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Elizabeth Drye
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FOLDER TITLE:
FDA Reform 1996 [1]

2014-0046-S
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P1 National Security Classified Information [(a)(1) of the PRA]
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b(4) Release would disclose trade secrets or confidential or financial information [(b)(4) of the FOIA]
b(6) Release would constitute a clearly unwarranted invasion of personal privacy [(b)(6) of the FOIA]
b(7) Release would disclose information compiled for law enforcement purposes [(b)(7) of the FOIA]
b(8) Release would disclose information concerning the regulation of financial institutions [(b)(8) of the FOIA]
b(9) Release would disclose geological or geophysical information concerning wells [(b)(9) of the FOIA]

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

14-Feb-1996 12:15pm

TO: Elizabeth E. Drye

FROM: Christopher C. Jennings
Domestic Policy Council

SUBJECT: RE: 4:30 FDA reform mtg.

I have an invited for 4:30 in room 350. Maybe it would be good if I did come and sort of hand this issue off to you in their presence? (At least, day to day stuff, etc.?) I do have a 3:30 to 4:30 conference call that could run late, but I will do my best to get there if you think this would be a good idea...

cj

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Washington DC 20204

MAR 28 1996

Senator Nancy L. Kassebaum
Chairman
Committee on Labor and Human Resources
United States Senate
Washington, D.C. 20510

Senator Edward M. Kennedy
Ranking Member
Committee on Labor and Human Resources
United States Senate
Washington, D.C. 20510

Dear Senators Kassebaum and Kennedy,

I am writing to express my very serious concern regarding certain of the actions taken yesterday by the Labor and Human Resources Committee during consideration of S. 1477, the Food and Drug Administration Performance and Accountability Act of 1995. We are committed to working with you to reach consensus on reform legislation that would accomplish our mutual goal of improving FDA's performance and accountability while at the same time preserving and strengthening the Agency's ability to protect and promote the public health. While we have made progress toward that goal, the bill as amended raises serious concerns. I am disturbed about a number of the provisions in this bill, but will focus on three of the Committee's actions from yesterday that are the most problematic.

Privatizing All Device Review Through A Mandatory "Pilot" Project

First, the Committee adopted an amendment that would require the Agency, within one year of enactment, to allow third party review, at the request of applicants, for all device applications. I understand that this provision was described as creating a pilot project for third party review, and that the Committee was informed that the Agency has been involved in the negotiation and preparation of the amendment. That is not the case. FDA did not participate in the development of this amendment.

Turning to the substance of the amendment, the "pilot" would allow medical device companies to pay private companies to review applications to market devices ranging from heart valves to testing products that are used in protecting the blood supply. While I recognize that FDA would accredit these organizations and would have a short time to review any decisions made by the private reviewers, these safeguards are not sufficient to protect

the public health. The result could be a loss of the public's confidence in medical device products.

In addition, a requirement that the Agency allow third party review for all device applications, at the option of the applicant, cannot be considered a pilot project. Although limited in duration, the program set forth in this amendment is all encompassing in scope. It leaves no discretion to the Agency to retain for review even the most complicated or potentially dangerous devices, or those devices about which the Agency has developed particular expertise or which present novel scientific issues that cut across a variety of disciplines. This amendment requires the Agency to delegate to the private sector the principal review responsibility for everything from devices that the public relies upon to assure the safety of the blood supply to devices each of us individually rely upon to diagnose cancer or sickle cell anemia. I fear that at the end of this so-called pilot project the expertise and knowledge base of the device review program could very well be damaged.

The Agency already has initiated a bona fide "pilot" project to test the feasibility of third party review for selected Class I and II devices. Through this pilot, we hope to address the many difficult questions that must be answered before we delegate critical public health protection activities to the private sector. I would urge the committee to allow this pilot to proceed so that we will know whether, or to what extent, the private sector can respond adequately to such a challenge.

Unreasonable Review Time Periods Guarantee That Critical Public Health Protection Activities Will Be Privatized

Of equal concern is the Committee's rejection of the amendment by Senator Kennedy to recognize the product review goals agreed to with enactment of the Prescription Drug User Fee Act of 1992 (PDUFA) and to eliminate the mandatory hammer provision for failure to meet existing statutory review periods. The Agency has not and cannot meet the timeframes set forth in the bill using existing resources. Moreover, Congress, the industry and the Agency mutually agreed under PDUFA to performance goals that were different from the statutory periods. These agreed-upon time frames would be overridden by the bill.

Under these provisions the Agency would be required to review the complex scientific submissions for novel products such as the fat substitute Olestra, the synthetic animal hormone bovine somatotropin (BST), and vaccines for communicable diseases that could threaten thousands of persons, in six months. The way the bill is structured, failure to meet a deadline for even one application could trigger the requirement that all future

applications in the same product category be contracted out to private companies.

As with the device "pilot," the result will be to undercut the public health protections that the American people now enjoy. Moreover, these provisions will not promote or enhance the expertise and professionalism of this Agency. Nor will they sustain the confidence that the American public now has in our food, drug, and device supply.

Eliminating FDA's MedGuide Program

Finally, the bill stops the FDA's MedGuide program. This program is our effort to work with private companies to ensure that consumers get accurate information about prescription drugs -- information about how to take the drug, side effects, and dangerous interactions with foods or other drugs. Misuse of prescription drugs accounts for many injuries and deaths and costs about $20 billion in health care costs per year. Since drug companies are permitted to promote prescription drugs, FDA should be permitted to require that consumers receive accurate information.

I urge the Committee as it considers this legislation to look at where and how the Agency has fulfilled its public health mission, and not just at the agency's shortcomings. This country has one of the safest food supplies in the world. We have been spared countless hundreds, if not thousands, of deaths and injuries from unsafe or ineffective drugs and devices. We are approving life-saving drugs as fast as any comparable country, and our pharmaceutical industry is one of the most internationally competitive industries we have. We need to continue to improve, and we will, but the fact that we have to do better does not justify lowering the statutory or regulatory standards on which the American public rely.

Sincerely,

David A. Kessler, M.D.

cc: All Labor and Human Resources Committee Members

ELIZABETH DRYE

USA TODAY
FRIDAY, JULY 12, 1996

Cheers Elizabeth

FDA reform: Health Care

Don't limit patient access

OPPOSING VIEW **Industry experts can oversee this new therapy. Don't shortchange the ill.**

By Larry Andreini and Paul Billings

If the Food and Drug Administration regulates cord blood-derived stem cells using its investigational new drug process, known as IND, it will cost thousands of lives. It also will eliminate a mother's option to personally store her newborn child's cells, and it will set promising research back significantly.

This is the opposite of what's needed.

As noted by the Department of Health and Human Services at the National Institutes of Health, "an IND will have two potentially adverse effects. The first is to limit access to this therapy; the second is to inhibit unnecessarily the development of cord blood cell therapy." To think regulation would improve development, given the FDA's history, is mistaken.

For 20 years, physicians have successfully used bone marrow-derived stem cells to treat cancers and other blood and genetic diseases. Unfortunately, the need far exceeds the supply, particularly for ethnic minorities. The American Medical Association reports 10,000 to 15,000 Americans who need a bone-marrow transplant each year are unable to find suitable donors.

But patients now have new hope. With over 4.3 million births in the United States annually, physicians can access a virtually unlimited supply of stem cells without the invasive, painful and risky process of extracting bone marrow from a donor's hip. Distressingly, FDA regulation would singularly limit access to this critical source.

Stem cells derived from cord blood should be treated no differently from those from bone marrow. Dr. Robertson Parkman, head of the bone-marrow transplant program at Children's Hospital in Los Angeles, states, "Biologically, we view that all hematopoietic [blood-producing] stem cells are the same; that based on clinical settings, the decisions about how you choose to get them will vary. And that is the most logical way to look at this, rather than this fragmentation that is being set forth."

Cord blood stem cells should fall under the practice of medicine, allowing physicians to decide on their use, and should not be regulated by the FDA. Even the National Heart, Lung and Blood Institute says stem cells "from matched newborn siblings can be transplanted to treat successfully children with a number of hematologic [blood-related] and immunologic disorders." Simply, cord blood saves lives.

Clearly, it is time to increase, not decrease, the supply of transplantable stem cells, but the FDA's proposed regulation would have the opposite effect. This would not be in keeping with the FDA's commitment "to streamline product approvals ... at a more reasonable cost."

As with bone marrow, accreditation and oversight by designated industry experts can fulfill the need for quality assurance and control without the devastating loss of life that would accompany FDA regulation.

Larry Andreini is executive director and Paul Billings, a physician, is president of the International Cord Blood Foundation.

Voices: Are you encouraged about Mideast peace after Benjamin Netanyahu's visit?

On his first U.S. visit as prime minister this week, Israel's Benjamin Netanyahu drove home a message of strengthening his nation's security while pursuing the peace process with Palestinians and Arabs. The message was met with both approval and apprehension. USA TODAY asked readers for their views about Netanyahu's visit.

Robert Rosenthal, 81
Retired lawyer
Washington, D.C.

I don't think it looks good for Middle East peace. It looks like Netanyahu is sticking to his campaign issues and that President Clinton is not going to oppose them before the November election.

Naomi Walker, 25
Community organizer
Columbus, Ohio

I really think it's too early to tell yet what his being prime minister will mean to the peace process. I think that we can at least try to be optimistic as long as the lines of communication are open.

Bill Denton, 49
School administrator
Bartlesville, Okla.

I was encouraged by the reports of his speech. I felt he was much more positive than the prior indications had been. I was encouraged to hear him say Israel would be depending less and less on financial aid from the United States.

Stephen Burger, 55
Rescue mission exec.
Kansas City, Mo.

I'm less encouraged due to his statements relating to Jerusalem and his actions relating to the West Bank settlements. There are some positive opportunities in that he seems to be open to discussion, but those are difficult areas and he has a definite pro-settlement position.

Patty DeDominic, 45
CEO
Los Angeles, Calif.

My jury is still out. I am encouraged because I hear many of the right words. However, sometimes the greatest strength is flexibility, so I'd like to have a chance to observe how he continues to lead.

MEDICINE

AIDS Conferees Debate How Early to Offer New Drugs

By MICHAEL WALDHOLZ
Staff Reporter of THE WALL STREET JOURNAL

Many of the people crowded into scientific sessions and lingering in hallways at the 11th International Conference on AIDS have spent much of the past few days debating a question that was too far-fetched to consider just eight months ago: When should a combination of drugs including the new protease inhibitors be used to try to eradicate the AIDS virus from patients' blood?

Throughout the week, research physicians astonished many of the 15,000 people who attended the conference in Vancouver, British Columbia, by presenting late-breaking reports showing that new protease inhibitor drugs, used in combination with older medicines, were suppressing activity of the AIDS virus. In several studies, patients whose level of HIV, the AIDS virus, was driven below the levels of detection also had an unprecedented rise in their disease-fighting immune cells, some felt healthier, and most had fewer life-threatening complications.

Yet before scientists and drug makers had time to congratulate themselves, they were thrust into a prickly argument over how early an infected person should begin using the combination drug therapies. Treating all 800,000 or so Americans infected with HIV would cost $5 billion or $6 billion a year. The regimen also has serious side-effects and requires patients to take 14 to 22 pills a day, perhaps for the rest of their lives. In addition, many researchers worry that early treatment could make HIV resistant, leaving patients with no effective drugs to turn to when the virus re-emerged.


David Ho

'I AM DOING EXPERIMENTS trying to see whether HIV can be eradicated,' says Dr. Ho. 'Whether it is practical to transform these experiments into practical medical care at this time is another issue altogether.'

"Based on the new advances, it now makes sense to me that we should be treating people as soon as possible," says John Mellors, a researcher at the University of Pittsburgh Medical School. "But I don't have proof that treating my patients early is better than waiting" until they develop the first symptoms of AIDS, which can appear five to 10 years after the virus is contracted. Conducting a clinical trial to provide such proof "will be a logistical nightmare, perhaps too costly and too long for anybody to undertake," Dr. Mellors adds.

The debate was triggered in part by the provocative research into the AIDS virus conducted by David Ho, a 43-year-old virologist and director of the Aaron Diamond AIDS Research Center in New York. After testing protease drug activity in patients several years ago, Dr. Ho became the first prominent researcher to suggest that it may be feasible to actually eradicate the virus from some patients' bodies. His theory and desire to test it in people have led some critics to charge that he is raising unrealistic expectations that will lead to disappointment and inappropriate care for many patients.

The protease drugs have been widely available only since last December, but already about 70,000 people world-wide have begun using them, mostly in combination with two older drugs. The three protease drugs currently on the market—Roche Holding Ltd.'s Invirase, Merck & Co.'s Crixivan and Abbott Laboratories' Norvir—work by blocking an enzyme crucial to HIV replication.

Dr. Ho says his work has convinced him that the virus should be attacked at the first sign of infection. In an experiment now under way, the Diamond Center is giving the combined therapy to 12 people newly infected with HIV. After a year of therapy in which the virus hasn't been detected, Dr. Ho hopes to remove the drug and see if the virus re-emerges or is still lurking in certain tissues in the body.

"I am doing experiments trying to see whether HIV can be eradicated," the researcher says. "I am not proposing that clinical practice be based on my experiments. My job is to push our studies forward as far as we can. Whether it is practical to transform these experiments into practical medical care at this time is

Please Turn to Page B3, Column 3

Continued From Page B1

another issue altogether."

Many AIDS activists have expressed concern that publicity about Dr. Ho's research and other preliminary studies of the combination therapy will lead people to think that AIDS has been cured. There are no data showing that the new therapy can keep the AIDS virus at bay beyond a year, notes David Barr of the Gay Men's Health Crisis, an AIDS advocacy group. "If these drugs are only effective for a year or two and you take them early on, you may have ruined your chances for life-prolonging therapy later on," he adds.

A formidable hurdle to early use of the drugs is also their immense cost, ranging from $12,000 to $20,000 per patient per year. Scott Hammer, a research physician at Deaconess Hospital and Harvard Medical School in Boston, says he personally believes that an expensive "protease combination shouldn't be considered for everyone" until later in the infection, perhaps after symptoms have begun to appear. But he adds that "cost should not be the principal factor in determining the right regimen to use."

Nonetheless, several doctors who treat large populations of poor people say the debate over using the therapies early or late is meaningless to them because many of their patients simply can't get the drugs at all. Margaret Fischl, a researcher at the University of Miami, says using combination therapy for all 2,500 HIV-infected patients who use the outpatient clinic at Dade County's Jackson Memorial Hospital would cost $21 million a year.

And doctors from less developed nations say the new therapies are still a dream. It will require triple Thailand's entire AIDS budget to pay for a therapy that combines two drugs and doesn't include the expensive protease pills, says Chaiyos Kunanusont, a Thai public health official.

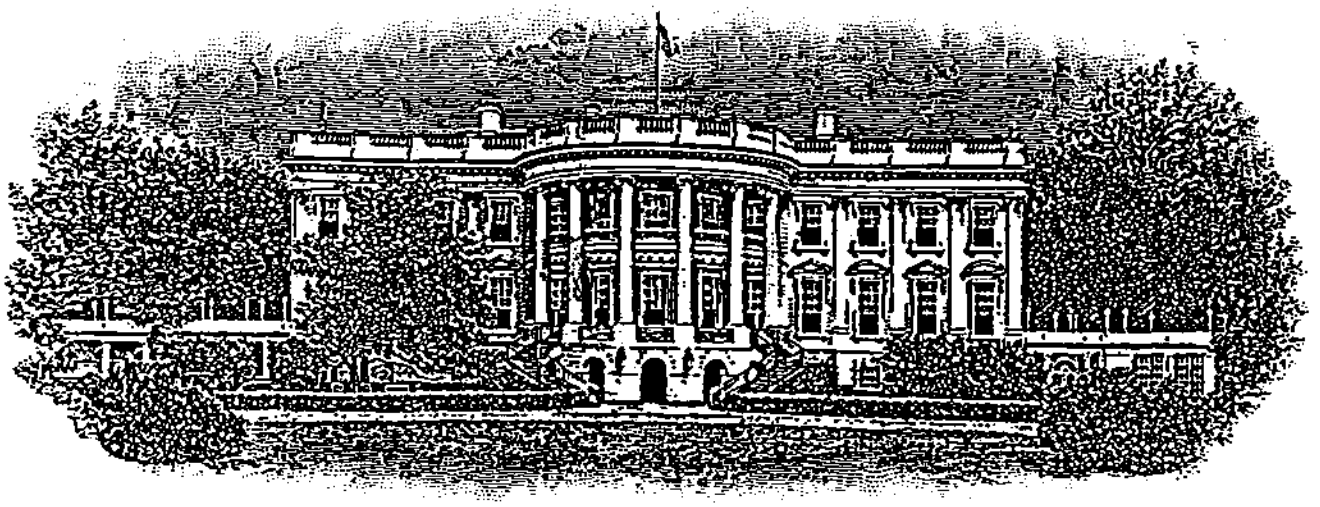
Still, some researchers and drug company executives say early, aggressive use of the combined therapy might well reduce health-care spending in the U.S. by tens of millions of dollars annually.

"If we can suppress the virus from the beginning of infection, we will, without doubt, block the rise of infections that are the main reason people become hospitalized, need other expensive drugs and require costly home health care services," says Martin Markowitz, a colleague of Dr. Ho.

Abbott Laboratories presented a study this week defending its product's high price and arguing that adding its drug, Norvir, to existing antiviral regimens will save $6,382 in medical costs per patient treated in the U.S. per year.

Asked why his company doesn't reduce Norvir's price, Andre Prenet, vice president of Abbott's research, says he is losing money on his AIDS research projects. "The reason our AIDS program has done so well is that I hire the very best researchers and scientists," Dr. Prenet says. "But that costs money. If I can't make money from this program, Abbott can't let it continue forever."

The White House



DOMESTIC POLICY

FACSIMILE TRANSMISSION COVER SHEET

TO: Rich Tarplin, Acting Asst. Secty for Legislation!

FAX NUMBER: 690-7380

TELEPHONE NUMBER:

FROM: Elizabeth Dryl

TELEPHONE NUMBER:

PAGES (INCLUDING COVER): 4

COMMENTS: ATLA talking pts on FDA reform bill's OTC provisions, per our conversation.

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BOSTON, MASSACHUSETTS

FACSIMILE TRANSMITTAL SHEET

DATE: 5-23-96

NUMBER OF PAGES: 3
(Including Cover Sheet)

TO: Elizabeth Drye

FAX #: 456-7028

FROM: Phil Buchan

PHONE #: 944-2815

COMMENTS:

Here is some info on the FDA preemption problem.

Thanks for your help on this, and please keep in touch!

If you have trouble receiving this transmission,
Please call the Public Affairs Department
202-965-3500, ext. 305.

Association of Trial Lawyers of America

1050 31st Street, N.W. Washington, D.C. 20007-4499 202 965-3500 http://www.atlanet.org

THE FDA BILL WOULD UNFAIRLY ELIMINATE PRODUCT LIABILITY FOR MANUFACTURERS OF FOOD, COSMETICS AND NON-PRESCRIPTION DRUGS

A little understood amendment adopted by the Senate Labor Committee could eliminate product liability for food, cosmetics and over-the-counter drugs. The amendment, offered by Senator Gregg (R-NH), added language to the bill which appears on its face to supersede state regulations, but which is similar to language, currently the subject of litigation in the United States Supreme Court, that has been read in some courts to totally eliminate the right of injured people to sue manufacturers. **Adoption of this language in the FDA bill would extend this prohibition on suits to cosmetics, food and non-prescription drugs.**

- **Ambiguous language already being challenged in the Supreme Court:** The provision prohibits "any requirement relating to the regulation" of food, cosmetics or non-prescription drugs regulated by the FDA. Similar language that extended regulatory authority of the FDA over medical devices has been interpreted in some circuits as eliminating the right to sue manufacturers of covered products. That means that people injured by defective devices in those jurisdictions are totally without recourse, and their manufacturers are totally without liability. This goes far beyond a cap on non-economic damages, or any of the other provisions in product liability bills. Injured people could not even go to court to hold manufacturers responsible for their medical expenses as a result of dangerously defective medical devices. This bill gives blanket amnesty for corporate carelessness to a broad new range of products -- non-prescription drugs, cosmetics and foods.

