics and anti-AIDS drugs.

SARA, PATIENT: Well, the Videx I take one-and-a-half teaspoons twice a day. And the Biaxin, I take one tablet twice a day. And 3TC, I take one tablet twice a day. And the Crixivan I take three tablets three times a day.

QUE: Crixivan, Sara's latest drug, is one of a growing class of new AIDS medicines called "protease inhibitors." Studies show when these drugs are combined with other AIDS drugs, they can reduce the amount of virus in a person's blood to undetectable levels. In the six months that Sara's been taking the protease inhibitor, her health has improved dramatically.

SARA: Yeah, I'm feeling great. I haven't gotten sick, you know, like really bad. And I haven't been in the hospital for like a year.

QUE: What was it like before you starting taking them?

SARA: Oh, yeah. I was really, really skinny. I used to always get sick. I used to always cough in the night. And I wouldn't eat at all. And now I'm eating and I don't get sick as fast. And I feel much better.

QUE: In fact, Sara has gained so much weight in the last few months that she worries that she's getting chubby. Her relatives hardly recognize her. Stories like Sara's have moved other families to ask their doctors to prescribe these drugs for their sick children. But the medicines haven't been fully tested and aren't available to most children with the AIDS virus, especially the younger ones.

Forty minutes away in a tiny Manhattan apartment, Marlene, a single mother, is pulling out pictures of her only daughter Margarita, who will turn four in February.

MARLENE, PATIENT AND MOTHER OF PATIENT: Here, she's like just three and a half.

QUE: Oh, she's adorable. This is Halloween? What was she dressed up as?

MARLENE: An angel...

QUE: Oh.

MARLENE: ... an angel with sneakers.

LAUGHTER

QUE: Marlene and her daughter are infected with the AIDS virus and Marlene is worried. Over the last several months, Margarita's health has been slipping rapidly. She's had one ear infection after another, has been hospitalized a couple of times and suffers from severe diarrhea.

MARLENE: You know, in the past seven months, she has not gained any weight or grown any. And it's not -- if she does gain some weight, when she does get sick, she's loses like a third of her body weight. That's significant. Imagine losing a third of your body weight in one bout of illness.

QUE: Marlene took protease inhibitors earlier this year and her health improved significantly. She quit when she developed a kidney stone. Even so, she really wants to get the drugs for her daughter. But her daughter's doctor refused, saying not enough studies have been done to prove that the drugs are safe and effective for children.

So Marlene is trying to enroll Margarita in a research study. If she can't get her into one and Margarita's condition worsens, Marlene says she may try giving her daughter some of her leftover protease inhibitors.

MARLENE: Since Margarita, because of her weight and because of her age, I don't know, I figured if I split one capsule in three -- but, I mean, I'm not a scientist. I mean, I'm a mom. You know, never in my wildest dreams did I think, I'd, you know, be confronted or pushed to do something like that. But I do have it squirreled away.

QUE: Doctors say no matter how desperate parents feel, they shouldn't try medicating their children on their own. Getting the right dose is extremely important. Too much of the drug could damage a child's liver or kidney and too little could allow the virus to mutate into strains that are resistant to the drugs.

Even doctors who prescribe the drugs struggle to come up with the right dosages. Peter Havens (ph) is a pediatrician and epidemiologist who treats children with the AIDS virus in Wisconsin. So far, he's put four of his patients, his sickest ones, on protease inhibitors.

PETER HAVENS, PEDIATRICIAN AND EPIDEMIOLOGIST: It's been a very frustrating time to see many adults having enormous benefit from protease inhibitors and to see these benefits denied to children, only because appropriate studies have not been done in a timely fashion. And it seems to me that one of the major reasons that that doesn't happen is because there's no financial incentive for the drug companies to do that.

QUE: The number of children with AIDS is relatively small. Children under 12 make up only about 7,000 of the half a million AIDS cases that have been diagnosed in this country since 1981. And it's estimated that only about 3,000 of them are still alive. That's why critics like Havens accuse drug makers of ignoring the needs of infected children.

But drug companies say coming up with a pediatric formula, something children could take, has been difficult. One company, Roche, which makes a protease inhibitor Sequenivir, tried making the drug into a liquid. But it didn't work. And many children were put off by the drug's bitter taste.

Lerod Fisher (ph), Roche's medical director, says another reason for the delay is the company always tests new drugs on adults first.

LEROD FISHER, MEDICAL DIRECTOR, ROCHE: You know, you can be criticized for bringing a drug too late to patients or too early. And I think we've been criticized both ways. I think that certainly, looking backward, it is easy to say that we should have done it earlier. And I would agree with that. We should probably have moved ahead earlier. But that's only now that we know of the incredible effect of these new drugs.

QUE: But as powerful as these new drugs are, they don't work for everyone.

DIALING SOUND

Back in the Bronx, nurse Lisette Rivera is making her last stop.

RIVERA: It's Lisette. I'm downstairs. I need someone to open the door for me.

QUE: This visit is to a girl with full blown AIDS who asked us not to use her name. The last time she was in the hospital, over Thanksgiving, was for a severe throat infection. To nurse Rivera's dismay, the infection is back.

RIVERA: Let me see, open your mouth. Ah, yeah. Stick your tongue out.

GIRL, PATIENT: Ohhh.

RIVERA: Yeah.

QUE: The little girl is painfully thin. She's 11-years-old, but she only weighs 33 pounds. She's been on a protease inhibitor for two months; but so far it isn't working.

What worries her doctors the most is her weight. They want to put her back into the hospital so they can put a feeding tube into her abdomen to bring up her weight. Her aunt says she just isn't interested in food.

AUNT OF PATIENT: She'll be all day without eating. Then when I do give her food, she starts crying and then she try cry (ph) and she throws it up. That's why she's so skinny.

QUE: What happens when you try to eat?

GIRL: My stomach is full.

QUE: Your stomach feels full. So you just don't feel like eating, is that it?

GIRL: No.

GIRL BEGINS TO CRY

QUE: As she begins to cry, her aunt gently picks her up and cradles her in her lap. She's tired, she explains, of all the doctors, shots and medicines. The girl's aunt read about protease inhibitors in the newspaper and begged Rivera to help enroll her niece in a research study so she could get the drugs.

