[New York Times, Letters to the Editor, February 1995]

…ban. That is so.
…ould be asking Presi…
…on. SCOTT NATHANSON
…armament Campaign Organizer
Peace Action Education Fund
Washington, Feb. 8, 1995

Include Cluster Bombs

To the Editor:

"Lifting the Land Mine Curse" (editorial, Feb. 8) identifies the problem of land mines and proposes

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TITUS PEACHEY
Lancaster, Pa., Feb. 9, 1995

We Still Need a Strong Food and Drug Agency

To the Editor:

"F.D.A. Becomes Target of Empowered Groups" (news article, Feb. 12) exposes attacks calculated to weaken and even dismantle the Food and Drug Administration.

Those who would do so should review the history of the sedative drug thalidomide.

From 1957 to 1961 it was taken by pregnant women for morning sickness, but it had an unexpected side effect that resulted in 8,000 cases of babies born with malformed arms and legs.

Virtually all of those tragic cases occurred outside the United States. Dr. Frances Kelsey of the Food and Drug Administration had virtually singlehandedly prevented marketing of the drug here despite pressure from irate American pharmaceutical companies, one of which distributed free samples to physicians and thereby caused a number of indigenous American cases.

Before the Food and Drug Administration was strengthened as a consequence of the thalidomide disaster, there had been considerable numbers of now-preventable deaths from even headache remedies and antibacterial agents.

A decade before the strengthening of the F.D.A., antihistamines hit the market like a tidal wave and within six months had been taken by millions of Americans. Luckily, there were no disastrous unpredicted side effects; if there had been (especially if delayed, preventing their early recognition) those antihistamines could have crippled the nation.

Pharmaceutic companies are Jekyll-Hydes that create many wonderful remedies, but are dangerously impatient to market their new products. That is why we need a strong F.D.A. JUSTIN DORGELOH, M.D.
Oakland, Calif., Feb. 12, 1995

The writer retired as associate clinical professor of pathology, University of California Medical School.

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EDWIN M. WOLF
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York City to provide a lawyer in each arraignment part to handle misdemeanors is consistent with that mandate, and may result in people being arraigned minutes sooner. However, the delay of hours and days must be addressed by asking the police to fulfill their constitutional obligations. DANIEL L. GREENBERG
Exec. Director, Legal Aid Society
New York, Feb. 9, 1995

NYT
The New York Times Company
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Too Harsh a Sentence For Convicted Juvenile?

To the Editor:

A Feb. 9 news article gives the strong impression that vicious murderers in a New York court case received a sentence of only 3⅓ years. It takes a careful reading of the article to learn that only one of the defendants was sentenced.

Tony Wilkins, who was 15 when he participated in two robberies, was, according to the article, sentenced to 3⅓ to 10 years with a recommendation of no parole.

Thus, it would seem that his chances of serving 10 years in state prison are more likely than his serving 3⅓ years. Further, it appears from the article that Mr. Wilkins was not armed (the article would certainly have mentioned it if he was) and clearly did not shoot or kill anyone.

A 10-year sentence for a 15-year-old participating in two robberies, unarmed and not injuring anyone himself does not seem insufficient to me. BENJAMIN ZINKIN
New York, Feb. 9, 1995

file FDA

FAREWELL MEETING WITH DAVID KESSLER
February 27, 1997

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

I. PURPOSE

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

II. BACKGROUND

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

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

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

III. CLOSED PRESS

IV. ATTACHMENTS

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

PROPOSAL TO ADDRESS THE LACK OF PEDIATRIC LABELING FOR DRUGS

BACKGROUND

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

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

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

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

PROPOSAL:

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

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

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

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

Pediatric Corner

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

By L. Miriam Pina, M.D.

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

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

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

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

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

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

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

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

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