- **More far reaching than any tort "reform" offered so far:** Previous product liability bills, as harmful to consumers as they were, allowed most plaintiffs at least some prospect of receiving a limited recovery. This provision would deprive anyone injured by a product it covers of their rights to be compensated -- no matter how old the product, no matter whether the damages are economic or non-economic, no matter if the product caused the injury through gross negligence or deliberate adulteration.

- **Even if the Supreme Court rules in favor of consumers' rights, this language will still be subject to litigation and could be interpreted differently:** A Supreme Court ruling in favor of consumers rights to hold manufacturers liable in the Medtronics case would not guarantee that similar language in other bills would be interpreted the same way. The court will look at the legislative history and the expectations of the Congress at the time of the passage of the medical devices amendments in 1976. Courts could easily hold that, in light of the interpretation of those amendments twenty years later, Congress could be expected to know that a "requirement" by the states was seen as including civil liability.

Even the strongest proponents of federal tort reform are not calling for a total bar to claims. Enactment of this extreme proposal would eliminate a vital check on corporate carelessness. **Vote to defeat this attack on the civil justice system.**

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Even the strongest proponents of federal tort reform are not calling for a total bar to claims. Enactment of this extreme proposal would eliminate a vital check on corporate carelessness. **Vote to defeat this attack on the civil justice system.**

Support Amending the FDA Reform Bill, S. 1477, to Avoid the Unintended Consequence of Eliminating All State Tort Law for Non-Prescription Drugs

Section 523 of S. 1477, the "Food and Drug Administration Performance and Accountability Act of 1996", seeks to provide uniform regulations on non-prescription drugs by preventing State and local governments from issuing non-prescription drug "requirements" that conflict with federal ones. Although the clear intent of the bill's authors seems to have been to provide uniform regulatory requirements, Section 523 could have the unintended consequence of preventing anyone killed or injured by a non-prescription drug from bringing a lawsuit to recover for their damages because such a lawsuit could be interpreted as a conflicting State regulatory "requirement".

In fact, the manufacturers of medical devices that can sometimes be dangerously defective have argued that nearly identical language in the Medical Device Amendments of 1976 has precisely this effect, as they have sought to dismiss claims brought against them by citizens who allege to have been injured by such devices. While the Supreme Court is currently considering the issue in the context of the Medical Device Act, *Medtronic v. Lohr*, S. Ct. Nos. 95-754, 95-886, the Senate should clarify this potential unintended consequence of the FDA reform bill by simply amending Section 523 to state that the definition of conflicting State or local non-prescription drug "requirements" does not include lawsuits brought by injured citizens.

I. Section 523 Arguably Bars All Lawsuits Involving Non-Prescription Drugs

- Unlike the Senate passed product liability bill which reformed standards of proof and placed some *limits* on damages, Section 523 could serve as an absolute ban on *any* lawsuits involving non-prescription drugs -- no matter how meritorious. Thus, Section 523 might protect: a manufacturer that obtained FDA marketing approval for its unsafe allergy medicine only by hiding information from FDA; a manufacturer that sold poisonous arthritis medicine that had been contaminated during production because of poor manufacturing practices; or a manufacturer that knew that its headache medicine caused liver damage and had failed to warn of that danger.

II. Section 523 Should be Amended to Specifically Exclude State Tort Law

- There will be two dramatic consequences if Section 523 is not amended. First, years of litigation will inevitably arise on whether Section 523 bars any lawsuits involving non-prescription drugs. Second, if Section 523 does bar such lawsuits, then those rare but notorious manufacturers of dangerously defective drugs will go unpunished.

- The Senate can avoid these unintended results of Section 523 by amending the Section to specifically provide that it does not apply to or preempt state tort liability laws.

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THE WASHINGTON POST
WEDNESDAY, JULY 17, 1996

Chris, Elizabeth

Reform Isn't Risk-Free

THE FOOD and Drug Administration's handling of the thalidomide crisis of the early '60s deservedly made that agency one of the most admired in the federal government. But the same caution and deliberation that saved the country from that tragedy have provoked criticism in the era of AIDS. Thousands of deformed babies were not born here because government scientists kept a drug off the market. But AIDS patients have, in recent years, deplored the slow pace of drug approval by this same agency and have added momentum to the cause, long favored by industry, of FDA reform.

Legislation that would make substantial changes in the way the government oversees the manufacture and sale of drugs, medical devices and food additives may come up in the Senate as early as next week. The House Commerce Committee is putting the finishing touches on a companion bill. The measures are not identical, but both, in their differing ways, would allow some privatizing of the FDA's responsibility to review and approve new drugs. Reformers also want to make it easier for manufacturers to advertise drugs as safe and effective for use in situations not specifically approved by the FDA. And both bills aim to speed up the drug approval process either by setting deadlines or by eliminating the paperwork drug companies find so burdensome.

There is not a single part of the federal government that can't be improved. Undoubtedly, the FDA is not perfect. And patients and their families, in addition to drug industry corporations, have legitimate concerns.

But those who would rush broad reform fail to consider two facts. First, pressure from AIDS activists already has produced changes that have cut new drug approval time almost in half since 1987. And drugs given special priority now are being moved through the system in six months, as opposed to 33 months a decade ago. European regulators often are cited as an example of speed and efficiency, but the FDA's review and approval times have been better—with far fewer recalls—for the past couple of years.

In addition, the most avid reformers do not appear to be giving enough attention to the risks involved. Do Americans really want the drug approval process to be primarily in private hands? Are they ready to accept without regulatory review a manufacturer's word that a product approved for use against infection also will be a safe and effective blood-thinner? Even when time is of the essence, is speed ever more important than safety?

Reform is a useful and generally positive exercise in any institution. But here the stakes are so high that change should be undertaken only with caution and after deliberation. There is no need to rush this legislation through in the current congressional session.

Dogs' Day

UNLIKE DISTRICT residents who still have a long wait before municipal services return to an acceptable level, dogs, cats and other animals in the District's custody have something to be happy about today. The Washington Humane Society, after a long and time-consuming struggle with the D.C. Department of Human Services, is back in charge of running the city's animal shelter. It was yet one more D.C. bureaucracy-created problem that both residents and animals need not have experienced.

The Washington Humane Society has been around more than a century—since Congress chartered it in 1870 to handle animal cruelty problems in the District. In 1980, after the city's scandalous operation of the New York Avenue shelter made the news, the D.C. Council authorized the WHS to take over municipal animal control services. As the city fell on hard times in recent years, the WHS was forced to take up the slack by subsidizing essential functions out of its own pocket. On top of that, the Department of Human Services would give the WHS only short-term contract extensions, although the nature of the work required the society to commit time and resources on a long-term basis.

Even as the WHS was attempting to negotiate a longer-term arrangement—which was permissible under the animal control law—the city was working quietly to bring in an untried, start-up animal shelter operator to replace the experienced WHS and its corps of volunteers. Worn down by the city's intransigence and sapped by more than a year of late or partial payments, the WHS opted to bow out. Enter DHS's choice, Animal Link Inc. Enter also a new set of problems.

Shelter volunteers, after witnessing Animal Link's management of the city's shelter, announced that they would not work with the new group because it was disorganized and the animals were ill-kept. Next, the WHS and the Society for the Prevention of Cruelty to Animals of Anne Arundel County—in separate actions—removed animals from the shelter out of concern for the care they were getting. Animal Link, having experienced financial difficulties, decided against bidding on the current contract. Reenter the Washington Humane Society.

Today, DHS leadership has changed, the WHS has returned to run the shelter on a long-term contract, and the dogs and cats are in good hands again. All in all, not a bad day for the animals.

URGENT

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF MANAGEMENT AND BUDGET
Washington, D.C. 20503-0001

4/29/96

LEGISLATIVE REFERRAL MEMORANDUM

LRM NO: 4248

FILE NO: 1746

Total Page(s): 3

TO: Legislative Liaison Officer - See Distribution below:

FROM: Janet FORSGREN /B. Pellicci (for) Assistant Director for Legislative Reference

OMB CONTACT: Robert PELLICCI 395-4871 Legislative Assistant's Line: 395-7362
C=US, A=TELEMAIL, P=GOV+EOP, O=OMB, OU1=LRD, S=PELLICCI, G=ROBERT, I=J
pellicci_r@a1.eop.gov

SUBJECT: HHS Fact Sheet on "one-pager" of concerns about S. 1477, Kassebaum's FDA reform bill.

DEADLINE: 10:00 a.m. Tuesday, April 30,1996

In accordance with OMB Circular A-19, OMB requests the views of your agency on the above subject before advising on its relationship to the program of the President.

Please advise us if this item will affect direct spending or receipts for purposes of the "Pay-As-You-Go" provisions of Title XIII of the Omnibus Budget Reconciliation Act of 1990.

COMMENTS: HHS staff intend to distribute the attached "one-pager" to congressional staff tomorrow afternoon.

DISTRIBUTION LIST:
AGENCIES: -Executive Office of the President - EOP Review Only, See Distribution -
EOP: Nancy-Ann Min
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Jim Murr
Janet Forsgren

RESPONSE TO LEGISLATIVE REFERRAL MEMORANDUM

LRM NO: **4248**

FILE NO: **1746**

If your response to this request for views is short (e.g., concur/no comment), we prefer that you respond by e-mail or by faxing us this response sheet.
If the response is short and you prefer to call, please call the branch-wide line shown below (NOT the analyst's line) to leave a message with a legislative assistant.
You may also respond by:
(1) calling the analyst/attorney's direct line (you will be connected to voice mail if the analyst does not answer); or
(2) sending us a memo or letter
Please include the LRM number shown above, and the subject shown below.

TO: Robert PELLICCI **395-4871**
Office of Management and Budget
Fax Number: 395-6148
Branch-Wide Line (to reach legislative assistant): 395-7362

FROM: _____ (Date)

_____ (Name)

_____ (Agency)

_____ (Telephone)

SUBJECT: HHS Fact Sheet on "one-pager" of concerns about S. 1477, Kassebaum's FDA reform bill.

The following is the response of our agency to your request for views on the above-captioned subject:

_____ Concur

_____ No Objection

_____ No Comment

_____ See proposed edits on pages _____

_____ Other: _____

_____ FAX RETURN of ____ pages, attached to this response sheet

KASSEBAUM BILL

A. Most Serious Concerns

1. Contracting Out/Timeframes/Hammers (Sections 103, 403, 404, 709, 806)
2. Privatization (Section 709)
3. Off Label Use (Formerly Section 607)
4. Health Claims (Section 903)
5. Medication Guides (Section 607)

B. Serious Concerns That Probably Can Be Readily Resolved

1. Product Approval Standards (Sections 602, 703, 802(a))
2. Product Erosion (Manufacturing Changes/Modifications)(Sections 604 & 702(d))

C. Other Significant Concerns

1. Mission Statement (Section 102)
2. Information Systems/Policy Statements (Sections 105 and 106)
3. Advisory Committees/Appeals (Sections 107 and 108)
4. Access to Unapproved Uses/HUD Exemptions (Section 202 and 203) (Humanitarian Use Device)
5. Clinical Research of Drugs, Biologics, & Devices (Sections 302 & 303) Sponsor 30 Days - 30 days in writing (they'll give us 15)
6. Effectiveness Determination (Uses not on label)(Section 408)
7. Pediatric Labeling (Section 411)
8. State and Local Requirements Respecting OTC Drugs (Section 608)
9. Initial Classification of Devices (Section 702(b))
10. Device Tracking (Section 704)
11. Combination Animal Drugs/Minor Species (Sections 802(b) and (d))
12. Indirect Food Additives (Section 902)

* Section 406 - Environmental Assessment Provision - should be Reviewed by CEQ/White House.

HIMA
HEALTH INDUSTRY MANUFACTURERS ASSOCIATION

JAMES S. BENSON, SENIOR VICE PRESIDENT
TECHNOLOGY AND REGULATORY AFFAIRS

May 6, 1996

The Honorable Sally Katzen
Administrator
Office of Information and Regulatory Affairs
Office of Management and Budget
Old Executive Office Building, Room 350
Washington, DC 20503

Dear Ms. Katzen:

I am writing on behalf of the medical technology industry, specifically the Health Industry Manufacturers Association (HIMA), to thank you for arranging our meeting last month to discuss the critical issue of FDA reform legislation. We concur with your assessment that legislative reform this year is appropriate.

We welcomed the candid discussions that covered a wide range of issues, and we appreciate the Administration's desire to establish a meaningful dialogue with industry. There is no better way to achieve common ground than through meetings such as the one you conducted

We look forward to working with you again You and your staff are always welcome to call me at (202) 434-7220.

Sincerely,

James S. Benson

cc: Gregory Simon
Elizabeth Drye
Rachael Levinson
Daniel C. Tate
William Corr
Jerry Klepner
William Schultz
Mary Pendergast
Eddie Evans
Dominique Cahn
Walter Moore
Reid Detchon
Tony Podesta

1225 I STREET N.W. SUITE 500
WASHINGTON, D.C. 20005
(202) 783-8700
FAX (202) 783 8750

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

15-May-1996 01:04pm

TO: Lisa Kountoupes

FROM: Jim R. Esquea
Office of Mgmt and Budget, HD

CC: Barry T. Clendenin
CC: Richard J. Turman
CC: Michael A. Fitzpatrick

SUBJECT: FDA Language Re: House Budget Resolution

Below is revised FDA language for the Director's letter to Rep. Kasich re: the House Budget Resolution.

The revision is based on the laguage the Health Division faxed you last night. The underlined sentence in the language is new. If you have any questions, please call me at 5-7841.

"Food and Drug Administration -- The Budget Resolution assumes $622 million in savings between FY 1998 and FY 2002 associated with structural reform of FDA through the three House FDA reform bills (HR 3199, HR 3200, HR 3201). The Administration has worked consistently to reform FDA review procedures to expedite the approval of important drugs, biologics, and medical devices while maintaining high standards of safety and efficacy. However, the Administration has very serious concerns that the House Budget Resolution and the House reform bills, as currently drafted, would undermine the FDA's ability to ensure the safety and efficacy of products under its jurisdiction. In addition, given the Congress' concern that FDA streamline its approval process for medical devices, biologics, and drugs, the $622 million reduction in budget authority associated with these structural reforms could impede FDA's ongoing efforts to speed up review times."

FDA e-mail

- Following mtg w/ four offices and ~~cap~~ —
— conference call / or mtg. — Dee
where they are —

— early next week
right after that — let us know
they —
unified democratic position —
to Kassebaum. —

Donna's mtg w/
House Commerce Cmte. Cosponsors —
down
Eshoo, Palone, Gordon —

Talking to Mikulski

Jane SLV

Nell

FDA Reform

FDA Reform

Mark up —

Kennedy amendment delaying time frames —

#2

Breakthrough drug deadlines

- ~~Mark~~ Cement law (PDUFA) is 12/6 yrs/priority

Isakson/Harkin mark goes 6/6 —

Kennedy argues vote prior to markup —

no add'l resources. — Hammer falls

p. 37-38

95% ⇒ 90% and — instead of hammer falling —

Secty will report to Congress.

(Hamer modification) —

fails party line vote

Craig — CT decision — Lee Vs. Riley —

— Requires enforcement —

Delaney — Kennedy —

Authorizes Secty HHS — establish 3 or more centers.

to perform research on drugs, devices, biologics.

— physicians education and research

— university based

Off-label

Kassebaum — promises to strike off-label use from the bill - Sec. 407 - and work on it before floor consideration

Dodd — committing to work v. closely trying to get agreement — Harkin/Wellstone will work with us.

Frist — goal is to have no barriers to open scientific discourse of peer-reviewed science. — Think there are barriers now that need to be removed that we don't get info. about there.

Kennedy — We had a fascinating hearing on this information —

[Bare (not clear which sections — there are two

Pending Amendments

Substantial Equivalence" Issue —

— wants to finish this today as possible —

Frist, Dodd, Harkin, Mikulski, Kennedy

term-limit Symphonie

Coats / Senator Greg Frist Kottelaun PM

Coats Term Limit amendment —

- 5 yr Commissioner Term
- only can be removed from office - for neglect or malfeasance..
- Doesn't apply to Kessler -

Simon - extends clinical pharmacology program.

5 amendments — will be offered. —

health claims

Gregg - Food - allows producers & packers to make health claims that have been passed by other Federal agencies - e.g. NCI, NIH

Folic Acid - after CDC approved - took FDA a long time to step forward

NPR recommendation on leg

6-6777
8721

— 4/4/96 —

Evelyn, Jodi, Kitty — co-dvg grp. — follow up.

— Rep. of Fed gov't at every one of funerals —

— Short prayer service across the street today —

— not "positive id." of Brown — but general not confusion — Pros. transmitting that to Brown's family ... "no positive id" — been identified.

— 33 bodies; 35 manifested — no resolution

— v. bad weather / foggy. —

— Dorm mtg 10:30

— brfg. w/ Harold, Tony Lake, Laura Tyson —

11:45 sign LI veto, Farm bill w/ photo.

p.m. - phone and office time

— Evelyn — 9:00 mtg. Leon's office

Brigadier General Canavan, Ambassador Galbraith, Croatian officials — press conference.

9:00 General Estes briefing

Planning proclamation re. flags -

State. Dept. 10:00 release manifest.

Later morning prayer vigil.

Unabomber – DOJ – will announce charges ~~at~~ this morning.

p.m. Farm bill / line item veto — early afternoon

~~LI veto~~
Sending pens to former presidents, sponsors

Study on Hg in atmosphere
~~coal~~ coal fire utilities / seafood industry –

Kessler testimony

Prior incorrect practice decisions — unnecessary appendectomy, hysterectomy, common cold.

Review Process

"be demonstrative net benefits that are greater than the risks"

Safe enough (in view of its benefits and comparative benefits of other available treatments

review of primary data:

- responses were correctly categorized; judgmental endpoints are supported by objective data;
- adverse events are correctly categorized as to severity and causality;
- assess impact of drug on parameters not summarized by sponsor
- facilitates faster analysis - pp. 18 ff

Proposed review time

- compromise during public health protection
- no opportunity to obtain clarifications
- companies ready to manufacture so FDA can start pre-inspection approval
- compromise effectiveness of advisory cmt.

Cost - add'l review cycles

- ↓ work on other functions (e.g. advising on clinical design phase, ↓ production and post-approval reviews)

-↓unrelated activities - safety of blood supply, food safety and tampering

Sound medical practice (78)

~~Opposed~~

eliminate approval of devices for specific uses. (730) Sec. 702

recognize any use "included within a general use for a predicate device" as an approved use for 510(k) devices.

- no assurance of clinical
- independent review
- accurate labeling to help doctors sort out uses.

Accept scientifically sound studies

- Don't like waiting FDA approval

- Don't care that it's Class I-III pilot project
  - but want FDA to approve
  - some randomization - e.g. 1/4 or 1/6...

problems - manufacture arrangement —
- manufacture negotiates w/ third party —

Med Crude — 2000 50% "med grade" quality
2006 95% " "

per OMB — Hamm is not finalized in bdw proposed and final

POTUS schedule
- Mtg w/ 150 Religious leaders
- CA Dem convention in Nevada —
- may have a grain shortage before corn is harvested in the Fall —
- Memorial ~~Schedule~~ service for Chuck Reasner

Monday . 8:15 4/8/96

10:00 Easter Egg Roll

Mtg.'s w/Leon, Gen McAffrey

4 hours office time

5:45 NYT interview

this evening 2 DNC dinners

Line Item Veto - Signing tomorrow
Partial Birth - will be vetoed this week
State Auth - will be vetoed

Pension event Thurs.