And even though the medications haven't worked so far, she plans to continue giving them because there is nothing else.

I'm Vicky Que reporting.

EDWARDS: Tomorrow, NPR's Mandalit del Barco reports on AIDS in the Latino community in Los Angeles.

<Dateline: Vicky Que, New York; Bob Edwards, Washington, DC>
<Guest: >
<High: In Part Two of our week-long series, NPR's Vicky Que reports on the issue of whether to give children some of the new AIDS-fighting drugs. Protease inhibitors have proved very effective so far in adults, but remain unproven in children.>
<Spec: AIDS; Diseases>
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<End-Story: Protease Inhibitors and Children>
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By LAURAN NEERGAARD

Associated Press Writer

WASHINGTON (AP) -- Rosemary Johnson finally felt healthy thanks to powerful new AIDS drugs. But she was still in torment -- unable to give her sick daughter the same medicines because no one knew how they would affect children.

Since none of the three new and potent medicines revolutionizing AIDS care is yet approved for child use, pediatricians and parents have begun struggling on their own to determine safe doses -- fearing that otherwise the children will die waiting as drug companies study the question.

``I looked over to my daughter and thought, `How could I sit here and try to save my life and not my daughter's?'" Johnson, of Baltimore, angrily told government AIDS experts last week. ``We are not going to let our children die without a fight."

Under a pediatrician's care, Johnson's 9-year-old now is one of just a handful of children nationwide taking one of the new drugs. So far, she is doing well. ``I want other children to have this chance," Johnson said.

Drug makers say they're working hard to get the new drugs, called protease inhibitors, to children. They have studies planned for early 1997 on everything from liquid formulas to drug ``sprinkles" that parents would mix into applesauce.

The drug companies say children spit out earlier liquid formulas because they were too bitter. And the companies had problems getting the right drug absorption.

Still, ``in hindsight, perhaps we should have moved forward to get some experimental data" sooner, said Dr. Miklos Salgo of Hoffman LaRoche, maker of the first protease inhibitor, saquinavir.

The issue doesn't just touch AIDS. Eighty percent of prescription drugs are sold with no information on how safe or effective they might be for children.

A little more than 10,000 of the nation's half a million AIDS cases have been in children and teen-agers. Some 3,156 children under 13 and 1,452 teens are still alive and in need of medicine compared with tens of thousands of adults.

But doctors say it's unethical to ignore children just because there are fewer victims.

``AIDS kills children just like it kills adults," said Dr. Nancy Hutton of Johns Hopkins University's Children's Center. She wants drug makers to test new AIDS medicine in children as soon they test adults, changing decades of scientific practice.

Of the nine AIDS drugs sold, four of the oldest are approved for children.

But the new protease inhibitors are so effective for adults that pediatricians want to use them in children. They just don't know how. The Pediatric AIDS Foundation surveyed over 950 child patients and found only 74 taking proteases.

``I had parents who said, `Well, I'll just give my child some of mine,'" Hutton recalled.

That's dangerous, because the wrong dose can cause drug resistance. So Hutton furiously sought early data from drug makers to calculate her own doses of ritonavir, the only liquid protease sold, for six very ill children, including Johnson's 9-year-old daughter.

A few months later, all six children are doing well, although Hutton warns that she doesn't know how long the effect will last or what is the best dose.

Of the three proteases:

Merck & Co. began child testing indinavir in July 1995, hoping to seek Food

and Drug Administration approval for children and adults simultaneously. But one formula didn't dissolve properly in children's stomachs. Adult-sized capsules did fight HIV in children's blood, but not as much as they do in adults nor for nearly as long. Children probably metabolize the drug too fast, theorizes Merck's Dr. Paul Deutsch, who is hunting a better child's dose.

Ritonavir was created as a liquid for children, but Abbott Laboratories says it believes in ensuring a drug is safe in adults before testing children, something it says couldn't be done in the three years between ritonavir's discovery and its sale. A study in 46 children unveiled last summer suggests 500-800 milligrams a day is safe and may fight the virus; confirmatory studies begin by spring.

Not only did Roche's liquid saquinavir taste bitter, it didn't dissolve into blood properly. So Roche created tiny ``sprinkles'' of saquinavir that children would swallow in applesauce, providing just mild bitterness if they crunched the bits. Testing begins by spring.

The FDA's outside scientific advisers issued a stern warning to drug makers last week not to seek approval for any more AIDS drugs without at least preliminary data on children.

But the FDA says the only way to enforce that is to refuse to approve new AIDS drugs without child data -- unfair to desperate adults also awaiting the medicines.

FDA pediatrician Sam Maldonado says angry parents have more clout. Their activism, she says, ``creates more pressure than we can.''

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THE WALL STREET JOURNAL.

MARKETPLACE

Toddlers Take Drugs That Haven't Been Tested for Efficacy

Continued From Page B1

that poison control centers received 670,0
reports of over-the-counter drug problem
in young children in the five years throu
1989.

In the CDCP study, mothers of 8,1
children were asked whether they h
given their child an over-the-counter me
cation in the previous month. Cough/co
medications and Tylenol led the li
distantly followed by other pain relieve
and anti-diarrheal medications. Previo
studies have found that about half
mothers keep seven or more differ
types of medications on hand for th
children, the authors noted.

Well-educated, white women w
higher incomes were more prone to g
their children over-the-counter medi
tions. Those women might be better abl
afford to buy medications and be m
comfortable in treating their child
themselves, suggested Michael D. Kog
the study's lead researcher and an epi
miologist at the CDCP's National Cen
for Health Statistics.

Toddlers Taking Many Drugs, Mostly Untested

By Elyse Tanouye
Staff Reporter of The Wall Street Journal

MEDICINE

American parents have a very free hand in giving over-the-counter drugs to their young children even though many of the most popular children's remedies, especially cough and cold medications, may not work, a new study says.

The study, led by researchers at the Centers for Disease Control and Prevention, found that 54% of all three-year-olds had been given some over-the-counter medication during just one month in 1991. Cough or cold medications had been used by two-thirds of the children who received over-the-counter drugs. But the few tests conducted on these medications in children have found the drugs didn't produce any benefit, the researchers noted.

The children's over-the-counter cold remedy market has been growing fast, with sales rising about 25% a year to $170 million in 1993, estimates Kathryn Griffie, manager of the health care practice at Kline & Co., a market research firm in Fairfield, N.J. The top-selling cough and cold medications in 1993 were Dimetapp Elixir, Triaminic, PediaCare and Children's Tylenol Cold, Ms. Griffie says.

Despite the widespread use of over-the-counter drugs for children, industry and government officials acknowledge that the drugs largely haven't been tested in children to determine efficacy. The Food and Drug Administration doesn't require drug makers to test drugs in children—as it does for adults — before putting them on the market, in part because of ethical questions.

"Given that there's little data to show cough and cold medicines are effective, and given there may be side effects produced by these medicines in infants and children, it doesn't make sense to use these medicines for . . . benign and frequent infections like the common cold," says Anne Gadomski, a researcher at the Mary Imogene Bassett Hospital in Cooperstown, N.Y., and a pediatrician. "Without clinical trials, there's no way of knowing what dose is appropriate or effective [in children]," she says.

In an editorial accompanying the study in today's issue of the Journal of the American Medical Association, Dr. Gadomski suggested that "the high use rate of these medications may be a tremendous waste of money and may unncessarily expose children to toxicity."

In addition to ethical issues, little drug testing is done on children because many pediatricians have been reluctant to participate in such studies, the FDA says. Drug research often involves drawing blood and other uncomfortable procedures that are hard to explain to children. "Children have been called jokingly the therapeutic orphans of OTC and prescription drugs; we just don't have the information," says Michael Weintraub, head of the FDA's over-the-counter drug division.

In the next few months, however, the FDA will formally explore whether and how to conduct clinical trials using children, he noted.

In the meantime, Dr. Weintraub said, "all we can offer the mothers and fathers who are treating the children is the label: We say, be very careful, be sure the child needs the drug, make sure to give the drug according to the dose on the label."

One of the few drugs that has been well tested on children is acetaminophen, which studies have shown does reduce fevers and relieve pain in children, the researchers note. Tylenol, which contains acetaminophen, was used by two-thirds of the children in the study who took non-prescription drugs.

"Nonprescription, over-the-counter cough and cold medicines offer safe and effective relief of symptoms," says the Nonprescription Drug Manufacturers Association, an industry trade group. Although OTC drugs don't cure, relieving symptoms is "a useful goal," it adds in a statement.

Whitehall-Robins, a unit of American Home Products Corp. and maker of Robitussin and Dimetapp, said in a statement, "We note that our cough/cold medications have a long history of safe use and consumer acceptance."

Although over-the-counter medications are generally considered to be safe, the CDCP researchers point out that they can cause adverse side effects. Parents could also overdose their children. They note

Please Turn to Page B6, Column 2

Children's Medications

Over-the-counter sales in millions

	1983	1993
Pain relievers	$85	$185
Cold preparation	20	170
Cough syrup	0	30

Source: Kline & Co. estimates

UNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION
ANTIVIRAL DRUGS ADVISORY COMMITTEE
MEETING

FRIDAY
22 NOVEMBER 1996

to the parents of HIV-infected children. I want you to talk to the children, some of the voices you hear now.

I want you to talk to HIV-infected pregnant women, and I want you to explain to them why they are the only ones denied these new life-saving drugs. And then I want you to look at them as they get sicker and sicker and explain why in this epidemic their lives are less important than others. Thank you.

CHAIRMAN HAMMER: Thank you.

The next speaker is Bonita Judan from the AIDS Policy Center for Children, Youth, and Families.

MS. JUDAN: Mr. Chairman and members of the advisory committee, my name is Bonita Judan, and I am the mother of a three-year-old, and we both live in Atlanta, Georgia.

I come before you today filled with hope and fear, and to ask for your help in two areas. I hope you will advance drugs like rescriptor that have shown early hope to improve the lives of people living with HIV and AIDS. I also hope that you will recognize that a majority of children and pregnant women with HIV are not receiving promising AIDS therapies like protease inhibitors or rescriptor

because pharmaceutical companies have been slow to determine how safe doses and actual ways that children can take these drugs, therefore, these drugs have not been approved by the FDA for children and pregnant women. Without FDA approval, children and pregnant women do not have real hope to use these drugs.

As a woman living with HIV, I have been greatly helped by the latest advances in AIDS treatment. In my case, the combinations of new AIDS drugs has given me new hope that I will be able to have a healthier life with my son and our family.

This has been the case for several women I know, both in Atlanta and around the country. However, as drugs like rescriptor are being developed, approved, and distributed to people with HIV and AIDS, there are thousands of people who are not being allowed to share my hope of a healthier life. These people are our children living with HIV and AIDS, as well as pregnant women.

Of the nine drugs that have been approved for use in HIV infection, only three have been approved for use in children, yet women and children are the fastest growing group of people in the country to be affected by HIV and AIDS.

How then can companies who have a long

history of making drugs that can be safely used by children develop and ask for a drug to be distributed to the community when it has ignored a vital part of the community? How can these companies and the FDA say that the number of children with HIV and AIDS is too small to create a trial on drugs for them? How can these companies turn a blind eye to the thousands of children with HIV right under their noses?

As many other woman who has been helped by the combination therapies of protease inhibitors with ZDV or ddI or ddC, they all ask why these treatments cannot be given to their children who have HIV. No one can give them an answer except to say they are not approved for children as of yet.

Mr. Chairman and members of the committee, I am here today to tell you that no mother is going to allow her child to suffer and die if there is a treatment that has helped her with her illness. Mothers on their own are giving their children these new drugs. Unfortunately, they and their providers do not know what is a safe dose or what is the best form in which to take the drugs because the companies have not performed sufficient clinical trials to children.

These companies have waited until all the data is complete in the adult population before they

began to study children. This has allowed thousands of children to die before they were able to try a new hope for life. While the children are getting these new AIDS drugs via their mother, then what is the problem?

It is one thing to have a life-saving new drug like rescriptor be created. It is another thing to have the drug actually in your hands. Women and children have four ways to access AIDS drugs; cash out of pocket, insurance program either private or Medicaid, state AIDS drug assistance program, or the ADAP or pharmaceutical company studies.