POTUS leaves for Korea Sunday; returns following Sunday

Secty Brown Funeral/Burial Wed.

Harold —

"simple, moving ceremony"

Met w/ 33 families individually — "How many more of these ever have to do."

Evelyn - Secty Brown lay in repose at Commerce tomorrow
- Wake tomorrow night at church
- 1:15 service Nat Cathedral — Wed. -
- Alma Brown reserving 500 seats — 4000 capacity
- Ticketed event.

Many Good Actors Secy of Commerce. —

Fighting broke out in Liberia / Monrovia
— may recommend evacuation of Americans.

N. Korea – violate armistice agreement for 3rd time in 3 days –
cautionary exercises in demilitarized zone

John Hilley
next
– Senate Tues cloture vote on WW 16
– main event – immigration bill – [illegible] amendment
to deny public ed. to children of illegals
– [illegible] motor/voter

Both
– Houses are working on conference on anti-terrorism bill –
hoping to finish by 19th (anniversary of Ok. City bombing)

– Senate expected to take up K-K h.c.

– House – constitutional amend "very stupid"
– 2/3 ~~maj~~ vote to ↑ taxes
– take trust funds out of budget – Hoy
– makes it impossible to balance budget.

Legal
– Montana Freeman – no new developments
– Unabomer – no comments

N. Affairs – sign something w/cooperation on Mexico. –

Rahm –
prohibiting
Working w/cons who oppose ~~tax~~ schooling of illegals

x Evelyn updated schedule this afternoon.

Katie – timber swap to address to worst sales. –

– HRC –

TALKING POINTS

- Crime Bill included Jacob Wetterling Act
  - provides workable incentives so that states will require convicted child molesters & sexually violent offenders to notify whereabouts for @ least 10 yrs after release
  - If not mandated, states lose funding federal grant $.

456-7028

need all she needs

Walk Through

	Kessebaum	FDA
TITLE VII		
Device Approval / CLASSIFICATION	702(a) Automatic exemption of Class I devices (like the provision that gives authority to exempt Class II)	① Permit FDA not to reclassify those that raise health concerns, or ② reclassify class I into II by legislation where appropriate.
"SUBSTANTIAL EQUIVALENCE"	702(c) Substantial equivalence determinations would recognize any use "included within a general use for a predicate device" (i.e. device marketed for one indication could be marketed for another w/ 510k application)	– eliminates safety and efficacy requirement for new uses. – Compromise?
	702(d) shall not require add'l 510k if modification... can be shown to ~~adversely~~ not affect safety and efficacy.	ensure FDA is not prevented from seeking 510(k) when a adversely affects safety
	703 Agency must accept retrospective or historical clinical data as a control if valid data available.	historic data ok if sufficient and FDA can require concurrent clinical trials
	702(b) – allows anyone in 510(k) to go to advisory cmte that goes to class III.	Narrows scope — but allow applicant.

Device performance Standards	708	FDA must recognize performance stds. of certain std-setting organizations	FDA should have authority to identify and decide which std.'s to recognize.

Title IV — Fair Product Review

3rd Party Reviews	403 (a)		
Sound Medical Practice	407	allows approval based on sound medical practice.	- performance goals for efficacy supplements. - Create a small office - report back to Congress

Don Baer mtg. —

12 months avg times → 2-3-4 months. —

Drugs that have been approved at other Countries →

Patrick

— prostate, cancer, pediatrics

Separate brfg. for science reporters.

5 min from 1:30-1:35 w/genois in oval before event

10 min before that for POTUS briefing. —

Kessler brief here on Friday —

Facts
- How many drugs
- What kinds of cancer
- When will

Title I

105. —

106. - Policy Statement: —
- Agency wants discretion.
- issued a FR notice w/ 3-tiered approach.

P. 14. Advisory Cmt. may ask for add'l info (rare)
Normally act w/in 60-90 Days.

Title II

Expanded Access — add'l requirements for data

Sec. 543 — Codifies what Agency does now.
- Humanitarian Use

Sec. 203 - Hand hammer ok (regs out in June)
- 30 Days Authorities has
- Never been used —

Sec. 204 - time frame too short (12 vs. 6 month)
- shift resource
PDUFA → 12 all
6 Expedited approval
They want to switch to 6 and 4

Title IV

403 contracts for Expert review
Ambiguous - whether discretionary or mandatory

See pp 42-43 Broadly drawn.

407 Efficacy Supplement for a new use of approved drug or device. —
Current law — may be able to use prior safety studies
Mark — No incentive to do the study —
— require that they submit efficacy supplement.

Encainide / Flecainide / Life threatening arrythmias
Bradycardia
Asymptomatic arrhythmia...

p. 47 - Device provisions is broader. —
— 90 Days — allows for cursory review. —

p. 53 - sound medical practice.

Sec. 410 p. 56

Title VI

Sec. 604 - [both drug and device centers have put out manufacturing changes.

USP monographs?

pp 78-80 — Drugs center — has issued guidance on what is manufacturing changes.
Devices — took tiered approach

pp 80-82 — probably can be handled in compromise

Title VIII

Delegate and send → Other wavers rocks down current std.

Suggested
- one or more +
- Where appropriate, field investigations are required.

Sec. 802 — Combination drugs —
don't have to show efficacy

DATE: 5-15-96

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
200 INDEPENDENCE AVE., SW
WASHINGTON, D.C. 20201

PHONE: (202) 690-7627 FAX: (202) 690-7380

OFFICE OF THE ASSISTANT SECRETARY FOR LEGISLATION
ROOM 416-G HUMPHREY BUILDING

TO : Elizabeth Drye

OFFICE :

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FAX NO : 456-7028

TOTAL PAGES (INCLUDING COVER): 7

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[ ] HAZEL FARMER

REMARKS:

O:\BAI\BAI96.315 S.L.C.

104TH CONGRESS
2D SESSION

S. _____

IN THE SENATE OF THE UNITED STATES

Mr. D'AMATO introduced the following bill; which was read twice and referred to the Committee on _____

A BILL.

To amend the Federal Food, Drug, and Cosmetic Act to clarify that any dietary supplement that claims to produce euphoria, heightened awareness or similar mental or psychological effects shall be treated as a drug under the Act, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. DEFINITION OF DRUG.

Section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(g)(1)) is amended by adding at the end thereof the following new sentence: "Notwithstanding the preceding sentence, a dietary supplement shall be considered a drug under clause (C) if the label

or labeling of such drug claims or implies that the dietary supplement produces euphoria, heightened awareness, or similar mental or psychological effects".

DRAFT

May 15, 1996

Floor Statement of Senator Alfonse D'Amato
on Legislation to Control Herbal Street Drugs

Today I am introducing legislation to control the growing problem of dangerous herbal stimulants -- products actually marketed and sold as alternatives to powerful and illegal street drugs. This bill will make these products subject to the same premarket safety and efficacy review as any other drug and will give the Food and Drug Administration (the "FDA") the necessary tools to take prompt and decisive action.

I strongly support the right of the American people to have access to legitimate dietary supplements, and I want to clearly state that this bill will not limit that access. Herbal street drugs are not legitimate dietary supplements and should not be afforded the protections given to those products. They do not improve the health of the American public. They are quite simply dangerous products masquerading as dietary supplements in order to evade FDA review and sanctions. This is wrong and was not the intent of Congress when it passed the Dietary Supplement Health and Education Act of 1994.

The slick peddlers of these herbal street drugs target their advertising at our nations's young people. They sell their products in novelty shops, instead of pharmacies, using flashy signs and posters, and give their products names like Cloud 9, Herbal Ecstasy, and Ultimate Xphoria. Using the Internet and showy brochures, they hawk their dangerous wares with promises of "euphoric stimulation, highly increased energy levels, tingly skin sensations, enhanced sensory processing and mood elevations." One of these products even states that "It is a carefully formulated and thoroughly tested organic alternative to actual MDMA or Ecstacy" -- a powerful and illegal street drug. Most importantly, many of these products are advertised as "100% legal and FDA approved" and as "100% natural . . . with no side effects". But they are none of these things.

Last March, one of these products killed 20-year-old Peter Schlendorf

of North Eastport, New York. Peter, a junior at the State University of New York at Albany, died from a lethal combination of four stimulants found in one of these products. A statement issued by the medical examiner's office in Panama City, Florida, where Peter died, stated that his death "was a result of the use of Ultimate Xphoria, an herbal product containing Ma Huang." Ma Huang -- also known as Ephedra -- is a botanical source of the powerful stimulant ephedrine. According to the medical examiner's statement, Peter's cause of death was listed as the "synergistic effect of Ephedrine, Pseudoephedrine, Phenylpropanolamine and Caffeine." The medical examiner's office noted that these four stimulants "can have an adverse effect on the heart and central nervous system." How could the producers of this product claim it was safe and tested when it can produce such tragic results?

The legislation that I am introducing today will help to ensure that no other young people die from these products and that no other parents have to endure an early-morning visit from the local police to learn that their child has died from a product advertised as safe and thoroughly tested. This bill amends the Federal Food, Drug, and Cosmetic Act to clarify that any dietary supplement that claims to produce euphoria, heightened awareness or similar mental or psychological effects shall be treated as a drug under this Act. As a result, dangerous herbal street drugs, like the one that killed Peter Sohlendorf, will be subject to the same premarket safety and efficacy review as any other drug. In addition, the FDA will have enhanced authority to take prompt and decisive action against herbal street drugs. This legislation is necessary to protect the health of the American public, particularly its youth, who are obviously the target of these products.

Again, let me clearly state that this legislation will not limit the public's access to legitimate dietary supplements. It will not limit access to over-the-counter drugs, such as Sudafed, that contain ephedrine. Nor will it limit access to legitimate dietary supplements that contain ephedra or ephedrine, such as herbal teas. I want to note, however, that ephedra and its related products are so powerful that the FDA is reviewing the use of these products even in these legitimate forms.

Some will argue that this legislation is unnecessary and that the FDA already had the authority to take against herbal street drugs. But the clever producers and marketers of these herbal street drugs have been careful to take advantage of the protections afforded legitimate dietary supplements under the Dietary Supplement Health and Education Act of 1994 (the "Dietary Supplement Act").

The Dietary Supplement Act amended the Federal Food, Drug, and Cosmetic Act in a number of respects. One change was to provide that a dietary supplement would not be subject to regulation as a drug simply because its label or labeling bears a truthful, non-misleading claim regarding its effect on the body. This provision significantly limits the FDA's ability to take action against the peddlers of herbal street drugs who use carefully worded labels to evade FDA review and control.

Moreover, as a result of the Dietary Supplement Act, the FDA must take action against each product individually instead of being able to regulate herbal street drugs as a class. The FDA must prove that a particular formulation of an herbal street drug "presents a significant or unreasonable risk of illness or injury" if used as directed or, if no directions are listed, as it is commonly used. Therefore, a manufacturer can evade enforcement action by changing the composition of the product, while continuing to make the same labeling claims for drug-like mental and psychological effects. Each time the product formula changes, the FDA must evaluate the new formula and build its case from the beginning. The product formula thus becomes a moving target that the FDA must chase. The FDA should not have to chase herbal street drugs.

The Dietary Supplement Act did give consumers some additional protections, but these are inadequate in the case of herbal street drugs. For example, the Act gives the Secretary of Health and Human Services the authority to declare that a dietary supplement poses an imminent hazard to public health or safety. Once such a declaration is made, the dietary supplement can be banned. However, a formal imminent hazard declaration

requires lengthy formal rulemaking procedures, including a trial-type hearing before an administrative law judge. In addition, because what sells the product is its claims rather than its ingredients, the imminent hazard declaration can easily be defeated by a formulation change without any label change. One can easily imagine the slick peddlers of herbal street drugs switching a single ingredient -- from ephedra to kava-kava, another powerful herbal stimulant -- just as the FDA is knocking on their door.

The marketing of herbal street drugs as dietary supplements, rather than as drugs, does not promote any of the goals identified by Congress in the Dietary Supplement Act. The Dietary Supplement Act was intended to promote the public health. Congressional findings in Section 2 of that Act cite the role of a healthy diet, including safe dietary supplements in disease prevention, long-term good health, and reducing health care costs.

Far from promoting the public health, herbal street drugs endanger the health and safety of consumers and give rise to unnecessary medical costs. They are not taken for nutritional purposes or to otherwise improve health and thus are not within the intended coverage of the Dietary Supplement Act. The manufacturers of herbal street drugs should not be permitted to abuse this Act by using it to legitimize the marketing of dangerous products. A statutory amendment to correct the inclusion of herbal street drugs in the language of the Act would achieve the intent of Congress by closing a loophole that Congress never intended to create.

Herbal street drugs killed young Peter Schlendorf. We have to make sure that this does not happen again. We have carefully drafted this legislation to target the class of products that killed Peter. We must take action quickly. I urge my fellow Senators to support this effort and quickly pass this legislation. If we wait, herbal street drugs may end another promising, young life(?)

* call David Nelson 2:00 709 Hart

* Defn.—

— Four Dems Tuesday.
Kennedy — and four dems Wednesday

- Time frames/hammers —
  - take hammers out —
  - time frames are current law —

- animal drugs.

3rd Party Review —
3 issues class III

Staff request
include class II devices that have clinical elements to them

Scope / size of pilot

- FDA has been trying to draw a line on clinical data.
- FDA alt. — some in class III that don't have clinical data (really class II).

— Alex — Wellstone's office —

— Industry was enthusiastic about pieces of class III going out —
— adopt as guidelines

Scope — Guidance in order to get consistency from 3rd parties
30-40% of class II — (and class I non-exempt).

— Brought into the fact that you have guidelines —

Status of guidances — some exist —

device categories that go into pilot. — 250 in first year
— 100 in second year
— 100 in third year

FDA 5/13 Safety office (L)

"Other"

① - add word safe, effective — will push
rev. order won't push v. hard

② No FDA wants
Pokes stones - ok

③ ok

④ ok

⑤ ok — ~~goes out~~

⑥ May not be.

? ⑦ Pediatric labeling - didn't have language cleared from WH —

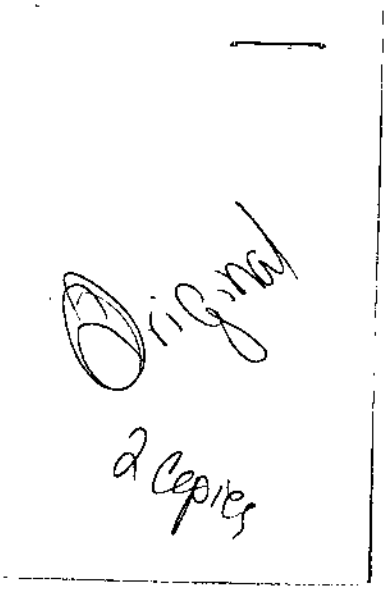
⑧ people pushing also — w/Jane to get studies done up front. —

Tomorrow's mtg

— We go to Kassebaum's staff —

— narrowing of Coats/broader device proposal. —

- Thank you for dialogue
- summary of areas of agreement
- sent by us that we want a bill
-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FDA BACKGROUNDER

U.S. FOOD & DRUG ADMINISTRATION

FDA: A Record Of Accomplishment

Faster Drug Approvals

- 82 new drugs approved in **16.5 months** (median) in Calendar Year (CY)1995, compared with 62 new drugs approved in **19 months** in 1994

- 28 of the 1995 approvals were new molecular entities (NMEs)—brand new drugs as opposed to new formulations —and were approved in **15.9 months** (median), compared with 22 NMEs approved in **17.5 months** in 1994

- 15 of the 1995 approvals were "priority" drugs —having important therapeutic value—and were approved in **6 months** (median), compared with 17 "priority" drugs approved in **15 months** in 1994

- 13 of the 1995 "priority" approvals were user fee drugs approved in **5.9 months** (median), compared with 12 "priority" user fee drugs approved in **10.4 months** in 1994

Improved Device Reviews

- 5,594 510(k)s (which account for about 98% of medical devices) reviewed by FDA in **138 days** (mean) in Fiscal Year (FY) 1995, compared with 5,498 in **182 days** in FY 1994

- 27 PMAs (premarket applications for certain Class III devices) reviewed by FDA in **20.2 months** (mean) in FY 1995, compared with 26 PMAs in **21.6 months** in FY 1994

The Record on Reinvention

As part of Vice President Gore's National Performance Review, the FDA has announced more than 30 FDA regulatory reinvention initiatives since March 1995. These initiatives will reduce regulatory burdens and streamline the regulatory process, while maintaining vital public health safeguards and speeding the marketing of safe and effective new drugs and medical devices. Following is a partial listing of these initiatives:

- Speed up approval process for cancer drugs by using tumor shrinkage as surrogate marker for accelerated approval decisions
  Impact: Cut years off development times and months off FDA review

- Expand patient access to experimental cancer drugs approved in other countries
  Impact: Make it easier for patients to have access to promising but still experimental therapies

- Increase patient representation on cancer drug advisory committees
  Impact: Give patients more of a voice in the drug review process

- Clarify requirements for doctors studying already approved cancer drugs
  Impact: Reduce paperwork for doctors and free FDA staff for other priorities

- Eliminate Establishment License Application (ELA) for most biotech drugs
  Impact: Reduce paperwork burden for industry and speed up marketing of biotech drugs

- Eliminate lot release requirement for biotech drugs
  Impact: Save time and resources of industry and FDA

- Commit FDA to respond to clinical hold submissions on drugs, including biotech drugs, within 30 days
  Impact: Speed up drug development

- Harmonize application forms for drugs and biologics
  Impact: Improve quality of submissions and reduce paperwork for industry and FDA

- Eliminate preapproval requirement for promotional labeling for biotech drugs
  Impact: Speed up marketing of products and free FDA staff for other priorities

- Allow companies to distribute certain textbooks and journal articles that discuss unapproved uses of drugs and devices
  Impact: Increase access to important scientific information without threatening effectiveness standard

- Allow companies to submit toxicology findings based on first analysis of studies and reduce manufacturing data needed to begin drug tests in humans
  Impact: Speed up drug development

- Develop pilot program for review of low- to moderate-risk medical devices by outside organizations
  Impact: Determine if outside review speeds up process and if integrity of review process can be maintained while allowing FDA to focus resources on higher risk-devices

- Collect user fees for medical device reviews
  Impact: Speed up device reviews using program similar to one already achieving success for drug reviews

- Expand opportunities for export of unapproved drugs and medical devices to industrialized countries
  Impact: Widen industry markets for products and encourage American companies to keep operations in United States

- Exempt up to 125 categories of low-risk medical devices from premarket review, adding to 441 categories already exempted
  Impact: Speed up marketing of medical devices and free FDA staff for other priorities

- Allow manufacturers of biological drugs to get licenses for pilot facilities instead of having to build full-scale manufacturing plants
  Impact: Reduce manufacturers' start-up costs and speed up marketing of drugs

- Exclude drug and biologics manufacturers from requirements for most environmental assessments
  Impact: Reduce industry costs in preparing assessments FDA has found unnecessary

The International Record

- The General Accounting Office reported in October 1995 that **approval times for NMEs were shorter in the United States than in the United Kingdom.**

  - in FY 1994, 32 NMEs were approved in the United Kingdom in a median time of 30 months
  - in CY 1994, 22 NMES were approved in the United States in a median time of 18 months

- FDA's median approval time for new drugs approved in CY 1994 and 1995 was **as fast as** that in the United Kingdom and **faster than** those in France, Spain, Germany, Australia, Japan, Italy and Canada according to preliminary data from the Centre for Medicines Research (CMR), an industry-funded, not-for-profit research group in the United Kingdom. The median review time in the United States and the United Kingdom was approximately 1.3 years according to *CMR News,* Spring 1996.