These drugs, however, are very expensive and there are not too many women who can afford to pay thousands of dollars each month for drugs alone. Insurance programs and ADAP programs require that a drug be approved by the FDA for use by women and children before they will pay for the drugs. Otherwise, the state has to offer to pay for the drug.

A mother has to hope that her state will have enough money to provide these drugs. In my case, I am on a drug study with saquinavir. If I weren't on this study, I wouldn't be able to afford the drug because Georgia's Medicaid program does not pay for saquinavir, and I don't qualify for the ADAP program.

Even worse, since protease inhibitors have been approved by the FDA for children, these drugs are not part of the Medicaid or ADAP program for children. This is not fair. This is not right. This is flat out wrong. Why are mothers having to watch the life die out of their children's eyes, while mothers themselves are given a new lease on life?

Why are life-saving treatments only being developed for those over 18? How are we to have a nation of healthy adults if our children do not -- are not given the chance to grow into healthy adults?

We all hope for the day that there will be a cure for HIV and AIDS. We all hope that mothers will not have to watch their children die from HIV. We hope that rescriptor will continue to help people with HIV and AIDS live healthy lives. We hope that rescriptor will be part of the treatment plans for all people with HIV and AIDS.

We also hope that rescriptor will be the last AIDS drug that comes before the FDA for approval without dose and safety information for all children. I believe that when drugs are in trials and being used for adults, it should happen the same for kids as well. Thank you.

CHAIRMAN HAMMER: Thank you.

and careful monitoring of untested combinations. While Pharmacia and Upjohn has been responsive to the activist community on the issue of drug interaction studies, other companies have not.

The FDA has an opportunity to take a leadership role in assuring that pharmaceutical companies cooperate with the community and with other members of their industry to address this important issue. Act Up Golden Gate will continue to investigate the issue of drug interactions. If the FDA fails to address this situation, then it will be left to activists such as ourselves to do so, drug-by-drug, combination-by-combination. Thank you.

CHAIRMAN HAMMER: Thank you.

The next speaker is Deborah Scheer.

MS. SCHEER: Good morning. My lovely and wondrous son, Dillon, and I live on the Russian River in Sonoma County in northern California. Sonoma County has the largest population of people living with AIDS in any rural county in America. I chose to live there because my son has HIV, and I felt that the services in the community would help support both of us.

As it's happened, we've been embraced and surrounded by many people with deep compassion and

direction. Our new friends are proactive and front runners with the relatively new HIV treatment therapies and from the studies done with adults and the new drugs. Their doctors are informed about the drugs' efficacy, dosing, side effects, et cetera, and, therefore, are better able to help their patients make treatment decisions. Their doctors understand viral load testing results and use it as an important diagnostic tool in keeping the virus under control.

With the viral load test and a combination therapy, our friends are doing a lot better. Through the passing summer, Dillon and I watched our friends feel stronger and more hopeful. For many of them it's the first time since their diagnoses that they are thinking about their future and the possibility of growing old.

It was truly a joyous summer, and Dillon and I enjoyed and shared the excitement with our friends. But then came the end of the summer, and I learned that our children and their families can't, and don't, have the hope that the adult community has. Our children have only three drugs approved for pediatric use. This is less than one-third the availability for adults.

The drug that we want approved today,

delavirdine, will be the tenth drug to use by HIV. However, even this drug doesn't have any pediatric data. And while they've been doing viral load testing on children for a while, the pediatric HIV doctors haven't been informed of their findings and what this means in children.

My son, Dillon, is a bright and active child with few symptoms thus far. He had a wonderful summer, and I hope he has many, many more. But Dillon has already lost several friends, young friends, and a foster baby brother to HIV. And at the end of this summer, I learned that three of Dillon's closest friends, Sam, Josh, and Sammy, had rising viral loads and their CD4 counts were dropping.

Sam's mother shared with me her conversation with his doctor. The doctor was crying with her over the results of the lab tests. What could possibly make this doctor cry? Could it have been that she didn't have new drugs to treat Sam? He had already exhausted the only three drugs available to him. Or perhaps it was her fear of treating Sam with drugs that have not yet been tested on kids and, therefore, she could have been taking an incredible risk with his life. Or was it that she could see his end coming because she had nothing to offer him, and

it was tearing her apart.

Josh's parents, another friend of Dill's, have chosen not to disclose his diagnosis to him to protect him from additional stress in his already complicated life. His mother has been frantic over the last couple of years. Josh has a T-cell count of under 40 and a rising viral load. I'm sure to ease his mother's absolute dread, Josh's doctor rarely points to the fact that they really don't know what viral load results mean in children, and that clinically he looks great, so don't worry.

Well, I need to ask would, or could, a doctor who is treating a child with leukemia tell his mother that though the lab tests were showing disease progression, not to worry because the child looks great. I don't think so.

Josh deserves, and needs, combination therapy, but his doctor won't put him on any of the other five or six approved drugs because they haven't been tested for dosage, side effects, and efficacy in children.

The grandmother of another one of Dillon's friends, Sammy, drives him eight hours a month for lab tests. She returns home with horrifying results and with the same treatment that has been failing to stop

the virus from further destroying his immune system. Sammy is a bright and beautiful six-year-old boy who goes to the schools in his community and talks about HIV, how it impacts him and how the students can protect themselves.

He and his grandmother are well known and loved in their community. Little Sammy is a hero, and it looks like he is going to die.

My son is strong and healthy right now. I love him with all my heart, but love will not stop the virus. I can't protect him alone, and I need your help. We had a chance to love a little baby, Justin. All my love could not protect him from HIV. HIV claimed his live on his fifth month birthday, and with so few treatment options for children, Dillon is not walking far behind Sam and Josh, Sammy and Justin.

Without major changes in our whole system now, we are setting up Dillon and his friends and many other children for very, very short lives. This is unacceptable to me and families across the nation, let alone all the families from other countries who look to the United States for therapies and direction. Even if you could be persuaded to act now, start making changes now, I hope to God it's not too late for Sam and Josh and Sammy.

We need six different things to happen to save Sam, Josh, Sammy, Dillon, and all the other HIV-positive children. One, we need safety studies in children to begin immediately upon preliminary efficacy data in adults, regardless of formulation. For example, if a company doesn't have a suspension, it can still start research for young children who can swallow pills and capsules.

Two, our children need equal and early access to promising therapies to expanded access programs such as compassionate use and parallel track.

Three, we need industry sponsors to approach the FDA for revised labeling as soon as safety data is available on any pediatric population. We want conditional approval given to drugs -- excuse me.

Four, we want conditional approval given to drugs when a sponsor seeks approval without pediatric data.

Five, using existing technology, pharmaceutical sponsors should seek more palatable suspensions or ways of making them more tolerable, especially in young children.

And six, so that pediatricians will have a better understanding of the practical application of

viral load results as a monitoring tool, the Secretary of Health and Human Services should convene a task force to compile, interpret, and disseminate existing pediatric viral load data.

On behalf of my son and all the children with AIDS in America, I thank you for your attention, and urge you to address these issues with speed and compassion.

CHAIRMAN HAMMER: Thank you very much.

The next presenter is Emily Gordon, director of the Just Kids Foundation.

MS. GORDON: Thank you. The Just Kids Foundation is a group of mothers, caregivers, and health care professionals dedicated to improving the quality of life for HIV-positive children adolescents. Our goal is to educate and empower parents so that they can provide their children with the longest lives possible.

We have an extensive telephone support and peer support group,we have monthly meetings, we have empowered parents to the point where they can speak out and organize at international conferences, at community advisory boards, at ACTG meetings, and I had hoped today to be able to bring one of the parents to speak to you rather than myself. Her name is Sandra

	91	96
"New Drugs"	26	53
% potential Reds use	15	40
Some labeling	7	10
Phase 4 studies required	7	13
Executed studies	1	

David – 3, 5, 10 yrs later academic researchers developed data and you can go to literature.

Phil Pizo —

Regulations – make reg real
approve for adults
enforce by court order. —

New drugs – create a presumption that the study would need to be done first.

– burden on them to explain why studies shouldn't be done.

Companies that have done it. —

Agaron – on protease inhibitors
- failed for first 3 proteases

Pand – Grade 6 level of science – not breakthrough science. —

Women / pediatrics / elderly. —

Looking at drugs on the market. — ~~will not~~ ~~to~~ look at drugs ~~on~~ the market —

Pediatric AIDS Foundation

Research Division

Hope for Children with AIDS

February 23, 1996

The Honorable David Kessler, M.D.
Commissioner
Food and Drug Administration
5600 Fishers Lane, Room 1471
Rockville, MD 20857

Dear Commissioner Kessler:

We have been informed that Abbott Laboratories will be testifying before an advisory committee of the Food and Drug Administration on February 29, 1996, on behalf of its drug, ritonavir, a protease inhibitor. We have also been informed that Abbott will present no data on HIV-infected newborns, infants, or pregnant women. While we will join in celebrating any advance in therapy for people with AIDS, we are profoundly disappointed that once again the youngest patients with HIV infection will be left out of such progress and that they will be forced to run the risk of needless infection, illness, and death because of a lack of will by industry and regulators alike.

We emphasize that this is not a matter of convenience or academic interest. The delay in approving AZT for use in pediatric populations delayed the eventual ground breaking research showing that the administration of the drug to pregnant women and their infants could prevent infection in these infants. We estimate that this delay alone resulted in 3,000 unnecessary infections in children. Most of these children, if not all, will ultimately die of this progressive disease. This is over and above the number of infected children who died prematurely because the drug was not available for their use. Since all accounts make it appear that protease inhibitors like Abbott's are even more potent than AZT, the failure to develop indications for pregnant women and infants will perpetuate and enlarge these tragedies.

This is wrong.

It is not simply wrong in the case of Abbott's drug; it is wrong in case after case after case of AIDS and non-AIDS treatments in trial and before the FDA. We are at a loss to explain how this problem remains unsolved.

CO-FOUNDERS: Susan DeLaurentis/Elizabeth Glaser/Susan Zeegen
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In a meeting of the National HIV Task Force in October 1994, the FDA publicly committed to requiring a pediatric plan from all pharmaceutical companies developing drugs for serious and life-threatening diseases in children. This mechanism clearly has failed.

In other settings you have publicly committed to reducing approval requirements for pediatric indications as a means of inducing industry to conduct the limited trials necessary for pediatric indications. This incentive has also clearly failed. At the White House Conference on AIDS in December, you also acknowledged that efforts had been made by the agency to ensure that pediatric data were gathered. At that time, you yourself acknowledged that this effort had failed.

A most critical need for potent anti-HIV therapy exists in pregnancy and the population of infants under three months of age. As President Clinton has said, the elimination of HIV infection in children is an achievable goal and is among the highest priorities for the Administration—and obviously for the pediatric HIV/AIDS community.

The specific failure of Abbott Laboratories to conduct its own trials or even provide ritonavir for pregnant women, newborns, and infants, after repeated requests from pediatric investigators, is particularly difficult to understand. Abbott Laboratories and its subsidiaries have extensive expertise in infant formulas, nutritional products and drugs; a market with over three billion dollars in sales. With their stated commitment to pediatrics, they should be able to initiate studies in infants in sufficient time to include data for an NDA, especially since the requirements have been abbreviated.

We request that the final approval by the FDA of ritonavir be made contingent upon the submission of an obstetric and pediatric protocol which includes pregnant women, infants and newborns and the identification of investigators who will perform the necessary studies. This requirement will not delay approval of the drug for adults, but it will demonstrate that both the FDA and Abbott recognize the right of women and their infants to lifesaving therapy in a timely manner. We believe that this is our only course, in view of the failure of the FDA to elicit a pediatric plan for pregnant women, newborns, and infants, the failure of Abbott to make ritonavir available to pediatric investigators to study these populations, and the subsequent, continued, and already inevitable loss of life and health of HIV-exposed and infected infants.

We also request that you meet with us at your earliest convenience to discuss requirements, incentives, and structural changes that will prevent this problem from recurring in infants with HIV, with other infectious diseases, with cancer, and with other life-threatening and serious conditions. The status quo is unacceptable.