- The United States has had **more first launches** of worldwide NMEs than any single European country since 1990. In fact, analysis of worldwide NMEs launched in the United States and Europe showed the United States has had a higher percentage of first launches than the top three European countries combined, according to *CMR News,* Spring 1996.

  - United States: 33%
  - United Kingdom: 14%
  - France: 9%
  - Germany: 7%

#

Our perspective

Risky reform

Go slow in making FDA changes

In 1955, while preparing a new anti-polio vaccine, Cutter Laboratories of Berkeley, Calif., accidentally introduced live polio viruses into what was supposed to be a dead-virus serum. More than 100 patients contracted the disease and 11 died before the tainted vaccine could be pulled from distribution. Congress responded by greatly expanding the authority of federal regulators to scrutinize every step of a drug's development and manufacture.

Those powers are among dozens that would be curtailed by a far-reaching Republican proposal to streamline — indeed to weaken — the federal Food and Drug Administration. The agency approves new drugs, medical devices and food additives.

The legislation goes way too far, way too fast.

A package of bills, moving separately through both houses of Congress, would tighten FDA deadlines, ease the paperwork burden on medical manufacturers, sweep aside state regulations that exceed federal standards, greatly expand the use of private laboratories to test new drugs and medical devices, and reduce the FDA's powers in a variety of ways.

The reforms are propelled in part by a legitimate concern: that FDA paperwork may keep promising drugs off the market and hamper American manufacturers in the race for cutting-edge technology. But these bills rely on untested techniques and remove too many of the safeguards that keep risky products off the market. Making modest changes, in the direction the FDA is already heading, is the way to go.

If the problem is a bottleneck in new-product approvals, for example, why not give the FDA more staff or the power to employ outside laboratories? These bills allow manufacturers to hire private labs directly, then submit their results to the FDA. If private labs come to depend on repeat business from manufacturers, the potential for conflict of interest is simply too great.

If the goal is merely to expedite FDA review, why do the bills allow manufacturers to shield basic test results unless the FDA specifically asks for them? Currently, this "primary" clinical data is part of the routine application. Separating that data only adds an extra step to the review process and invites the suspicion that companies have something to hide.

And if the legislation's authors don't mean to dilute FDA standards, why do they shift the burden of proof — from the manufacturer who must now prove a product safe before bringing it to market, to the FDA, which would have to prove that a product is dangerous before blocking its introduction?

The bills' sponsors say these measures are necessary because the FDA is incapable of reforming itself. But that is demonstrably false. Since 1987, the FDA has cut approval time for new drugs by half, to 16.5 months, and has cut the review time for most new medical devices by more than one-fourth. A recent study by the General Accounting Office found that in 1994, the FDA approved new drugs faster than its counterparts in Great Britain, Germany, France and Japan.

This is not to say that FDA reform is unnecessary. The review process for new medical devices remains tortuous and overlong. Manufacturers such as Minnesota-based Medtronic deserve a more "transparent" FDA so they can track their applications through the regulatory pipeline. And, as Rep. Jim Ramstad, R-Minn., has pointed out, third-party review has been used successfully by other agencies and could be expanded at FDA with proper safeguards.

Under some pressure from Congress and industry, the FDA has started pilot projects to expedite medical-device approval and use outside labs for new-drug applications. Those pilot projects should be expanded and accelerated. But it's too soon to say that the risk of good drugs kept off the market outweighs the risk of bad drugs unleashed on it. Since the subject is science, the FDA deserves to be tested by scientific method, not reformed by untested methods.

EDITORIALS

Sniping at the FDA

REPUBLICANS have gotten themselves into such a snit about the excessive amount of time the Food and Drug Administration spends reviewing new drugs that they are in danger of losing sight of the big picture.

Namely, the agency has tackled the problem itself, done a lot to streamline the review process and continues to move in the right direction.

GOP critics say patients and businesses are hurt because the FDA takes too much time to approve drugs and medical devices. No one disputes that in the past the agency has moved slowly. However, some GOP spin doctors overlook the fact that the median approval time for new drug applications has been cut in half. Today some drugs are approved in just six months.

Furthermore, the agency has an excellent track record for safety. Its regulators are very careful, but their thoroughness pays off in quality and patient confidence. Drugs approved by government regulators in Great Britain, Germany and France have had to be withdrawn far more often those that have won the FDA's stamp of approval.

Also to their credit, officials of the FDA are making special efforts to speed up federal approval of cancer drugs — aiming to knock a year off the process. And they're doing more to make cancer drugs that have been declared safe abroad available here.

Even so, frenzied House and Senate Republicans press ahead with demands to overhaul the FDA as though none of this were going on. Particularly troubling is the insistence on requiring faster reviews and permitting some parts of the drug-approval process to be contracted out to private vendors.

Certainly these accomplishments need to be understood. It's hard to believe that congressional Republicans could try to undercut such efforts — unless their goal is political gain rather than the health of America's people.

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Tuesday, *May 7, 1996*

HOW WE SEE IT

Keep watchdogs on job

Imagine going to court against a powerful manufacturer only to learn that the judge had been selected and paid by your opponent with promises that if he handled the case appropriately he'd likely be hired again. Does that sound like justice? Does it sound fair? Of course not. But that would be the result of three bills currently under consideration by the U.S. House of Representatives to privatize the Food and Drug Administration's review functions.

Pity the chickens: If the measures pass, the safety of drugs, medical devices and foods would be controlled not by the public's watchdogs at the FDA but by industry-retained reviewers. The foxes themselves wouldn't be watching the henhouses, but they would be writing the guards' job descriptions and paying for their work. Meanwhile, all of us chickens would become fair game.

The contention among pharmaceutical companies, medical device manufacturers and certain food producers is that it takes too long to receive approval for new products, and they've pumped thousands of dollars into the political campaigns of many legislators to influence their votes.

On the other side are the FDA and many consumer groups who fear what could happen to public health if monied special interests determine which products could go on the market and when.

Fastest approvals: According to the General Accounting Office, in 1987 the average approval time for new drugs was 33 months. In 1995, approval time had been reduced to a median of 16.5 months. For the 15 highest priority drugs, the median approval time was six months. Studies both by the GAO and the British-based Centre for Medicines Research all demonstrate that American patients have access to therapeutically important new drugs that have been proved safe and effective sooner than the citizens of any other nation.

While the three bills under consideration are called "reform" bills, none of the so-called reforms does anything to improve public health or safety. Currently, FDA reviews are conducted by scientists, engineers and medical researchers who work for the public. They comply with stringent financial disclosure and conflict-of-interest requirements designed to protect the decision-making process against bias.

A reviewer paid by a drug company to decide the future of that company's products can hardly be unbiased. We don't think the public good is served by such an arrangement.

The Buffalo News/Friday, May 3, 1996

Make sure new drugs are safe

Don't sacrifice FDA safeguards for speed and profit

THE FEDERAL Food and Drug Administration has made considerable progress in loosening its regulatory strings to approve new products faster to the potential benefit of patients and consumers.

Changes in the process used to approve cancer drugs and to provide quicker access to drugs already approved in other countries are among sensible reforms already implemented at minimal risk to the public.

However, changes being pushed now in Congress go too far, too fast. They risk the public's health in a mad rush to deregulate without due regard for the consequences.

The FDA's historic mission has been to protect the public from dangerous drugs, medical devices and food additives. Proposals in the House to shift much of that duty to the private sector — the same sector that profits from new products — are akin to having the fox guard the medical hen house.

One, for instance, would shift the burden of proof for new food additives. Instead of manufacturers having to prove that products are reasonably safe, the FDA would be saddled with having to show that additives are unsafe. That's a nearly impossible standard to meet for products on which not enough studies had yet been done.

Another proposal would take the impartial FDA out of the business of doing safety reviews for new products. Instead, the reviews would be done by an FDA-approved contractor to be picked by the very company seeking the approval.

It doesn't take much imagination to see the potential for chicanery and conflict of interest there. But even assuming the private sector is strictly scrupulous, FDA Commissioner David Kessler is persuasive when citing another shortcoming.

Kessler notes that FDA workers who review data about various products have a broad base of knowledge to draw on when assessing a new item's claim. For example, he said, an FDA reviewer a few years ago uncovered fraudulent data being used to push a skin cream designed to protect U.S. soldiers from chemical attack. The FDA specialist was able to spot the phony data only because they were out of line with results from other products he had reviewed.

That kind of safeguard would be lost with the congressional proposal to let independent contractors take over the task. When high-risk products are involved, the results could be deadly.

The FDA already is further streamlining its operations. It has begun work on pilot projects to involve third parties in reviewing low- and moderate-risk products. New, less rigorous standards for testing and using cancer drugs were announced a few weeks ago. And approval time for drugs has been significantly reduced.

Republican prodding and anti-regulatory fervor no doubt played a part in many of those improvements, and most make sense.

But reform can go too far. These do, and so do some of the other efforts being pushed by a House subcommittee on health. Congress should heed Kessler's warnings and let the FDA keep putting safety first

MONDAY, FEBRUARY 6, 1995

"WE DON'T WANT ANYONE INTERFERING WITH OUR SALES"

Edward M. Kennedy

Prescription for Disaster

Republican legislation in Congress to "reform" the Food and Drug Administration would dramatically weaken the FDA's ability to protect the public health. The ..t on the FDA is particularly ous, because the agency is responsible for the safety of a quarter of all the products in the American economy—especially the food we eat and the prescription drugs we take.

The Republican bills would water down requirements that guarantee these products are safe and effective. They would turn over t / of the FDA's most important functions to private industry, with built-in conflicts of interest. They w give preference to products approved in Europe and other foreign countries, where the public is less well protected. And they would saddle the agency with so / new bureaucratic requirements and so much red tape that it w be unable to do its job. If the Republican proposals are enacted, Americans can expect many more drug disasters like thalidomide and DES, medical device failures like the Dalkon shield, lethal vaccines like the Cutter polio vaccine, threats to the blood supply and even threats to the food supply, such as the "mad cow disease," which has rocked the British beef industry.

The Republican proposals, by eliminating essential FDA oversight of the production of medical products, threaten the safety of drugs, medical devices, blood and vaccines. A minor manufacturing change that alters the solvent used to kill viruses in blood products can result in ineffective sterilization of the blood, risking the transmission of AIDS or hepatitis. A change in the filters used to produce vaccines can turn a protective vaccine into a killer. A change in filters used to produce the Cutter polio vaccine resulted in 200 cases of polio in the 1950s, before the FDA required more rigorous standards. Under the Republican bills, the agency would no longer be permitted to review such manufacturing changes in advance to ensure that the public is protected.

The House Republican bill eliminates existing requirements for the FDA to approve certain products that can be dangerous to public health—such as leaky surgical gloves or faulty diagnostic tests. In recent weeks, it was revealed that a defective new AIDS test kit was distributed to 2 million patients abroad. American consumers, however, were spared exposure to this dangerous product.

The Senate bill gives the FDA only 90 days to review certain new food additives, even though these additives can result in the involuntary exposure of millions of Americans to potentially harmful substances.

The Dalkon shield, used to prevent pregnancy, injured 90,000 women because of a design flaw. This tragedy led to legislation strengthening FDA oversight of medical devices. The Shiley heart valve proved vulnerable to breakage, killing the patients. Before the valve was withdrawn, the manufacturer proposed a new version six times more dangerous than the original. The FDA rejected it, but 4,000 patients received it in Europe. Under the Republican bills, the FDA's ability to prevent such tragedies would be seriously compromised.

The House bill would reduce standards for approving a new use for a drug already approved for another purpose. The lower standard would restore the pre-1962 requirements that brought us DES. In recent years, drugs approved for life-threatening heart arrhythmias were widely prescribed for mild arrhythmias. This "off-label" use of the drug has been estimated to have caused as many as 50,000 deaths.

Both the Senate and the House bills contain an inherent and outrageous conflict of interest. They are designed to shift responsibility for product approval from the independent experts at the FDA to private businesses. The profitability of these firms would depend on the fees they attracted from the very companies whose products they review. The Senate bill pretends to give the FDA final approval of the decisions of these private reviewers, but the time frames for action are so short and the rules for oversight so limited that the agency would be reduced to little more than a rubber stamp. The House bill is even more extreme, removing the FDA from certain product approvals altogether.

As hard as it may be to believe, another provision in the bills would prohibit the FDA from requiring companies to make information available to patients on possible dangers of prescription drugs. At a time when hospitalizations from improper use of prescription drugs by senior citizens cost Medicare $20 billion a year, it is foolish to deny patients information they need to monitor their use of medications.

The Republican bills also contain provisions to micromanage the agency. The strategy of the Republicans and their special interest constituency is clear: Set up procedures that make it impossible for regulatory agencies to protect the public, and then use their failures as an excuse to dismantle them.

The assault on the FDA is fueled by a well-funded campaign alleging that patients are suffering because foot-dragging by the agency is denying them needed drugs already approved in foreign countries. Much of the funding for this campaign comes from tobacco companies, who have their own reasons to discredit the FDA. In fact, FDA drug review time was cut by 40 percent between 1987 and 1993. According to the nonpartisan congressional General Accounting Office, by 1993 the United States was reviewing drugs as fast as, or faster than, Great Britain and other foreign countries. Review times in the United States have dropped even farther since.

And unlike foreign approval authorities, the FDA has combined speed with safety. Between 1970 and 1992, 56 drugs were introduced in France, Germany, Great Britain and the United States that subsequently had to be withdrawn because they were unsafe. Only nine had been approved in this country, compared with 31 in France, 30 in Germany and 23 in Great Britain.

The FDA is not perfect, but it is still renowned as one of the most effective regulatory agencies in the world. There is always room for improvement, but the Republican proposal is a blueprint for demolition, not modernization, and Congress should reject it.

The writer is a Democratic senator from Massachusetts

The Boston Globe

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The FDA and Shannon McDermott

Janet McDermott is waging a valiant struggle to get medication that will prevent the seizures suffered by her daughter Shannon. But Shannon's plight should not encourage support for a bill in Congress that would force the Food and Drug Administration to speed up the approval process for new drugs.

The McDermotts, who live in Marshfield, have tried every treatment recommended by Shannon's doctors to relieve the seizures. The latest drug prescribed for the 8-year-old is Sabril, not yet approved in the United States. Shannon's mother must go to Canada for it.

Mrs. McDermott has also traveled to Washington, at the expense of a pharmaceutical trade group, to lobby on behalf of a bill that would shift the balance of regulatory power at the FDA. This measure would apply to every experimental medicine, from cancer treatment to baldness cure, and to medical devices like heart valves or prostheses.

Under present law, the FDA is exceedingly careful about which drugs it qualifies for use. Before an application can be accepted, medicines must undergo animal tests and at least two clinical trials on people. Approval for Sabril was delayed when the first use on animals showed that it might cause holes in the brain. Subsequent tests showed that this condition did not apply to humans.

It is reassuring that federal law demands rigorous testing. The legislation, which just cleared the Senate Labor Committee over the objections of Sen. Edward Kennedy, would change the emphasis of the FDA from review to approval. In the most extreme case, the FDA would have to accept a drug cleared by the European Union unless it can state in writing why approval for the medicine should be withheld.

Only four years ago, Congress imposed a user fee on the drug industry. The money is being spent to hire 600 additional reviewers, and approval times have been reduced to 16 months, compared with 33 months in the late 1980s.

In response to public pressure, the FDA has already expedited approval of drugs that fight AIDS and cancer. Other improvements in the process may well be in order, but these are best recommended by an unbiased group before being considered by Congress. An independent review of FDA procedures should be undertaken only when the impact of the user fee can be assessed.

As for Sabril, an FDA spokesman, James O'Hara, says the drug could be offered to Shannon McDermott on a special, individual testing basis. Hoechst-Marion-Roussell, the manufacturer, demurs, saying that it would rather devote resources to testing the drugs on large groups. Shannon would not qualify for such group trials.

That decision is well within the company's rights as a maker of medicine. Julie O'Dell, a company spokeswoman, says the Sabril work should be completed by the end of the year and the drug available for widespread use in 1997. That's a long time in the life of an 8-year-old, but in matters of drug safety, caution is better than haste.

WEDNESDAY, APRIL 10, 1996 THE WASHINGTON POST

The FDA Legislation

UNTIL RECENTLY, the Senate bill to streamline some drug and device approval procedures for the Food and Drug Administration was moving forward cautiously. The bill that emerged from committee, though, is incautious—loaded with last-minute changes that destroy any claim to judiciousness.

An amendment by Sen. Dan Coats (R-Ind.) seizes on and vastly expands what would have been an FDA pilot program—an experiment allowing companies to opt for a private third-party route that might speed up the more onerous parts of the approval process, whose results the FDA would then look at before giving the final sign-off. The Coats amendment turns this into a procedure in which any manufacturer could request the third-party review for any device, could itself choose the private company or companies to perform the review and could decide how much to pay for it—a process that gives huge and obvious incentives to third-party review companies to be as fast and undemanding as possible. And under this scheme, the chosen outside reviewers, not the FDA, would effectively have the final say. (The FDA would have to prove harm in order to prevent a device's coming to market, rather than, as now, the manufacturer's having to prove safety.)

The idea of prodding the FDA to offer third-party review as a road to efficiency, without recklessly dismantling safeguards, was at least consistent with the stated argument from "reform" proponents that the purpose is not to weaken safety protections but merely to serve industries' and patients' interests better by bringing the long, drawn-out approval process to conclusion more quickly. Accordingly, the pilot program would have limited the experiment to devices classed low or moderate risk already, limiting the chances of danger in case the untested system proved too porous. The Senate committee, though, changed that, extending eligibility for the third-party system to all devices—including the ones classed as high risk.

These risks aren't exactly abstractions. Medical devices get embedded in the human body, hold people's bones together, are carried in the body for years. Does anyone seriously think for a moment that there is a public outcry for the removal of incentives to double-check the safety of things that shunt fluids from the human brain, clear heart patients' veins, are buried in the skin of people's arms? Or, for that matter, for the removal of an independent check on the safety of drugs and the food supply?

Arguments over efficiency and how best to get the job done are legitimate, but the public interest in having the FDA ride herd effectively on the safety of these miraculous medical devices and incredibly powerful drugs remains high. The Senate committee add-ons don't sufficiently recognize or respect that fact.

New York Times, Saturday, April 6, 1996

Streamlining the F.D.A., Safely

The Clinton Administration is making it easier for cancer patients to get promising drugs that have not been fully tested. By loosening some of the Food and Drug Administration's rules to accelerate access to experimental drugs, the White House may defuse more sweeping and dangerous reforms under consideration by Congress.

The F.D.A.'s job is to insure that drugs and medical devices are safe and effective and that food additives are risk-free. The agency gives approval only after lengthy clinical trials by the manufacturer. But many companies complain that the F.D.A. is slow to respond, escalating costs. In addition, some groups representing AIDS and cancer patients say that its bureaucracy denies them faster access to promising remedies.

Congress, the companies and the agency are now struggling to get drugs and medical devices to needy patients as quickly as possible without jeopardizing public health or sacrificing the standards of safety and efficacy that give consumers confidence in F.D.A.-approved products.

The Clinton Administration proposes faster approval for cancer-fighting drugs. Previously, the F.D.A. asked for proof that an experimental drug would help a patient's chances for survival or improve that patient's quality of life. Under the new rules, a drug can be approved based on a "partial" positive response, like shrinkage of a tumor. In addition, companies making experimental drugs that have already been approved overseas can seek permission to distribute those drugs to American cancer patients even before the F.D.A. has given final approval. These measures, which need no further approval, will take effect immediately and could apply to about 100 drugs under study.

The new initiatives are welcome but unlikely to appease Congress, which is pressing for more sweeping F.D.A. reform. Last month the Senate Labor and Human Resources Committee approved a bill sponsored by Nancy Kassebaum, Republican of Kansas, that calls on the agency to expedite clinical investigations of new drugs, devices and biological products as well as breakthrough drugs for life-threatening diseases. If the agency fails to review most applications within six months, the product sponsors could force it to contract with outside experts to complete the process.