Sincerely,

Arthur J. Ammann, M.D.
Director of Research
Chairman, Health Advisory Board
Pediatric AIDS Foundation

(Signatures on file)

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AJA/ak

Public Testimony to FDA Drug Advisory Committee
November 22, 1996
Gaithersburg, Maryland
Arthur J. Ammann MD

I want to begin by reminding this committee that the FDA is the result of the Federal Food, Drug and Cosmetic Act established by congress in 1938. It followed the tragic deaths of 107 children from the ingestion of an unsafe drug. Congress mandated that drugs for use in children be safe. It was not their intent to exclude children form access to life saving drugs. Further, the FDA has recently stated, "...an application for marketing approval should contain data on a reasonable sample of patients likely to be given a drug once it is marketed. This conclusion, stated explicitly in a guideline on the need for data in both genders, applies equally to age subgroups, including pediatric and geriatric populations. FDA may refuse to approve an application that fails to contain sufficient information to determine whether the product can be safely and effectively used in populations likely to receive it." (FR December 13, 1994 , 64243.)

Now I want to show you the scoreboard for approval of drugs to treat HIV infection in infants, children and pregnant women since the very first antiretroviral drug was approved.

AZT was approved for adults in 1987. After a two year delay it was approved for children. ddI was approved for both adults and children in 1991, proving that drug development could be performed simultaneously in adults and children, but to this day, now four years later, approval for infants, the youngest of the population affected, has not been obtained even though clinical studies have shown that ddI is more effective than AZT. ddC was approved for adults in 1992 - - but not approved for children. D4T was approved for adults in 1994 - - but not for children. There was a ray of hope in 1996 when 3TC was approved for adults and children simultaneously. Now in 1996 we have witnessed an explosion of approvals for the greatest number and the most powerful antiretroviral drugs in the history of the HIV epidemic. And they have been approved in record time for adults - - but not for children. Saquinavir was approved for adults in 1995 - but not for children. Ritonavir was approved for adults in February, 1996 - - but not for children. Indinavir was approved for adults in April, 1996 - - but not for children. Nevirapine was approved in June 1996 for adults and yet, in spite of 4 years of studies in infants and children - - it was not approved for them. And today, you are reviewing delaviridine with data only in adults. In less than one year this advisory committee will have approved five of the most potent antiretroviral drugs in history while none has been approved for children. The score since 1987? Ten life saving drugs approved for adults. For children , three. The children of this nation and the world have lost in game of survival. And the gap increases by the months. And what of the score for HIV infected women who are pregnant and who neither wish to see their disease progress by withholding unapproved drugs nor to have an infected infant - only one approved drug - - AZT. Their choice? Stay on effective combination therapy to control their disease during pregnancy and risk unknown effects on the fetus, stop effective therapy for themselves and risk progression of disease or development of viral resistance, or abort their infant.

How many children are being denied life saving anti-HIV treatment? We have just completed a survey of over 950 children, eight years of age and older, who were infected at birth. Only 74, about 10%, were on a protease inhibitor. The news from the International AIDS Meeting in Vancouver reporting dramatic recovery of immunity and long term suppression of HIV with combination therapy is meaningless to our HIV children who are relegated to monotherapy or the least potent drug combinations. Yet, their virus is the same in infants and adults and their outcome without treatment the same - - death. What is different about children is that they die faster and that they cannot access drugs to treat HIV - - because most of the pharmaceutical companies have failed to do the required studies and the FDA has failed to require them and the pediatric ACTG has failed to move quickly in performing phase 1 studies. And if the thousands of the children of this nation cannot access these drugs, then tens of thousands of children in other countries who look to us as a compassionate nation cannot access them either. As a result, tens of thousands of children will become infected and die each

year and tens of thousands of children already infected will progress rapidly to death. Everyday physicians refuse to prescribe unapproved life saving drugs. And every day insurance companies refuse to reimburse for off label use when physicians decide to take the risk and prescribe these drugs. You can and must change this. Pregnant women and infants and children cannot remain therapeutic have-nots.

Today you can begin to solve these ethically and therapeutically unacceptable circumstances. You are here to review the data for a drug to treat HIV. You are responsible for determining whether a drug which is to be used in all populations, and I quote from the Food Drug and Cosmetic Act statutory and regulatory document, "contain data on a reasonable sample of patients likely to be given a drug once it is marketed." And in the FDA's own words, this applies "equally to pediatric populations." You have no option but to recommend enforcement of these rules. HIV-infected children and pregnant women cannot be the only population denied life saving drugs, denied compassionate use, denied entry into drug lotteries.

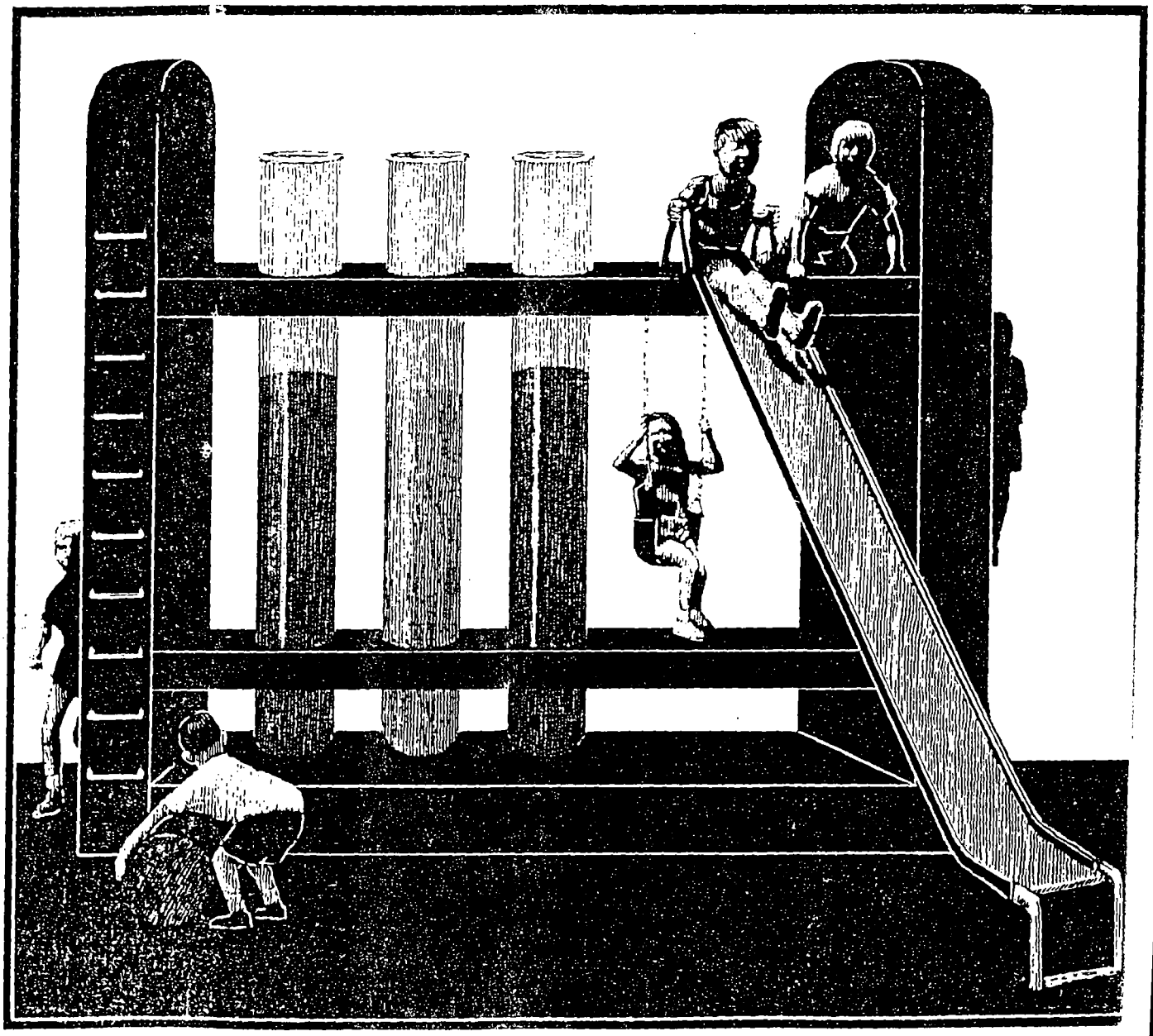
We, the pediatric HIV/AIDS community, are trying to do everything we can. We are talking to pharmaceutical companies. We present recommendations to right people for solutions. We participate in advisory committee meetings such as this. We made the needs known before the right people at the National Task Force for AIDS Drug Development. We support incentives for pharmaceutical companies. We supported the Better Pharmaceutical for Children Act. We have made the needs known to you.

Today we have five specific recommendations for you. First: approve this drug for use in adults. Second, as a condition of approval for use in adults, require pediatric safety and pharmacokinetic data for phase 4. Third, if the company does not perform the required pediatric studies, go to court to seek an injunction requiring them to do so. Fourth, review all ongoing drug research for which you have given permission for human trials. When you find a drug that has potential pediatric use for a chronic or serious life threatening condition, review the research plan to see if the company is making adequate progress toward having pediatric safety and pharmacologic data at the time it seeks approval. If it does not, initiate warnings to the company that you will not be able to grant approval for adults only. Fifth, require that all compassionate use protocols for drugs which have a pediatric use include infants and children.

Commissioner Kessler, Dr. Valentine, members of the advisory committee, FDA staff, members of the pharmaceutical industry, members of the academic community - - I want you to take these recommendations seriously. I want you to talk to the parents of HIV-infected children. I want you to talk to the children. I want you to talk to HIV infected pregnant women. I want you to explain to them why they are the only ones denied these new life saving drugs. And then I want you to look at them as they get sicker and sicker and explain why, in this epidemic, their lives are less important than others.

July/August 1991
FDA Consumer
p75-77

Why FDA Is Encouraging Drug Testing in Children



Testing drugs in children is more complicated than in adults.

Paula Botstein, M.D., is deputy director of FDA's Office of Drug Evaluation I. As a pediatrician, she takes more than a casual interest in the development and testing of drugs for children. She was recently interviewed on this subject by Lawrence Bachorik, a speech writer in FDA's Office of Public Affairs. An edited text of that interview follows.

Paula Botstein, M.D.

Q. *Dr. Botstein, the FDA has been focusing more attention recently on drugs for children. Why is that?*

A. There's a simple answer to your question: Pediatricians are infiltrating the FDA.

Q. *(Laughing) Perhaps. But what's the real reason?*

A. It's that children need medicines. Some drugs have already been well studied and approved for use in adults. To use one of these drugs for the same disease in children, it's important to figure out what doses work best in kids and what kinds of adverse reactions are likely to occur.

Other drugs are for diseases specific to children, and these need adequate and well-controlled studies of their effectiveness and safety.

Q. *Can you tell me about the current situation? Are there lots of drugs approved for adults that are perhaps not well understood or well labeled for use in children?*

A. The majority of drugs have been studied in adults and labeled for use in adults. Their physician labeling includes a disclaimer that says safety and effectiveness have not been established for use in children. That's the usual and common situation.

Q. *So it's much more often the case that drugs have not been studied in children?*

A. That's right. Even a drug like morphine, which is a standard, necessary pain medicine, has not had explicit labeling for use in children.

Q. *Why haven't these drugs been studied in children?*

A. In 1963, Dr. Harry Shirkey coined the phrase "therapeutic orphans" to describe children. Shirkey was alluding to the plight of children for whom many drugs have not been studied. The reasons for this are complicated. Pharmaceutical firms have had little incentive to study drugs for use in children because the population—and therefore the financial return—is likely to be small. Moreover, testing drugs in children is more complicated than in adults. Pediatric drug trials are often done in children's hospitals and may be more involved because people take pains to make sure that parents and children understand what's going on. Children are less likely than adults to be used as "normal" volunteers in clinical trials; most children in trials have the disease in question.

People are more reluctant to use a drug in children if there is no potential benefit to the specific child.