Similarly, a bill being pushed on behalf of the House G.O.P. by James Greenwood of Pennsylvania sets tight approval deadlines and would turn over some F.D.A. review authority to third parties.

The F.D.A. would retain a supervisory role. But the outside experts and "third parties" envisioned in both the Senate and House bills could, under the guise of regulatory reform, lead to the privatization of many of the F.D.A.'s functions and undermine its role as an independent government protector of public health.

The drive to reform the F.D.A. comes at a time when the agency has been improving its performance. In 1994, 96 percent of new drug applications were approved within the 12 months allotted under current law, and the agency has been streamlining many of its internal procedures. Important life-enhancing drugs and medical devices should obviously get to consumers as quickly as possible. That is what the Administration's new cancer drug initiative aims to do. But safety and effectiveness should not be sacrificed for efficiency. At the moment, the Administration seems more mindful of that than Congress.

Houston Chronicle March 23, 1996

Don't let Congress cripple the FDA

By JOE GRAEDON
and TERESA GRAEDON

People's Pharmacy

Americans are an impatient people. We have grown accustomed to instant coffee, one-hour photo processing, fast food and taxes.

Delay is irritating. If you don't believe us, just try stepping into the express checkout lane with more than 13 items.

Obsessed with speed, we tend to forget there can be risks to rushing. We see every innovation as progress and rarely pause to examine its potential problems.

This may explain why the current legislative proposals to "streamline" the Food and Drug Administration seem so appealing. Everyone wants a quick cure for cancer, AIDS, Alzheimer's disease and arthritis. In its haste to hurry the FDA's approval process, Congress may well hamstring this critical agency.

We are not big fans of the FDA. We often criticize this bureaucracy for its insensitivity and inflexibility. But without this watchdog, Americans would be at far greater risk of injury and illness.

Even under the current system, there are flaws. A General Accounting Office study revealed that more than half of the new drugs approved by the FDA are later found to have serious or even life-threatening consequences that did not show up in the original data.

It is estimated that more than 100,000 Americans die each year as a result of prescription drug problems. That's the equivalent of a 727 going down every day. If that many people were dying in plane crashes, there would be an outcry for the Federal Aviation Administration to crack down.

Prescription drug companies are aggressively promoting their products directly to consumers in magazines, newspapers and TV. In addition, many drugs that were once available only by prescription are now sold over the counter. Instead of cutting back on the FDA's oversight, this country needs better protection of the public health.

Millions of women are worried about the unresolved question of whether female hormones promote breast cancer. Reports that Ritalin and a common ingredient in laxatives cause cancer in animals has consumers concerned. And some people are frightened about the possibility that certain blood pressure pills may increase the risk of heart attacks.

Whether Congress cuts the FDA's authority, consumers are more vulnerable today than ever before. Doctors, overwhelmed with paperwork, have a hard time staying current on powerful new drugs. Pharmacists are being stretched to their limits, and managed care is affecting everyone.

As eager as we all are to have new and better treatments, cutting back on drug testing and speeding FDA review may not improve health overall.

Q: My husband has been on Mevacor for years to lower his cholesterol. We read that this drug causes cancer in animals. Is there any danger?

A: We wish we knew. An article in the Journal of the American Medical Association (vol. 275, p. 55-60) noted that lovastatin (Mevacor) and related drugs produce tumors in rodents. Whether this is a problem for humans remains controversial. The FDA does not have a good system for evaluating such long-term risks.

Joe Graedon is a pharmacologist. Teresa Graedon holds a doctorate in medical anthropology and is a nutrition expert. *The People's Pharmacy* with Joe and Teresa Graedon is a call-in show syndicated to many public radio stations.

King Features Syndicate

The New Haven Register

March 21, 1996

EDITORIAL

Keep hands off drug safety checks

Bill before Congress would strip away basic protections on new drugs, medical devices.

Here's a one-word reason why U.S. Sen. Christopher J. Dodd, D-Conn., should vote against a radical overhaul of the Federal Food and Drug Act: thalidomide.

Between 1959 and 1961, thousands of pregnant women in Europe, where the drug was approved, took it for nausea. They and American women, taking the drug in trials, gave birth to some 10,000 infants with deformities ranging from legless torsos to toes and hands attached directly to the body.

In 1962, Congress passed a law requiring that companies prove drugs are safe and effective before being sold in the United States. It's hard to imagine such a basic health protection being stripped away.

However, a bill before the Senate's Labor and Human Resources Committee on which Dodd sits, would do just that. Drugs already approved in Europe, as was thalidomide, would be approved for use here if the Food and Drug Administration did not meet stringent review deadlines.

The possibility of another thalidomide baby tragedy is just one of the horrific possibilities raised by this bill.

In 1976, Congress again expanded the FDA's authority to regulate medical devices after another medical disaster the Dalkon Shield. Before the birth control device was withdrawn, thousands of women were left infertile and an estimated 15 died of injuries it caused.

Again, protection from a similar catastrophe would be stripped away by the pending legislation if an FDA review isn't speedy enough.

This bill would also end the FDA's approving medicines for specific uses. However, a drug that is safe for one use may not be safe for another.

This legislation is deliberately destructive of basic medical safeguards. It demands cuts in time taken for reviews by a third. But, it offers no extra money for staff to do the reviews effectively.

While the FDA review process has been laggard, Congress solved much of the problem with 1992 legislation that has let the FDA work with pharmaceutical companies to speed reviews. Ten years ago, it took nearly three years for FDA action. Now, most new drugs are approved within 12 months.

In recent years, the FDA has actually approved new drugs more quickly than Germany or Great Britain. Further, the FDA has a far better safety record. Between 1970 and 1992, only nine drugs were withdrawn because of safety reasons in the United States. In Great Britain, 32 dangerous drugs had to be taken off the market; in Germany, 30. The most serious side effects of the withdrawn drugs were death, paralysis, heart attacks and liver damage.

The FDA's speed and procedures can use improvement. But the alternative in this bill is nothing short of a medical hell of unnecessary death and tragedy.

The Des Moines Register

A GANNETT NEWSPAPER

THE REGISTER'S EDITORIALS

Rushing drugs to market

If the FDA *speeds approval,*
mistakes are more likely.

The nation's drug companies invest fortunes in researching new drugs, and every day that the Food and Drug Administration delays approval of marketing the drugs, it causes the makers to lose big bucks.

It also saves lives. But that gets little attention.

A bill in the Senate would speed up the approval process, forcing the FDA to meet tighter deadlines. If the FDA missed the deadline on a drug already approved for use in Europe, use here would be approved by default. Because European standards are not as tough as the FDA's, that could be dangerous. Thirty years ago, thalidomide was approved here on an experimental basis after approval in Britain. A few paid an agonizing price in birth deformities.

The Senate bill would enable "off-label" use of any drug for a purpose other than that for which it was developed and approved, even if the off-label use had not been tested. In the late 1980s, two drugs approved for treatment of abnormal heartbeats began to be routinely prescribed for milder heart problems, based on the assumption it was safe, although the FDA had not completed testing for such use. What the agency discovered was that use of the drugs for the "off-label" condition doubled the patient's risk of dying.

The FDA has speeded its drug-approval process markedly in recent years. But there are limits, rooted in safety. The agency is already approving drugs for life-threatening ailments in less time than the bill would require. But an unending push for more speed can be satisfied only at the expense of care. "One of these days," said FDA Commissioner David Kessler, "we are going to make a mistake."

The bill poses the FDA as the national enemy, pitted against the best interests of the drug firms and the ill. In truth, FDA is a national guardian, protecting the public from the consequences of undue haste.

The speed-up bill, sponsored by Kansas Republican Nancy Kassebaum, is up for a vote Thursday in the Senate Committee on Labor and Human Resources. Iowa's Senator Tom Harkin is a committee member. He and his colleagues should vote "no."

The Washington Post

AN INDEPENDENT NEWSPAPER

Prodding the FDA

IF YOU'VE heard the ideological fervor with which anti-regulatory types habitually attack the Food and Drug Administration, you might be surprised at the sorts of issues that are occupying the warring sides on FDA "reform" legislation in the Senate. The bill, sponsored by Sen. Nancy Kassebaum (R-Kan.), has little in common with the plans that came out of Speaker Newt Gingrich's Progress and Freedom Foundation or the Heritage Foundation last year. Those groups regard the FDA as a particularly noxious and burdensome example of regulatory excess, and their visions include stripping or privatizing the FDA's enforcement powers or eliminating the requirement that a drug be "efficacious" as well as "safe" in order to go on the market.

None of these approaches got the support of the mainstream pharmaceutical industry, which relies on the FDA and gleans both legal and marketing advantages from its stamp of approval both here and abroad. What the drug companies, the medical-device companies and the young biotechnology industry wanted was to prod the agency out of longstanding habits of bureaucratic backlog, foot-dragging and unnecessary paperwork. The Kassebaum bill does this by a complicated system of deadlines, structural changes and "hammers"—points in the development process at which the FDA would have to approve or disapprove a drug or explain why it hadn't acted. As it happens, these are areas where the FDA has itself made strides, with agency head David Kessler instituting reforms to reduce backlogs and bottlenecks.

The Hill fight turns out to be mostly about whether this is happening fast enough, how much further and faster it can safely be pushed and who—FDA or Congress—should have final say over its shape. Parts of the bill are designed to speed up the progress of big drug trials and reduce the time needed to file certain kinds of applications. The questions here are simple scientific ones: What is the optimum setup for a big drug trial involving 4,000 college students? Can that number be safely cut to 1,500 students?

It may very well be, as the drug companies complain, that years of FDA caution have "barnacled" the process till a push like this was needed to get things moving faster. But aside from the motivational qualities of the threat of legislation, you've got to wonder whether these are questions best settled by a legislative body containing, on the Senate side at least, exactly one doctor.

The New York Times

NEW YORK, TUESDAY, MARCH 12, 1996

Go Slow on F.D.A. Reforms

Americans who remember the thalidomide disaster in England 35 years ago, when many mothers who had taken the drug had babies with serious birth defects, were grateful that the Food and Drug Administration kept it off the market in this country. But now the F.D.A. has come under fire for taking too long to approve drugs and medical devices. Congress is considering legislation that is designed to speed things up, but that may go too far in loosening regulatory safeguards.

The F.D.A. aims to insure that drugs and medical devices are safe and effective and that food additives are safe. Companies applying for approval of new drugs and devices submit their research data to the F.D.A., which assembles expert advisory committees to help determine whether the safety and efficacy standard has been met.

But over the years there have been complaints that the agency's regulatory machinery grinds far too slowly. Many companies that manufacture drugs and medical devices complain that the process often takes years. Some patients with serious or terminal diseases like cancer or AIDS have been frustrated by agency rules that prevent them from trying experimental drugs.

Senator Nancy Kassebaum, Republican of Kansas, recently introduced legislation designed to ease the rules. Her proposal would set a deadline of four months for the review of breakthrough drugs, down from the present six months. It would cut approval time for all other drugs from 12 to 6 months. In addition, the proposed bill would allow approval of medical devices on the basis of less rigorous research than is now required.

If the agency fails to meet the specific review times, a company could still market its product on the basis of approval by the European Union. That's a return to the days before the agency was required by a 1962 law to make an affirmative finding of safety and not just rely on the testing of others.

Dr. David Kessler, the F.D.A. Commissioner, insists that internal management reforms have already brought good results. Approval time for new drug applications was reduced from an average of 33 months in 1987 to 19 months in 1992. In 1994, 96 percent of new drug applications were acted on within the allotted 12 months. With the F.D.A. already making good progress, Congress should be wary of pressing it to move too fast in approving new drugs. Haste could prove hazardous.

Sugar-Coating a Bitter Pill

Sweet Talk Aside, the GOP and the Pharmaceutical Industry Want to Cripple Safety Testing

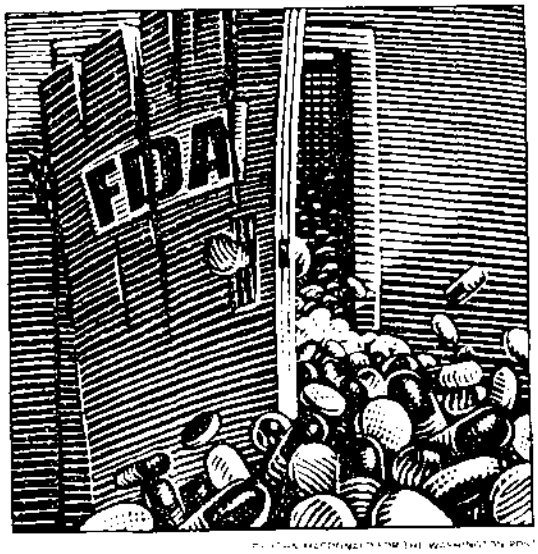
By Thomas J. Moore

THE DRUG industry and its allies call it "streamlining the Food and Drug Administration." Patients are promised they will get new drugs more quickly. Hidden behind this slick sales pitch is the most frightening effort to roll back drug safety and efficacy laws since federal regulation began in 1906.

With Senate Republicans promising floor action as early as next month, this legislative blitz may succeed before a broader public realizes what's at risk. On Wednesday the Senate Labor Committee meets to mark up its bill. While described in some press accounts as "moderate," it would achieve an unprecedented cutback in drug testing requirements. The House Commerce Committee—whose chairman is highly critical of the FDA—has promised to get a bill to the floor promptly. The Pharmaceutical Research and Manufacturers Association and its allies already have a major lobbying campaign in high gear. It features ads attacking the FDA, a letter-writing effort and the usual generous campaign contributions. Industry lobbyists are even rounding up patients dying of serious diseases or their relatives and flying them to Washington to plead with key members of Congress.

Indeed, why do we insist on a powerful FDA that requires elaborate clinical testing of each new drug that can take 10 years to complete and a year to evaluate? Why not let medical researchers, doctors and patients make the judgments about drugs with minimum government interference? We test because prescription drugs regularly cause the most painful injuries imaginable—hideous birth defects, irreversible brain damage, life-long addiction and thousands of preventable deaths.

Other damage is less severe but more widespread. For example, 20 of the 200 most commonly prescribed drugs cause sexual disfunction. Two of the most widely used classes of drugs—beta-blockers and benzodiazepine tranquilizers—impair judgment and the ability to think clearly. Painkillers, including aspirin, cause thousands of hospitalizations each year for perforated ulcers or internal bleeding.



Having recently studied the toll of death and injury from prescription drugs under existing law, I shudder at proposals to weaken an already inadequate system. Based on my research, I estimate that each year prescription drugs injure about 5 million Americans enough to require medical treatment. Another 1 million are injured so severely they require hospitalization. Deaths could be 100,000 or more. Overall, you are 10 times more likely to be severely injured by a prescribed drug than in an automobile accident.

These figures have to be approximations because there is no systematic monitoring of the adverse effects of drugs. In most states, you must report an auto accident with a few hundred dollars damage. But when a prescription drug is suspected of causing death or serious injury, neither doctors nor hospitals have any legal obligation to report it. In one famous study of Rhode Island doctors, only 55 of 27,000 significant adverse drug reactions believed to have occurred in one year were ever reported. Injuries occur when anything goes wrong in the complex system that requires thorough clinical testing, intensive FDA review, effective post-market surveillance, alert physicians and knowledgeable patients. But without adequate clinical testing the whole system is crippled from the start.

Thousands of lives are also at risk when drugs that the FDA-approved for one medical condition become widely prescribed for another. This is called "off-label" use, and two Senate bills being championed by the industry would encourage still more of this practice. Such off-label use helped create the nation's worst drug disaster.

A family of drugs that were FDA approved for life-threatening heart rhythm disturbances were widely prescribed for patients with mild irregular heart beats. In 1989, a government-sponsored clinical trial proved conclusively that two of these drugs killed 6 percent of the heart patients who took them in just one year's time. That would mean an estimated 50,000 deaths among similar patients taking all brands of these drugs in just a few year's time—a death toll comparable to U.S. losses in the Vietnam War.

Another loophole in existing law allows drugs to be sold for long-term use without long-term clinical testing. The most frequently prescribed drug today is conjugated estrogen, a hormone that women take after menopause. Last year a large—but not definitive—epidemiological study showed that taking estrogen increased the risk of breast cancer. On the other hand, another study—also not definitive—suggested estrogen may cut the risk of death from heart disease. Here is a drug on sale for decades to millions of people and generating hundreds of millions of dollars in revenue every year. But because even now we haven't done the proper clinical studies—costing a fraction of those sales—we don't know whether it is harmful or beneficial over the long term.

Even more lives are at stake in new questions about the safety of calcium channel blockers—a family of heart drugs taken to lower blood pressure and prevent chest pains. They are taken daily by 7 million Americans. Last year three studies appeared in peer-reviewed medical journals suggesting that some—or possibly all—of these agents may cause heart attacks instead of preventing them. The evidence persuaded an expert panel at the National Institutes of Health to issue an unusual warning, saying the safety of all calcium channel blockers was "unclear" and urging doctors to avoid one of them, short-acting nifedipine (sold as Procardia and Adalat). It doesn't do us any good to get new drugs quickly if we can't tell their effects.

The experience with Prozac, Paxil and other anti-depressants shows that even when a drug proves beneficial, we also need to take a careful measure of its adverse effects. Talk to patients who are taking these popular drugs and you will often get passionate testimonials about the benefits. But you will also hear the sorrow of those who say they've lost their interest in sex. At last official count, there were 242 different adverse effects of Prozac, including 39 separate problems related to genital or urinary systems. About 1 in 5 people who take Prozac experience an adverse effect.

All this explains why clinical testing is so essential, but not why it is so expensive or needs to take so long. Despite its aura of high-tech wizardry, drug research remains a hit-or-miss game where researchers grope in the dark, wrestling with immensely complex biological systems that no one yet understands. This is one reason why 90 percent of drugs that enter human testing fail to win FDA approval. "Drug

development is like watching people who learned how to make a transistor but don't yet know how a radio works," notes experimental pathologist Christian Haudenschild. Biological ignorance is an argument for more drug testing not for less.

Escalating costs of drug development is often used to justify less test-

ing. A Tufts University study estimated it costs $291 million to bring a new drug to market—and the industry claims it costs even more. But the amount spent on the actual human and long-term animal tests is less than $16 million. Where did the rest go? To test the other nine drugs that didn't make it, to ongoing research and to the interest costs of the money over the full period.

Costs are also driven up by drug companies scrambling to copy someone else's winner. There are currently in development 127 drugs that work on the same mechanisms as Prozac or Elavil. Most will never make it to market, but they will help run up the research bill. And finally, testing is so expensive because the effects of many popular drugs are so small that it takes observing thousands of people for several years to detect any measurable effect. Cholesterol-lowering drugs are the classic example. Look at the evidence from the clinical trial of Pravacol, one of the most effective: Among the 3,302 people who took it for five years, there were 74 fewer heart attacks and deaths. Those promoting the drug can say correctly that it reduces the risk of death or heart attack by 31 percent. But of every 1,000 persons who take Pravacol for one year, 995 get no benefit. To produce just this evidence involved screening 81,000 patients, took more than five years and cost millions.

With the health of millions of people at stake, certifying that a drug is safe and effective is one of the most difficult and complex scientific judgments made in our society. Not only do we need rigorous clinical studies, we also need an expert and impartial FDA to judge them. If the final tests of a drug show tell-tale signs that it might be dangerous, I want an agency smart and tough enough to stand up to a powerful pharmaceutical giant with millions already invested.

In the User Fee Act of 1992, Congress showed that we can indeed speed drugs to patients without cutting corners on safety and clinical testing. Using fees collected from industry, the FDA has hired more experts to review drugs—which are now being approved in about half the time it took in 1987. But much still remains to be done.