Q. *But is this really a problem? Why can't physicians simply give a child less of a particular drug than would be given an adult?*

A. It's not that simple. Young children may metabolize or absorb drugs at a different rate from adults, and therefore a suitable dose is difficult to estimate from the size of the children. The same is true for older adults, compared to younger adults. In recent years, FDA has paid more attention to establishing specific dosages for elderly patients, and we are now doing the same for children.

In the past year or two, we have seen a definite increase in the number of new drugs approved specifically for children.

Q. *So how do pediatricians know the proper dose of a drug if it is not specifically labeled for use in children?*
A. That question goes to the heart of why FDA is encouraging clinical trials in children.

The answer is that there is no standard source of information. Pediatrics textbooks usually give drug dosages, but the source and reliability of the information are seldom specified. Mostly, pediatric doses of drugs that have not been formally studied in children are simply established by experience. Some drugs are used all the time in children. Anesthesia drugs would be a good example. They may not be labeled or approved specifically for children, but children routinely need major surgery. So physicians build up the experience in using the drugs. It's not the ideal way.

Q. *You've established that many drugs currently approved for use in adults are not specifically labeled for use in children. But you mentioned a second category of drugs—new drugs specifically for childhood diseases.*
A. Children have various types of diseases, the most common kind being acute infectious diseases—for which they need antibiotics, anti-fungal agents, and anti-viral agents. Some antibiotics are in fact studied and labeled for use in children—for meningitis or otitis media [middle ear infection], for example—while they are being studied for adults. But other major antibiotics, such as piperacillin or metronidazole, have no labeling for use in children.

Q. *What are some other types of pediatric diseases for which adequate testing of drugs in children might be an issue?*
A. In addition to the acute diseases, there are the chronic diseases of childhood, such as seizure disorders. Children also can have congenital diseases, such as cystic fibrosis and enzyme deficiencies.

Q. *Are the drugs on the market without labeling for pediatric indications being used illegally?*
A. No, doctors may legally use approved drugs for whatever uses they think appropriate, according to their medical judgment.

Q. *As a pediatrician, you must be concerned. What sort of things is FDA doing to make more drugs available for children?*
A. We're doing a number of things to be active in this area. As we meet with drug companies to discuss the drugs they are studying, we are encouraging them to test those drugs in children when appropriate. We are finding that companies are often responsive to the need. We are changing our internal procedures to foster the availability of new drugs for youngsters. We routinely ask our FDA drug review divisions to sift through their INDs [the formal requests to test a new drug] to identify drugs that might show particular promise in children. It is these drugs with potential pediatric uses that we encourage drug companies to develop for children, either before or after approval for use in adults.

We have created what we call a "pediatric page" as part of our review of new drug applications. This is a summary of what is known about the drug from the perspective of pediatrics: whether it has been tested in children, what uses are promising, and the like. It's basically a management tool, so that FDA's own people will think more in terms of drugs for children—and to explore this potential with the drug sponsors.

Q. *Those steps might help with drugs now under development and testing. What about drugs already on the market?*
A. We have a way of dealing with that, too. Currently, according to the regulations, no drug may be labeled for use in children unless it has been subjected to "adequate and well-controlled studies" in children. But the regulations also give FDA the authority to waive that requirement, if there have been adequate and well-controlled studies in adults.

Q. *Under what circumstances will FDA consider granting this waiver?*
A. We have specific criteria. First, the disease has to be the same in adults. Then, the drug must have been well stud-

Perhaps the most important thing parents can do is to consider allowing their own child to participate in clinical drug testing.

ied in adults. To use the drug appropriately in children, you need to have information on dosing and on adverse reactions, which may be different in children.

Q. *Are there any recent examples?*
A. We have granted two waivers of controlled trials in children. The first one, granted in 1990, was for AZT [zidovudine, or Retrovir], which had been previously approved for treating AIDS in adults. In January of 1991, we granted a waiver for ondansetron—a new drug for nausea and vomiting from cancer chemotherapy—in children at the same time we approved it for use in adults.

Q. *Is this kind of waiver permanent?*
A. Yes, for these drugs. We granted the waivers because we thought there was adequate information from available sources to give dosing for children and for appropriate use of these medically important drugs.

Q. *The FDA recently proposed a regulation requiring drug firms to include a "geriatric use" section in drug labeling for physicians. Would something like that work for children's drugs as well?*
A. Absolutely. We are already at work on proposed regulations that would revise the present pediatric use section in physician labeling for all new drugs to allow use of information that is not from controlled trials—if we think it appropriate. The waiver is an interim solution.

Q. *Have the FDA's increased efforts begun to pay off?*
A. We are very encouraged. In the past year or two, we have seen a definite increase in the number of new drugs approved specifically for children. FDA approved two new drugs for pediatric diseases in 1990, and we have already approved one this year. Exosurf is a pulmonary surfactant for respiratory distress syndrome in newborn babies. Adagen is an enzyme, ADA, to replace an enzyme missing in children with a severe immunodeficiency. Chemet is an oral drug for treatment of lead poisoning in children. FDA has classified all three as important new therapies.

We are seeing a burst of pediatric studies; other drugs for pediatric diseases are being studied or are close to approval.

Q. *Do you see any areas where there is a particular need?*
A. One in particular stands out: drugs for newborns. With the advent of neonatal intensive-care units and increased survival of tiny babies, we are seeing the need for new drugs to treat these small creatures. One success involves the pulmonary surfactants, drugs that help the survival of premature infants whose lungs have not yet fully developed. Pharmaceutical manufacturers have been vigorous in developing surfactants. We at FDA have considered it important to make these life-saving therapies available as rapidly as possible. We approved two treatment INDs for therapy before approval, and the first surfactant was approved for marketing in a near-record five months after an application was submitted.

Q. *Dr. Botstein, what should parents do if they have any questions about drugs their children are taking?*
A. If parents have any questions about drugs, such as the proper dosage or possible side effects, they should always check with their physician or pharmacist.

Q. *Can parents do anything to help make more drugs available for children?*
A. Perhaps the most important thing they can do is to consider allowing their own child or children to participate in clinical drug testing if the opportunity is available. People often think of the practical difficulties—such as the need to draw blood samples—of studying drugs in the young. But we have found that parents are often eager to have their children participate, especially if they feel they can help family members or other children. ■