We need a coherent program to reduce the hundreds of thousands of preventable deaths and severe injuries from drugs. The whole system needs an impartial oversight agency modeled on the National Transportation Safety Board. We need expert panels to identify the drug studies that are too expensive—or not potentially profitable enough—for a drug company to undertake. We need to fix the information system that buries doctors under an avalanche of often biased and unnecessarily complicated data while depriving patients of basic facts about the drugs they take. Prescription drugs remain the biggest commercial source of accidental injury and death for which there is little or no hope of compensation.

Congress is now heading in the wrong direction. We should encourage drug companies to do more testing and less marketing, not enact a law that would achieve the reverse.

Thomas Moore is a senior fellow at the Center for Health Policy Research at George Washington University and the author of "Deadly Medicine: Why Tens of Thousands of Heart Patients Died in America's Worst Drug Disaster."

Allison M. Zieve
And Sidney M. Wolfe

Don't Weaken The FDA Laws

In his Feb. 1 op-ed piece, "Keeping Doctors Up to Date on Drugs," Sen. Bill Frist tries to sell the public on a dangerous idea. He wants to remove the 34-year-old ban that ensures that drug companies do proper testing before they promote a drug or medical device for a particular medical use. The proposal touted by Frist—that drug and medical-device companies be permitted to promote their products for uses never approved by the FDA—strikes at the heart of the processes used to ensure that drugs and medical devices are safe and effective. Not surprisingly, the drug and medical device industries have been pushing this idea for some time.

Referring to "FDA-approved products," Frist misunderstands the federal drug- and device-approval systems. The approval processes do not evaluate the safety and effectiveness of a product in general, but only for a specified use. The FDA weighs the benefits of that use against the risks to determine if, on balance, doctors should be prescribing it for that particular purpose. Manufacturers are permitted to promote and advertise their products only for approved uses—those uses that have been evaluated for safety and effectiveness.

Experimenting with an unapproved (off-label) use exposes patients to unknown risks, usually without their consent or knowledge. A few years ago, thousands of physicians prescribed Tambocor and Enkaid to treat patients

Taking Exception

with mild irregular heartbeats—an off-label use of a drug intended for life-threatening heart conditions. The doctors and drug companies hoped these drugs would prevent cardiac arrest. They were proven tragically wrong when a study funded by the National Institutes of Health discovered that the drugs frequently caused cardiac arrest in recent heart attack survivors. The death toll—measured in thousands—would have been even higher if the companies had been free to promote the drugs even more aggressively for this off-label use, as Frist advocates.

Frist also errs in suggesting that prohibiting sponsors from disseminating information about unapproved uses suppresses discussion or publication in journals of studies concerning off-label uses. In fact, the FDA's policy ensures that such discussion is objective and honest, untainted by the economic self-interest of a manufacturer seeking to expand its product's market. Under the FDA's recent draft policy statement, physicians are free to attend seminars on off-label uses and to publish and read articles on such uses. The product's manufacturer, however, cannot be involved in preparing, financing the dissemination of, or disseminating the material.

To permit written promotion of unapproved—including specifically disapproved—uses would be to pay mere lip-service to existing product-approval requirements and the clear intent of previous Congresses to protect the public from dangerous and unproven drugs and devices. Adoption of Frist's proposal would quickly halt much of the expensive clinical testing of unapproved uses needed to ensure safety. What corporation would invest millions of dollars in safety testing that might detect serious problems with its product when promotion for unapproved uses offers a faster, cheaper route to increased sales?

Finally, Frist states that a busy physician may not have time to seek out the latest information on all drug uses, apparently referring to unapproved drug uses. Yet he wants to relax the restrictions on off-label promotion because, he says, physicians should be trusted "to sort out" the information on unapproved uses. Senator, you cannot have it both ways. If physicians do not have time to seek out the latest information and are dependent on manufacturers sending them material on unapproved uses, manufacturers are likely to monopolize the information flow to physicians. Thus, these busy doctors will not see the complete story on the new use but only the information handpicked by the manufacturers to increase their products' sales.

In short, the purpose of the approval processes is to prevent doctors and their patients from being misled by unproven health claims. No system of after-the-fact enforcement would be adequate to that task. When an unproven assertion of safety and effectiveness is made and relied on, the resulting injury is often irreparable. Our strong pre-market approval system is essential to protect our health and safety. The proposal Frist advocates threatens that system.

Allison M. Zieve is an attorney with Public Citizen Litigation Group. Sidney M. Wolfe is a physician with Public Citizen's Health Research Group.

The Washington Post

Next Round on the FDA

A DRUMBEAT continues for what's being called "reform" of the Food and Drug Administration. Sen. Nancy Kassebaum (R-Kan.) introduced a bill in December that would push the FDA toward what her spokesman characterizes as "creating a collaborative process" with drug companies and device manufacturers and tightening the deadlines on the process by which the agency certifies drugs as safe and effective. A group called Citizens for a Sound Economy released a spatter of radio ads. Characters representing the worried families of sick people engaged in mournful dialogues about how the FDA still hasn't approved "that new treatment" and how maybe "Congress needs to shake them up, too."

Though the players are new, this is yet another round of a long-running oscillation between the two dangers any government confronts in regulating drug safety: being too careful and not being careful enough. The most famous public health disaster from not-careful-enough drug regulation was, of course, thalidomide. It was followed by years of increasing caution and eventually a fair amount of bureaucratic slowdown at the FDA. This brought the agency under attack from AIDS activists in the 1980s and the vice presidential government-reinvention initiative in the 1990s.

Between them, these two attacks have caused the pendulum to swing a considerable way back. The former sought and eventually got fast tracks for experimental drugs that, though they might be dangerous, offered hope to the dying. A General Accounting Office report last month certified that the FDA had all but eliminated its backlog and cut approval times by as much as half, in large measure because of a 1992 law that charged drug companies "user fees" to put more analysts on the case.

The restructuring bill seeks to push this process farther and faster and, in some cases, to remove the safeguards that make such speeded-up approval feasible. The Kassebaum bill proposes among other things to cut approval times sharply by bringing drug companies into the process, not merely of doing the experiments (they already do this) but of clearing and evaluating the results that are submitted to the agency for review. It also would lift restrictions on advertising for "off-label" or unapproved uses of drugs. Under current law, a doctor can prescribe a drug for any purpose, whether or not it's the purpose the FDA has tested and cleared, but the drug makers can advertise only where there is some evidence of effectiveness.

You can't do too much of this without careful attention to the safeguards that public health demands. Those weighing FDA "reform" should look carefully at the steps already taken before deciding whether to go farther down the path.

THE

"USA TODAY hopes to serve as a forum for better understanding and unity to help make the USA truly one nation."
—Allen H. Neuharth
Founder, Sept. 15, 1982

THE NATION'S NEWSPAPER
USA TODAY
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David Mazzarella
Editor
Karen Jurgensen
Editor of the Editorial Page
Thomas Curley
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Today's debate: REGULATING DRUGS

Rx for disaster: Peddling drugs for unapproved uses

OUR VIEW **Easing regulation of prescription drugs isn't the lifesaver the drug merchants claim.**

Hot on the heels of legislation recently introduced in Congress, the nation's $55.5-billion pharmaceutical industry is angling behind every closed door it can find to ease controls on the marketing of prescription drugs. If it succeeds, more Americans will be mismedicated; more will suffer unforeseen side effects; and more will die.

Briefly, drug makers want the right to tell doctors about studies that support "off-label" use of their products — uses not approved by the Food and Drug Administration. Experience says such studies can be flawed. And such uses can be dangerous:

▶ Flecainide and encainide, two drugs approved for specific types of abnormal heartbeats, were routinely prescribed for other heart problems in the late 1980s — until follow-on research indicated that such use more than doubled the risk of death.

▶ Centoxin, a drug engineered to fight septic infection, had to be yanked off the market in Europe. The FDA decided that the first clinical trials were insufficient, and a second set found many more patient deaths than predicted.

▶ Clonidine, an adult high blood pressure medicine, was prescribed off-label more than 200,000 times in 1994 to treat children with attention deficit disorders. Now, research has uncovered severe side effects and a handful of deaths.

Why risk more of the same?

Physicians are already free to prescribe for off-label uses; half the 2.1 billion prescriptions written each year are such. Within existing limits, most doctors can judge the benefits and risks of off-label uses.

But giving drug makers carte blanche to market their products for unapproved uses will swamp doctors with inadequate studies. Who should the public depend upon: the FDA and its objective mission to evaluate new drugs, or the companies that have wagered millions developing those drugs?

If drug companies can sell drugs based on studies of their choice, they have no reason to seek FDA approval for any use except the narrowest, easiest ones. That done, it would be simple to market the drug for another, more dangerous use.

Drug industry briefing papers say that "pharmaceutical companies ... are in the best position to provide current, scientifically accurate information about (their) products." Maybe, but that's a handy prescription itself — for conflict of interest.

The industry also says that seeking FDA approval for every use is time-consuming and costly. Reforms are in order, but off-label marketing doesn't repair the FDA; it just destroys the agency's quality controls.

There are many reasons why this idea, now in the formative stages in Congress, should be snuffed out. It undermines drug safety and endangers consumers. It also means lower costs for makers, who would spend less on trials and studies. But who do you think will pay *that* price?

THE LANCET

Volume 346, Number 8981

EDITORIAL

In defence of the FDA

The US Food and Drug Administration (FDA) has a massive remit and is a huge organisation. It regulates 25 cents of every dollar spent by the American consumer, or about $1 trillion worth of goods and services annually. To do that FDA employs over 9000 people and has a budget of $1 billion. The agency's regulatory and enforcement successes are too much for the anti-government minions. For example, the speaker of the US House of Representatives, Newt Gingrich, has accused the FDA of "Stalinist" tactics and has called its commissioner, David Kessler, "a thug and a bully". Wrong.

Kessler has managed to speed a government bureaucracy in the right direction. The perennial complaint that new-drug approval takes too long is now outdated. Since passage of the Prescription Drug User Free Act of 1992, median approval time for new drug applications has fallen from 27 months in 1992 to 19 months in 1994. Alendronate was approved in 6 months (see p 1028). For applications handled through the user fees process (not all are), the 1994 median was 13½ months. A backlog of nearly 700 drugs awaiting FDA action in 1992 has been cut to zero, right on schedule. And the improved performance extends to generic drugs, biological agents, and medical devices. An automated cervical-screening system was approved in just 7 months (see p 1029).

Not content with or perhaps frustrated by this impressive record, FDA critics have stooped to irresponsibility. One Congressman recently announced that "2888 Americans have died needlessly because the FDA took too long to approve the coronary stent". A conservative lobby group has bought newspaper space to proclaim "If a murderer kills you, it's homicide. If a drunk driver kills you, it's manslaughter. If the FDA kills you, it's just being cautious". The advertisement continues: "during the seven years it took to approve tacrine, thousands of Alzheimer's patients gradually lost their memories . . . 14 000 heart-attack victims so far have died who could have been saved by the cardiac-pump during the two years the FDA has delayed approval". *Lancet* readers will not have appreciated stents were uniformly successful, that tacrine was a wonder drug, or that the pump was such a marvellous invention. And readers will have seen enough drug tragedies to have learned the need for caution. 56 drugs were withdrawn from US, UK, German, and French markets in 1970–92; only 9 were US withdrawals.

The FDA has also been accused of slowing the pace of drug development in the USA by prolonging the pre-approval stages of pharmaceutical research. However, everywhere such development is taking more time. World wide, the lag from synthesis to marketing of a new drug increased from an average of 8 years in the 1970s to at least 12 by 1990. Of the 44 new drugs approved by the FDA in 1993/94, 17 were marketed first in the USA. Among the other 27 were 13 whose applications were not even filed with the FDA until an average of 7 years after they were introduced in another country. Indeed, the greener grass claimed to be growing in Europe seems less fertile to those who do business there. European pharmaceutical and biotechnology companies are pouring money into the USA.

Perhaps FDA critics would be silenced if other public health agencies—such as the Centers for Disease Control and Prevention—took up the slack of enforcement. The reforms that the FDA is making are streamlining drug development and approval; some of the more punitive measures that the industry finds burdensome are being lifted; and restrictions on minor drug manufacturing changes that pose no threat to public health are being eased. An additional goal is to speed device approvals by implementing user fees. And the FDA's stand against allowing drug companies to promote "off label" use of their products—surely an invitation to dangerous drug marketing—is welcome too. Much work remains to be done. For example, the acceptance of placebo-controlled evidence in preference to comparator drug trial data is a serious flaw in the regulatory process. Yet the absurd proposal that FDA functions be privatised needs fierce resistance, lest public debate over what is prescribed for patients be governed in private by the profit-makers.

The Lancet

The Dallas Morning News
Sunday, October 1, 1995

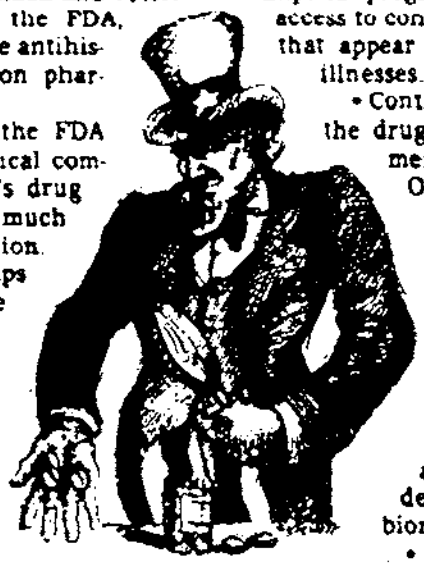
EDITORIALS

FDA REFORM

Agency needs moderate, not massive, change

Nobody — nobody sane — wants to abolish the Food and Drug Administration. America's admirably safe food supply depends on the agency's work. It ensures the safety of billions of dollars' worth of cosmetics, medical devices, and human and veterinary medicines. Without the FDA, snake oil would sit alongside antihistamines and bactericides on pharmacy shelves.

Nobody, however, says the FDA can't improve. Pharmaceutical companies complain that FDA's drug approval process costs too much in time, money and frustration. Some patient advocacy groups concur. Bioengineers voice similar gripes about winning approval for new medical devices and biomaterials. Many in Congress yearn to overhaul the agency — including Speaker of the House Newt Gingrich, who has inaccurately labeled the FDA "the leading job-killer in America."



First of three parts

Congress shouldn't base reform on such false and misleading claims. Instead, lawmakers should study how medicine has changed in this century. They must encourage the FDA's internal attempt to streamline drug approvals. Last, reformers must acknowledge what FDA Commissioner David Kessler calls "the inherent tension" between the agency's intertwined goals: to protect consumers against unsafe or useless products, and to make new medical technologies available as quickly as possible.

Here are some reforms Congress should support:

- Expand programs that allow patients access to conditionally approved drugs that appear effective against serious illnesses.
- Continue efforts to harmonize the drug approval process among members of the World Trade Organization.
- Relax some reporting and review requirements for slightly modified versions of previously approved drugs and devices.
- Create new and appropriate standards for judging the safety and efficacy of medical devices and, particularly, biomaterials.
- Consider revising the large human clinical trial process for new drugs that have appeared safe and effective in earlier phases of lab, animal and human testing.

Congress should note: These are incremental changes, not attempts to gut the agency. Americans may not like bureaucracy, but they're not enthused about unsafe medicines either. Lawmakers must be careful that their "cures" for the FDA don't make Americans sick.

nature

NATURE · VOL 376 31 AUGUST 1995

End of the line in sight for FDA?

The new Republican Congress is naturally antipathetic to the US Food and Drug Administration, but radical change will not be easily accomplished, which is just as well.

THERE are several reasons why the present US Congress distrusts the Food and Drug Administration. One is simple and ideological; the FDA is a bureaucracy, a device for administering government regulations (on the safety and efficacy of new medicines and medical equipment and on the quality of foodstuffs offered for sale). It is staffed by people who, of necessity, add nothing but their salaries and fringe benefits to the gross domestic product. Another reason is that the activities of the FDA most directly affect the pharmaceutical companies chafing at the delays between the development of new drugs and their arrival on the market. When the Congress returns from its summer break, there will be many who will have woken up to the fact that President Bill Clinton's new war against tobacco (see *Nature* **376**, 539–540; 1995) relies crucially on FDA's willingness to classify tobacco as a harmful substance and nicotine as a cause of addiction. The grumbling about FDA in the first year of the new Congress will become louder in the second. Even now, there will be congressmen seeking to win a little publicity for themselves by preparing bills that would abolish the agency altogether.

The reality is that, as always, there is room for reform, but that abolition of FDA would compel the need to reinvent at least substantial parts of it. The contentious issues mostly arise from the procedures for licensing new drugs for sale, by prescription or otherwise. These are the procedures that require manufacturers to spend large sums of money on clinical trials to demonstrate both the safety and the efficacy of the drugs they seek to have licensed. The delays occasioned are in themselves expensive, and may also be held to affect adversely the health of those who might have benefited from them if early licensing had been allowed. Yet the inventor of a new kitchen gadget, or a cleaning fluid, is not required by the present law to demonstrate the safety and efficacy of his products in advance. If they should prove unsafe, those who suffer damage from them can pursue product liability suits in the courts. If they prove ineffectual, the market (aided no doubt by consumer organizations) will quickly recognize that much, whereupon sales will collapse. Why not follow the same principles for medicines?

Safety

Whatever the logic (and it is not strong), FDA's most severe critics must be aware that it would not carry weight in the United States. One of the enduring legends of the nineteenth century is that of the snake-oil salesmen appearing regularly at country fairs, milking credulous audiences of their spare cash with promises of relief from this or that ailment. FDA is modern America's answer to those dubious characters. Or is part of an answer; the general craving for good health, longevity and even immortality has provided a rich market for those offering naturally occurring vitamins and natural oils of various kinds as recipes for continued health. The objection to letting modern synthetic medicines find their level in the market is that they do not enjoy the presumption of safety that applies to natural products, and that even the law of tort on product liability does not prevent suppliers from escaping their obligations behind the protection of the bankrupcy laws. In a country that specifies the safety equipment motor-car manufacturers must embody in their products, there is no political possibility that drug manufacturers would be freed from comparable restraints.

Efficacy

It is relevant, and even now important, that in the early 1960s Senator Estes Kefauver would have gone a substantial step further. In a seemingly endless series of congressional hearings, he set out to devise a way in which manufacturers would be discouraged from seeking licences for "Me-too!" drugs by requiring that the efficacy of a new drug should be demonstrated, in clinical trials, to be superior to others on the market. In the event, that goal would have been impracticable; even the most elaborate clinical trials are rarely so precise. But Kefauver was sustained in his long campaign by a groundswell of public opinion that is unlikely to have vanished in three decades. Even now, the opinion that the effectiveness of newly licensed medicines should be demonstrated in advance is likely to be widely shared by every congressman's electorate.

So is there nothing to be done to simplify the present procedures for licensing new drugs? As Republican luck will have it, the opposite is the truth. Everybody (FDA included) has learned a great deal from the special arrangements made five years ago for the licensing of drugs thought relevant to the treatment of AIDS; when no proven remedies are available, the seriousness of the condition to be treated must moderate the standards to

be satisfied by the proof of efficacy (as distinct from safety) required of a new drug.

Two other considerations arise. First, compounds offered as new medicines whose design is based on a testable physiological rationale deserve an inside track — a partial presumption of efficacy. That is already an important issue in biotechnology, where many of the compounds waiting in the wings for approval are synthetic versions of naturally occurring proteins, but the queue will become more clamant when more is known of the natural function of genes that, in mutated forms, are linked with important genetic diseases. If, for example, further study and understanding should suggest that there is a replacement therapy for Alzheimer's disease, what formal proof of efficacy would be considered necessary?

The second new opportunity is offered by means in which the design of clinical trials can be made less formal. 'Meta-analysis' is the slogan. The truth is that once the safety of a proposed new medicine has been established, an assessment of its effectiveness can be reached by the careful gathering of data in its tentative use. The outcome is neither as clean nor as decisive as that from a regular clinical trial, but none the less useful on that account. A few exercises of this kind might enable FDA (and similar organizations elsewhere) further to speed up the approval of new drugs. The difficulty, for the radical wing in the US Congress, is that neither of these opportunities can be enshrined in new legislation, but must be decided by a technically expert organization — one like FDA, for example. □

Care in the community

There will be no quick answer to the British government's call for better care for the psychiatrically ill.

THE British government's Department of Health has woken up to a scandal that has been simmering away for the past four years — the plain truth that its humane programme for moving people with chronic psychiatric illness from long-stay hospitals into the community at large is not working as intended. Last week, in the wake of two critical reports by differently constituted teams of inspectors, the minister at the department, Mr Gerald Malone, wrote to Britain's hospital trusts urging them to do better. He is right to ask. Whether he or his successors will be satisfied with the response is another matter.

That the policy of community care is enlightened is beyond dispute. In the bad old days, institutionalization was a disease in its own right, but in the absence of palliatives of psychiatric illness, also a necessity of a kind. Now that manic depression and clinical depression are reasonably well dealt with by means of drugs, and even schizophrenia is controlled by the phenothiazines and their derivatives, it makes good sense that those affected should live in circumstances comparable with those that others of their age enjoy. For any government, community care also offers potentially huge economic benefits; even psychiatric hospitals are expensive to staff and run, while circumstances usually dictate that they should be a public expense. So there is nothing wrong with the ambition that most of those suffering from psychiatric illness should live in the community rather than in hospitals. The difficulties lie in the way in which the policy is carried out.

When the British version of these arrangements was decreed in 1990, it was intended that health authorities and the social services departments of local authorities should devise a joint plan for dealing with the community care of psychiatric patients in their areas. The hope was that there would also be plans for individual patients, offering them programmes of health care, social support and even occupational activity. Last week's report of the Department of Health's own Social Services inspectorate is based on five local-authority social services departments; it says that only one of the five departments had drawn up such a plan, and that even that had been in place for just over a year.

Shameful though that may seem, it is not surprising (nor at odds with anecdotal evidence emerging in the past few years). The Health Service has been in the throes of huge administrative upheaval and is no position to seek out extra work to do, while even those local authorities with expertise in, say, the care of the elderly have not known enough to anticipate the needs of the psychiatrically ill. And among those, it is plain the people with schizophrenia habitually draw the short straw; the Department of Health's Clinical Standards Group (which acts as a kind of auditor of clinical standards) based a detailed survey of the treatment of schizophrenia in eleven health-service administrative units; none was found to be unequivocally "good", although four approached that ranking. Others were frankly "poor" in the quality of the care they provided for schizophrenia.

Extenuating circumstances abound. The administrative changes of the past few years have not helped. The attention paid to the needs of psychiatric patients as distinct from other claimants on public services almost inevitably depends on the fuss that individuals make. And psychiatric illness is still in many places a tainted kind of disability. But the real difficulty is the lack of adequately trained people able and willing to work peripatetically, as community care requires. Sadly, for the psychiatrically ill, that deficiency will not be quickly remedied. When they are found in sufficient numbers, they will turn out to be expensive. Then the government will be wondering whether it can afford the extra cost, and its critics will be saying that it cannot afford not to afford it. That is at least a tangible difficulty. The less tangible, and therefore the less easily remediable, is the persisting suspicion of psychiatric illness even in enlightened administrations such as the British. People with schizophrenia, who are notoriously awkward customers, are especially likely to be short-changed. But wishing that they would go away will serve no purpose. The lifetime suicide rate may be 15 per cent, but numbers are constantly renewed. □

ONCE OVER

No, the FDA is not killing people

In the early 1960s, an alert scientist at the U.S. Food and Drug Administration kept the sleeping pill thalidomide off the market in the U.S. That protected untold numbers of children from being born deformed in this country. Several thousand European children weren't as lucky.

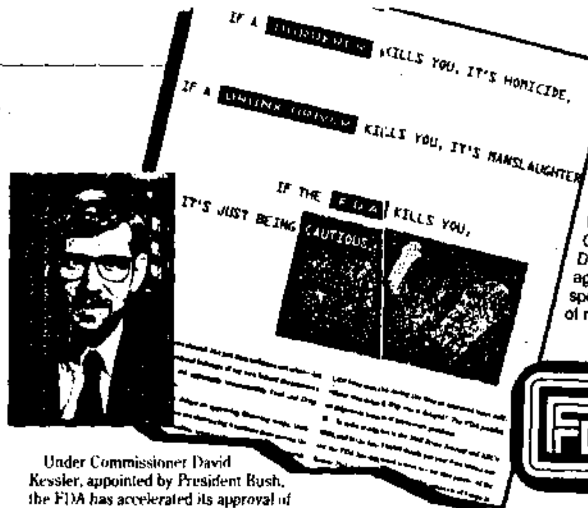
Since then, the FDA has enjoyed a public profile as a stalwart guardian of public health and a scourge of quacks and profiteers. That is, until the past few months.

The FDA is being attacked by politicians and by foundations with funding from drug companies. They include the Washington Legal Foundation, the Progress and Freedom Foundation, the Competitive Enterprise Institute, and Citizens for a Sound Economy. Such organizations accuse the FDA of menacing Americans' lives and health by tying up beneficial treatments in interminable red tape.

The most lurid charges have come in ads from the Washington Legal Foundation. Next to images of coffins and tombstones, the ads say: "If a murderer kills you, it's homicide . . . If the FDA kills you, it's just being cautious . . . The problem with health care in America is the FDA."

The solution, suggests the Progress and Freedom Foundation, formed by close political associates of House Speaker Newt Gingrich, is to turn most of the FDA's work over to private firms. But we have yet to see any proposal that makes clear how those companies would be held accountable and free of conflicts of interest. Some advocates would even let manufacturers sell any drugs they want, leaving customers to sue doctors or manufacturers if the drugs did harm. (At the same time, some in Congress have long wanted to make it tougher to file such suits.)

The FDA, spending $900-million a year, is a powerful agency with an awesome responsibility. And it was infamous not long ago for taking years to decide whether products got to market. But the bashing it's now getting isn't justified.



Attack ads
Recent ads like this suggest the FDA's red tape is hazardous to your health. But under Commissioner David Kessler, the agency has actually speeded up approval of new drugs.

Under Commissioner David Kessler, appointed by President Bush, the FDA has accelerated its approval of genuine breakthrough drugs. Last year, 17 of the 22 drugs it approved were these "priority" compounds. For 10 of those drugs, processed under a new user-fee system, the average approval time was cut in half, to less than a year.

The agency also fares well in international comparisons. Last year, of the world's dozen new drugs considered the most notable therapeutic advances, five were first introduced in the U.S., compared with three in Japan and no more than one in any other country.

The FDA also seems effective at keeping unsafe drugs off the market. Public Citizen's Health Research Group recently studied the 56 drugs withdrawn from the market in the U.S., England, France, and Germany since 1970 because of safety problems. Only nine had made it onto the market in the U.S., compared with 23 in England, 30 in Germany, and 31 in France.

The FDA's review procedures have revealed time and again that not every promising therapy turns out to work or to be safe. The Washington Legal Foundation's ads claim that people died because specific drugs or medical devices were trapped too long in the review process. Those assertions are misleading.

The foundation claims that "the lives of more than 150,000 heart attack victims may have been saved" if the agency had been faster to approve TPA, a drug that dissolves blood clots. In fact, another, almost equally effective drug, streptokinase, was already on the market before the FDA even started reviewing TPA. Any doctor or hospital was free to use it.

The ad complains that the FDA has "obstructed" approval of the Sensor Pad, a silicon-filled plastic pad that supposedly helps women feel breast lumps, while the product was released for sale in Canada "in less than 60 days." In fact, the FDA kept the product off the market because its manufacturer was unable or unwilling to do tests to show the pad worked as claimed. Last year, Canadian officials asked for the same information the FDA had sought. They couldn't get it either, and ordered the Sensor Pad off the market.

One gripe with some validity is that the FDA stopped tests of a portable heart resuscitation pump because test subjects—people who collapsed suddenly of massive heart attacks—couldn't, for obvious reasons, give "informed consent" to participate. The agency has belatedly promised new regulations to permit experimentation with resuscitation drugs and equipment.

Those organizing the assault on the FDA insist their motives are philosophical, based on a belief that such government regulation is wrong. But the anti-FDA groups are getting money from drug and medical-device companies that could profit from deregulation. These companies include Burroughs Wellcome, Eli Lilly, Genzyme, Glaxo, Johnson & Johnson, Pfizer, Searle, Siemens, and Solvay. The companies we contacted refused to endorse any of the specific proposals being floated, but said they are interested in hearing the groups' ideas. One company, Merck, has said it opposes dismantling the FDA.

CO detectors: Are some too sensitive?

Carbon monoxide detectors are essential safety devices in any household with oil or gas heat, a woodstove, or a gas range. But they may sometimes do their job too well, sounding off when exposed to low levels of the colorless, odorless gas.

To mitigate problems that have been blamed on ultra-sensitive detectors or improper installation, Underwriters Laboratories has proposed some significant changes to the standards governing the way the devices work. The changes, due to take effect next October, would require:

- Detectors to withstand exposure to 15 parts per million of CO for at least 30 days without alarming. The current standard tests only eight hours' exposure.
- A Hush or Reset button on all new detectors to temporarily quiet the alarm. Most AC-powered detectors already have that feature.
- More-detailed instructions, urging people who have no symptoms of CO poisoning to immediately contact a qualified technician when the alarm goes off. Manufacturers currently advise people to call the fire department.

Nuisance alarms made headlines last winter in Chicago, the only major municipality that requires a CO detector in most dwellings. Alarms sounded thousands of times—most at benign levels of gas. The worst outbreak occurred during 48 hours in December, when officials officials responded to some 2300 calls during a temperature inversion—a freak weather pattern in which atmospheric conditions trap pollutants from vehicle exhausts and other sources.

City officials voiced particular concern over the sensitivity of *First Alert* detectors. The Chicago Department of Consumer Affairs says the sensor in *First Alert* detectors is prone to CO buildup over time, which could cause the alarm to react to even low levels of the gas.

First Alert detectors do meet the UL standard. The company acknowledges that the detectors use a very sensitive sensor. But they say that isn't necessarily a drawback, since it provides the maximum level of protection.

Our tests last year—and those for a July report—have shown *First Alert* detectors to be somewhat slow to respond. But once they do, they need several hours to recover after the air clears. Other detectors—including the *American Sensors COS-200* we top-rated last year—clear themselves in a matter of minutes.

First Alert attributed the high incidence of alarms to several factors, including poorly maintained furnaces and appliances, blocked or damaged chimneys and flues, and detectors placed too close to a range or furnace.

As a goodwill gesture, First Alert offered refunds until January 31 to Chicago-area residents who were unhappy with their purchase.

CU needs a video engineer

We have an opening in our electronics department for an experienced video engineer. The person we hire must have at least a bachelor's degree in electrical engineering, with 10 or more years of experience in consumer-electronics engineering and testing, primarily in television and video. Applicants must have strong written and verbal skills and be proficient in the use of computers for test-data acquisition and analysis. A hobby background in electronics is desirable.

The salary will be commensurate with experience; CU also offers an excellent benefits package.

To apply, please send a detailed résumé and salary requirements to: Consumers Union, Box HC, 101 Truman Ave., Yonkers, N.Y. 10703. Consumers Union is an equal-opportunity employer.

Benefactors & Lifetime Members

Every few months in this space, we acknowledge our Benefactors & Lifetime Members, individuals whose generosity helps make CU's work possible.

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Dismantled FDA: A bitter pill we shouldn't swallow

STEVE WILSON
Republic Columnist

In the war against excessive federal regulations, the most intense battle is being fought over the rigorous reviews by the Food and Drug Administration.

FDA regulations hit close to home, covering the processed food, drugs and cosmetics we buy every day. Because U.S. standards are the world's highest, we have the safest food and drugs on the planet.

The effort to streamline drug approvals is led by conservatives who consider the FDA an enemy of free markets. They want to curtail its powers or have it privatized and contract the review work to research companies.

"Every year, tens of thousands of Americans die while the FDA delays approval of drugs readily available in Europe," says Citizens for a Sound Economy, a conservative think tank.

At a congressional hearing this week, Republican Rep. Jack Kingston of Georgia said the FDA does more to impede medical progress than to protect public health.

"You don't have a can-do attitude, you have a can't-do attitude," he said, addressing FDA Commissioner David Kessler.

That remark hit a nerve.

"You don't think I want to get devices that are important to save lives out there? Who do you think works at the FDA — (we are) real physicians who have lost real patients," Kessler replied.

The agency says its average drug approval in 1994 took 19 months — a 21 percent improvement over the previous year.

Critics consider that statistic misleading. Drug companies say it takes up to 12 years and $400 million to bring new drugs from the laboratory to the market.

I have no trouble believing that the FDA's 9,300 employees could work more efficiently. Many of its rules are decades old and ill-suited to today's biotechnology. I imagine approvals could be speeded up without significant risk.

But anyone who wants to gut the agency or grease the review skids ought to read a chilling new book, *Deadly Medicine*, by Thomas Moore, a health-policy researcher at George Washington University.

The book tells the story of a medication called Tambocor, which came on the market in 1985 as a treatment for arrhythmia (irregular heartbeat).

The FDA studied the drug for 34 months before approving it. Moore says the agency initially decided to give approval only for patients with life-threatening arrhythmia.

But its manufacturer, 3M Co., persuaded the FDA to permit its use for a much larger range of heart patients, Moore claims.

He says Tambocor and similar drugs produced "America's worst medical disaster," accounting for some 50,000 deaths. Instead of suppressing irregular heartbeat and preventing heart attacks, the drugs sometimes produced fatal heart attacks, he writes.

While the extrapolated death toll is disputed, there's no question that the drug caused many cases of cardiac arrest.

Moore believes additional testing could have prevented most of the deaths, a view supported by a National Institutes of Health study in 1989. Six percent of patients who took the drug for more than a year died, a rate 250 percent higher than a control group taking a placebo. FDA approval for Tambocor was narrowed in response to that study.

Moore argues that the Tambocor experience shows that, despite the FDA's elaborate review process, the system is still biased in favor of getting new drugs to market, since all parties — manufacturers, doctors and patients — are eager to reap the benefits.

As Congress debates whether to bust up the FDA, it might also think about another medicine with unforeseen effects: thalidomide.

That drug, a sedative developed in Europe and rushed into experimental use in America, caused severe birth defects and some deaths when taken by women during pregnancy. As a result of those 1960s tragedies, the FDA received more regulatory teeth.

I'm sure the pharmaceutical industry has valid complaints about the FDA bureaucracy. We're not well-served when excess caution keeps lifesaving medicine out of reach.

But as more-powerful drugs with more-potent side effects are being developed, and as all facets of health care become more dollar-driven, the need for safety assurance today seems greater than ever.

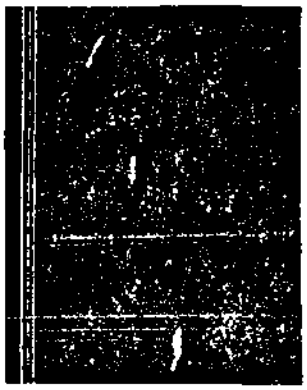
Drug companies don't want to sell harmful products, but neither do they want to see a competitor beat them to market.

The FDA's job is to check their homework and at times put on the brakes. The agency can be fine-tuned without being dismantled.

Editorial

Bulletin of Alleghany County
Medical Society
Pittsburgh, PA March 25, 1995

Can the "Grinch" steal the FDA?



Alvin P. Shapiro, M.D.

At the University of Pittsburgh School of Medicine in 1960, we started a program in clinical pharmacology in the department of medicine, at the urging of Jack Myers and with the generous support of a training grant from The National Institutes of Health (NIH). The discipline of clinical pharmacology was then in its infancy but rapidly expanded due to an "explosion" of new therapies developed in the ensuing decade, many of them related to my own major clinical and research interests, namely the diagnosis and treatment of hypertension. Together with Dr. Robert McDonald we conducted the program for about 20 years, teaching medical students and residents the principles of drug evaluation; the appropriate use of potent medications; and the pathopharmacology of side effects and drug interactions. We also trained 18 fellows who either went on to academic pursuits or to practice in broad areas of internal medicine.

Among our tasks in clinical pharmacology was understanding the work of the Food and Drug Administration (FDA), the federal agency charged since 1906 with the regulation of new drugs coming on the market. The purpose of the FDA is to protect consumers from quackery and "therapeutic misadventures" and to guide healthcare providers in prescribing medications. Originally it dealt only with interstate transfers of mislabeled drugs and adulterated foods, but in 1938, federal regulations requiring demonstrations of safety of new drugs were enacted after a disaster involved with a toxic preparation of sulfonamide. In 1962, the Kefauver-Harris amendments were added, which additionally required evidence of efficacy—a not unreasonable request!

The process of drug acceptance is now well-outlined and does indeed take some time, perhaps several years, but occasionally longer from "bench to bedside" as the drug undergoes: *animal testing*; *Phase I* trials in man, usually normal volunteers, to determine biological activity and metabolism; *Phase II* trials in selected patients to determine dosage range and duration; and *Phase III* trials to compare efficacy to known drugs and/or placebos in a controlled, often "double blind," fashion. If these phases establish safety and efficacy (the latter not necessarily better than an older drug) it can be released, but as it is broadly used, the drug may now become subject to a *Phase IV* surveillance, and the FDA can then order its withdrawal if new problems appear.

The FDA is not a political issue but a medical necessity . . . we must as physicians oppose Newt on this question.

These regulations are now well known to pharmaceutical companies who by and

large deal with them honestly and cooperatively, although with some grumbling about the time and expense involved. Occasionally, consumers fret about delays, most recently concerning drugs to treat AIDS. But the basic reason for the regulations are to protect the consumer and guard against extravagant and sometimes fraudulent claims about new "wonder drugs."

All of which leaves me, as a clinical pharmacologist, an internist, and a citizen, rather aghast at the pronouncements of Newt Gingrich that the authority of the FDA should be eliminated or "privatized" because its activities are expensive and result in "restraint of trade."[1-4] I do not sympathize with many of Newt's suggestions to "downsize," but I am particularly distraught by his attack on the FDA, which has a long history of protection of the public (e.g. the prevention of thalidomide use in the U.S.). After all, Newt *is* a historian and should know the background of the laws and the chaos which existed prior to their passage.

Under the leadership of Dr. David Kessler (originally a Republican appointee), the agency has upgraded itself further in recent years and made itself more visible, and hence perhaps more subject to attack by what must be a powerful drug company lobby; I do not think Newt has come to this on his own. The FDA is not a political issue but a medical necessity. If we are to continue the high standards of drug development in the U.S., we must as physicians oppose Newt on this question.

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Needed nitpicking

Before the drug industry emasculates the FDA remember the Thalidomide babies

By FRANK H. BOEHM, M.D

RECENTLY certain members of Congress have become concerned that the Food and Drug Administration (FDA) inhibits job growth by being overly strict on releasing certain drugs and technical devices to the public.


BOEHM

As a result, these members of Congress are trying to eliminate the FDA and replace it with an industry-dominated agency. Because of this, I feel compelled to tell an old but well known story.

It was 1960, and the FDA had received an application to market in this country a tranquilizer called Thalidomide. Believed by many to be a miracle drug, Thalidomide not only induced sleep but also had no known side effects. It was a very popular drug in Europe and Great Britain, and its manufacturers, the William B. Merrill Co., wanted the drug approved for sale in the United States. There was one small problem. Dr. Frances Kelsey, a newly hired employee of the FDA and an expert in the science of drugs, was given the application. Dr. Kelsey was not intimidated by Merrill's demand to speed things up, and she certainly was no pushover.

By law, Dr. Kelsey had only 60 days to study the Thalidomide application and render an opinion. Only if additional information was needed could that time frame be extended. Dr. Kelsey was concerned by the fact that, while Thalidomide induced sleep in humans, it did not do so in animals. Perhaps there were similar differences in animals and humans, and therefore the fact that no birth defects were noted in animals did not reassure her.

Dr. Kelsey was also concerned about a letter written to a British medical journal in which a physician noted inflammation of the nerves of fingers in individuals who had taken Thalidomide for an extended period of time. She wanted more information from Merrill about similar possible fetal effects. The Merrill Co. executives were not happy.

As later revealed, unbeknownst to the general medical profession, in 1959, 12 grossly deformed babies were born throughout Germany. This malformation was called phocomelia, a condition in which babies are born without arms or legs. At the time, no connection, however, was made between this extremely rare birth defect and any drug usage.

Meanwhile, West German clinics recognized that 83 cases of phocomelia had been reported by the end of 1960. The connection between Thalidomide and phocomelia was finally made by a West German pediatrician who noted that 50% of mothers interviewed who delivered babies with this birth defect remembered that they had taken Thalidomide early in their pregnancy.

Physicians from Australia and Scotland quickly confirmed this correlation and suddenly the William S. Merrill Co. notified the FDA that they were withdrawing their Thalidomide application.

Unfortunately, considerable damage had already been done. Because of Thalidomide, 10,000 deformed babies were born throughout Europe. Fortunately, because of a "bureaucratic nitpicker" (as Morton Mintz of *The Washington Post* referred to Dr. Frances Kelsey), babies born in the United States were spared such horrors. For her work, President Kennedy gave Dr. Kelsey a Distinguished Federal Civilian Service Award in 1962.

Since those Thalidomide days, the FDA has demanded considerable proof of safety as well as efficacy before releasing drugs and medical devices to the public. Because of these stringent rules and regulations outlined by the FDA, less drugs are withdrawn from the market in the United States because of serious previously undetected side effects than in comparable countries such as France, Germany and the United Kingdom.

Of 56 drugs withdrawn from the market in these countries between the years 1970 and 1992, 31 were withdrawn in France, 30 in Germany, 23 in the United Kingdom and only nine in the United States. This should indicate to our politicians that the FDA is doing its job in keeping more unsafe drugs from reaching the public than other similar industrialized countries. It should also reassure all of us that the FDA is doing its job well.

Go ahead Congress, reform medical care. We need it. And while you're at it, reform and simplify some of the FDA's truly burdensome regulations. But for all our sakes, let the FDA and its employees like Dr. Kelsey continue doing what they have always done best — protecting Americans. ■

(Boehm is professor and director of maternal/fetal medicine at Vanderbilt University Medical Center, and chairman of its ethics committee.)

Critics of FDA Are Out of Line

Public health is a national interest. The American people deserve the oversight of an agency such as the Food and Drug Administration.

Yet, listening to those who challenge the way the FDA operates and even its necessity, a careless person might believe the FDA is paternalistic, bad for business—and dangerous.

While there is always room for improvement—which the FDA contends it has been doing—FDA critics are themselves overzealous and, in some cases, self-serving.

The critics include an unlikely coalition of AIDS activists, Republican linked think tanks and public policy groups such as the Washington Legal Foundation and Newt Gingrich's Progress and Freedom Foundation. They charge the FDA is overcautious in approving life-saving drugs and medical devices and that delays have cost lives. They claim the process is swifter in other nations and, thereby, better for patients and the pharmaceutical industry.

True, there have been approval delays. But charges of deaths as a result are often hyperbole and in some cases, misrepresentation.

As the new forces in Washington tighten their grip on a smaller, less-restrictive vision of government, the FDA is a natural target because of its broad involvement in many health areas. However, drugs and devices must be judged for effectiveness, not merely harmlessness, as some attackers suggest. And yes, the process ought to be speeded up, not simply for savings to business but to further help those who may benefit from new medications.

Yet the FDA must not be dissuaded from its invaluable role against fraud, quackery and outlandish claims. We have the right to expect our government to act in the best interests in the health of its people, not just in the best interests of business.

The new forces in Washington must be cautious about dismantling or emasculating the agency, at least as long it continues its own efforts to face new challenges successfully.

Gingrich & Co.'s attack on the FDA can make anybody sick

Tom Bigler

One of the more preposterous and yet revealing proposals to surface in the still-evolving Gingrich manifesto is one that would greatly alter if not eliminate the federal Food and Drug Administration (FDA).

The FDA, among many other duties, has the responsibility of assuring the safety and effectiveness of the vast array of prescription drugs used in the United States. To ensure, for example, that there will not be an incidence in this country of the terrible experience in Europe that resulted from use of Thalidomide, the FDA requires exhaustive laboratory and animal studies before any new drug may enter the U.S. market.

This insistence on rigorous research consumes time — to which many pharmaceutical firms and patients object. The drug houses say that because of the delay they are losing money, while patients fear they are losing a cure.

It was the kind of complaint from a constituent which first got Rep. Newt Gingrich interested in challenging the FDA. As spelled out in two separate reports by two separate reporters for the Wall Street Journal in late January, his involvement says much about its inspiration.

In the summer of 1993, according to these reports, Gingrich introduced legislation designed to suspend duties on several drug components imported by Solvey Pharmaceuticals, Inc., which is headquartered in Gingrich's home district. Shortly thereafter, the company was approached by the president of the Progress and Freedom Foundation for a contribution. About six months later, Solvey gave $30,000 to the Foundation.

The Foundation president had been executive director of Gingrich's political action committee, Gopac. The Foundation is described as a conservative think tank created by Gingrich associates; its major functions are sponsorship of his nationally televised classroom lectures and the separate National Empowerment Television talk show.

The Wall Street Journal reports claim that a consequence of the Solvey contribution, and a host of similar contributions from other major pharmaceutical firms, is that the Foundation now also has the large task of preparing proposals to revamp or replace the FDA.

Gingrich's early explanation of why the FDA should be eliminated or radically changed was that its work should be taken away from "bureaucrats" who were wasting time and put into the hands of industry, which knew how to get things done.

What that proposal chooses to ignore is that once upon a time the responsibility belonged wholly to the private entrepreneur. Government stepped in only when it became evident that those creating products for profit, too easily measured their product only in terms of profit and not in terms of safety or effectiveness for the consumer. Too many worthless, even harmful products were marketed. Although business prospered, consumers suffered.

Moreover, human nature being what it is, there is every reason to expect that if nearly a century of protection by the FDA was terminated, the old practices would be quickly resumed. In just the last decade, a leading American manufacturer of baby food discovered a production error and was only narrowly prevented from marketing bottles labeled "apple juice," but which contained only sugared water. Some in the company protested that "It wouldn't hurt anyone," but would cost the firm millions to correct.

In this era when the bottom line has become the sole measurement of the success of a business administration — and a cost-benefit limitation would be placed on regulation — consumer protection would vanish virtually overnight.

This prospect fits neatly into columnist George Will's defense of "Engine" Charlie Wilson's declaration of forty years ago that "What's good for General Motors, is good for the country." Under that definition, the business came first while the country and its people became an after-thought — a "trickle-down" relationship. The sole criteria for any program's worth would be the volume of profit it allows.

While it may be revealing to some how rewarding it can be to "take care" of a constituent in this "new" Washington scene, most people will realize they've heard this song before.

Most people are consumers — and even his most indiscriminate supporters must wonder if they really want to lose their protections just so Gingrich & Co. can enjoy those "rewards."

No creation of man is perfect, and all of them can profit from honest periodic reexamination. If done in this case, it seems a sure bet that more would be found in the Food and Drug Administration to praise than to change.

In this case, however, the agency is damned in advance.

Tom Bigler is professor of communications at Wilkes University and a Times Leader columnist. His column appears on Sundays and Wednesdays.

The Des Moines Register

February 15, 1995

THE REGISTER'S EDITORIALS

Don't hamstring the FDA

It's all that protects the public from snake-oil peddlers, and worse.

It has been more than 30 years since the thalidomide disaster. Drug manufacturers assume it's a safe bet that America has forgotten. As a result, some of them and their allies in Congress, including House Speaker Newt Gingrich, think it's time once again to try to destroy the U.S. Food and Drug Administration.

The FDA is all that protects the public from the peddlers of snake oil and worse. In the 1960s, a single FDA official — Dr. Frances Kelsey — blocked a catastrophe. She refused to license U.S. sales of thalidomide, a tranquilizer formulated in Germany and intended for use by women in early pregnancy to combat nausea and insomnia. The drug, Kelsey argued, had not been adequately checked for side effects.

Those effects were finally noted — too late. Thousands of babies, including 6,000 in Germany alone, were born with gross deformities. Some lacked arms or legs.

While Kelsey kept thalidomide off the shelves of American drugstores, trial samples were sent to 1,800 U.S. doctors in 60 states. Results for American children were tragic.

Pharmaceutical manufacturers argue that that single instance has been the FDA's excuse for being far too cautious, withholding new drugs from the market for years during testing. They have a point. As one observer noted, caution will be rewarded far more often than haste.

Delay is costly to the manufacturers, because the 17-year patent life of a drug is ticking away while it awaits clearance. Congress recognized that long ago, adopting "patent restoration" legislation that puts years back on the clock to compensate for time lost to the approval process.

While the drug makers go through their poverty routine, Forbes Magazine's 1995 "Annual Report on American Industry" shows drug making to be the most profitable arm of the health industry, which in turn leads the field of 21 industrial groups in profitability over the past five years. Return on equity for drugs over the five-year span was a whopping 22.8 percent.

They'd show greater profits yet, of course, if their congressional allies succeed in emasculating the FDA.

Still, the manufacturers have a point: The quicker a worthwhile new product gets to market, the quicker the afflicted can benefit. Thus, the approval process should be handled as speedily as possible, giving priority to true "breakthrough" drugs and drugs developed to combat burgeoning epidemics. That argues for a stronger, better staffed and more efficient FDA. But the industry and its allies argue instead for dismantling it.

The campaigners are spending millions and their tactics are crude — likening the FDA to murderers for delaying new drug approval.

"These are inflammatory campaigns meant to terrify people," said Sidney Wolfe of the advocacy group Public Citizen. And if the campaign succeeds, consumers will have reason to be terrified.

DAYTONA BEACH NEWS-JOURNAL
Daytona Beach, FL
2/14/95

Taking apart the FDA

One could guess merely from reading his donor list that House Speaker Newt Gingrich would turn out to be an enemy of the Food and Drug Administration.

In 1993-'94, Gingrich introduced three separate bills to suspend duties on chemicals used by a drug company that gave his think tank $30,000. He also went to bat for the company before the FDA. Gingrich has dismissed the connection as mere constituent service for a company with headquarters in his district.

But that isn't all. Another drug company donated $41,690 to the Gingrich-controlled GOPAC, or GOP Political Action Committee. Pharmaceutical companies have poured hundreds of thousands of dollars into GOPAC.

Not surprisingly, the speaker and his allies have talked about weakening and dismantling the FDA. Gingrich has characterized the head of the FDA as "a thug." He also has called for a new agency to regulate drugs, one that would give faster approval with less testing and monitoring.

Gingrich is joined by a number of new right groups who are taking out ads urging the evisceration of the agency.

Their tone is similar to an ad by the Washington Legal Foundation which says: "If a murderer kills you, it's homicide. If a drunk driver kills you, it's manslaughter. If the FDA kills you, it's just being cautious."

Whew! That's high-octane rhetoric. But if FDA inaction can be worrisome, an FDA that allows dangerous drugs on the market is much scarier. Even though a weak FDA would allow fast profits for a few drug companies, it could damage the market for new drugs in the long run.

Most consumers take drug safety for granted in the current regulatory climate.

In a deregulated market, however, customers would resist new drugs because they would not have confidence in their safety. The result would make new drug discoveries a hard sell.

Chances are Gingrich's new-style toothless FDA would last only until the next time a drug with dangerous side-effects is released.

But why should we allow that to happen?

The FDA could stand procedural reforms and regulatory streamlining, but it's doing a generally good job of keeping dangerous products with misleading claims off drugstore shelves.

The U.S. Food and Drug Administration should not be taken apart because a few special interests are giving big money to Newt Inc.

St. Petersburg Times

Hard to swallow

For a disturbing example of what special-interest money can buy in Washington, look no further than the growing effort to dismantle the Food and Drug Administration. An unholy alliance of irresponsible drug companies and ultraconservative political organizations is bankrolling a congressional effort to gut the FDA's regulatory powers. If that effort succeeds, millions of Americans will no longer have any real reason for confidence in the safety or effectiveness of the prescription drugs, food additives, nutritional supplements and other products they consume.

Drug companies often are frustrated by the time it takes the FDA to test and approve new drugs that hold the promise for great medical breakthroughs — and great profits. But it is irresponsible to suggest, as some interest groups are now, that Americans would be better served if the FDA was abolished or neutered.

The FDA often is the only government agency standing in the way of distribution of a dangerous or ineffective drug. To take just one horrific example, when the tranquilizer Thalidomide went on the market in Britain in the 1960s without adequate review, pregnant women who used it gave birth to terribly deformed babies. Our government's stricter review process kept Thalidomide out of the American market. Those now advocating the dismantling of the FDA should explain how American consumers would be protected from the next Thalidomide if the practical testing of drugs were left to the marketplace.

The FDA is a prime candidate for constructive reform. It has been slow to adopt new rules to streamline the testing of drugs to treat AIDS, some kinds of cancer and other terminal illnesses. The agency also has developed a habit of embroiling itself in issues that have more to do with social policy than protection of the nation's health.

Despite those problems, the FDA's responsible critics acknowledge that it would be a terrible mistake to abolish the agency's central regulatory functions. "The tenets FDA enforces, and we live by, ought to remain in place," Dr. Eve Slater, head of regulatory affairs for the drug giant Merck & Co., told the *New York Times*. She supports managerial reforms at FDA but defends the agency's mission.

But some drug-industry interests have a more radical agenda, and they have contributed heavily to members of Congress who are willing to target the FDA as part of a broader effort to deregulate big business. And those same companies are also pushing for legislation that would serve to insulate them from large damages in future lawsuits. If those unscrupulous interests have their way, the victims of future drug scandals will be unable to receive fair compensation in court.

The attack on the FDA is being sold as a populist crusade, but it is anything but. This is a scheme to make a few rich drug companies even richer — even if it means jeopardizing the health of millions of Americans.

Before you swallow this anti-government line, remember how much you take the FDA's work for granted every time you swallow a prescription drug.

San Francisco Chronicle
Sunday, February 5, 1995
"Sunday" Section, Page 8

EDITORIALS

Dangerous Schemes To Overhaul the FDA

THE ZEAL FOR reduced government has turned reckless with sudden serious discussion in Washington of proposals to weaken or abolish the federal Food and Drug Administration.

For years, drug industry representatives have broached the idea of removing power from the FDA, the agency charged with overseeing the safety and effectiveness of drugs, medical devices and food. They charge that lives — and profits — have been lost because of the lengthy amount of time it takes to get products approved.

People who say you can dismantle the FDA 'don't know what they're talking about'

In the past, Congress has wisely ignored the call to undermine the agency, mindful that the FDA — while not perfect — has for almost 90 years proved a bulwark against tainted food, drugs that maim or kill and medical appliances that do more harm than good.

It was an FDA officer, Dr. Frances Kelsey, who prevented the use in the United States of thalidomide, a sleeping pill that was widely used in Europe in the 1960s and that was later shown to have caused birth defects in thousands of babies. Such protection continues. Daily, the FDA and its 9,300 doctors, inspectors and other employees keep harmful products away from consumers and allow life-saving ones to reach the market.

But House Speaker Newt Gingrich has made the FDA a target, describing the agency as "the leading job-killer in America" and calling FDA Commissioner David Kessler a "bully and a thug." Proposals to trim or even dismantle the agency are suddenly being taken seriously.

The Health Industry Manufacturers Association — which represents the medical-device industry — is circulating a proposal to "semi-privatize" the FDA by creating government-certified approval boards.

The Gingrich-affiliated Progress and Freedom Foundation, which has received hefty contributions from pharmaceutical companies, is writing a study on how to turn over many FDA functions to private industry, an obvious conflict of interest that would rob the process of supervision over life-and-death products of its independence and eliminate current FDA prohibitions against interested parties being involved in the regulation process.

Worse still, the Competitive Enterprise Institute, whose representatives testified before a House appropriations subcommittee last week seeking a cut in the FDA budget, wants to allow companies to market products without FDA approval. It would be up to doctors and patients to decide the risk.

FDA officials admit that the approval process was due for reform and that there is need to speed it up. But they have reacted to that need. Last year, they report, overall drug approval was faster by 21 percent and approval of drugs containing active substances never marketed in the United States was speedier by almost 50 percent. But they are right to insist that public safety must always be their prime concern.

Improvement is one thing. An overreaction that threatens the health and safety of Americans is quite another. As Charles Edwards, FDA commissioner during the Nixon administration said recently, "People who suggest that you can dismantle the FDA or piecemeal its work out to other agencies don't know what they're talking about." They also are dangerous.

Don't undermine the FDA; it's a needed protection

Speeding drugs to market isn't the only concern

THERE CAN BE a legitimate debate over whether the U.S. Food and Drug Administration is too cautious — or not cautious enough — in approving new drugs and medical devices for use in the United States.

But there's no justification for the assault on the agency that's being launched by right-wing groups and self-interested manufacturers intent on ruining it. It's an insidious campaign meant to tarnish the FDA as a death-dealing agency because it doesn't rush its approval of drugs and devices that manufacturers are anxious to market.

One of those in the forefront of the anti-FDA campaign is House Speaker Newt Gingrich, D-Ga., who wildly calls the agency "the leading job-killer in America" and FDA Commissioner David A. Kessler "a bully and a thug."

As it happens, executives and lobbyists for seven FDA-regulated companies are among the top money contributors to GOPAC, the controversial Republican political fund-raising arm headed by Gingrich.

Meanwhile, Gingrich's Progress and Freedom Foundation — so wondrously named — is working out a proposal to privatize the drug-approval process, an idea that should scare every American. Another bad notion would let any new device or drug be marketed as long as it is labeled "not FDA-approved."

Much of the criticism stems from the FDA's unwillingness to approve some specific drugs and devices in use in Europe. There may indeed be examples of undue caution by the regulators. But there are also cases where the go-slow approach paid off.

Americans with long memories are still thankful to the FDA for its caution in 1960 and 1961. The FDA held off approving a tranquilizer called Thalidomide because of its unusual chemical structure; the agency didn't think it had been tested enough. Europe raced ahead and used the drug. By late 1961, it was evident that Thalidomide had caused terrible deformities in about 10,000 newborn children in Europe and elsewhere. Americans were spared.

Gingrich is hot under the collar because the FDA has withheld approval of a Danish heart pump that is supposed to increase survival chances of those suffering a heart attack. It could have saved 14,000 lives so far, he insists. But the FDA contends conventional CPR provides as much benefit.

No human institution is perfect, and the FDA is no exception. It might, for instance, be quicker in approving drugs that could help bring relief to people with diseases that so far have proven to be terminal.

Overall, however, the FDA performs a tough balancing act well. It must decide in each case whether there is enough evidence that a drug is safe and effective to merit its sale to Americans. The ultimate buyers of drugs and medical devices are ordinary people who have to rely on its unbiased judgment. Public protection — not fast action to satisfy manufacturers — must be the agency's chief objective.

The FDA has a timetable for quickening its pace in reviewing new drugs and devices, but if speed is made the only criterion, Americans are clearly at risk.

Americans should not fall for the attacks on the FDA.

Abroad at Home

ANTHONY LEWIS

Reform Or Wreck?

BOSTON

In 1960 the Food and Drug Administration received an application to market in this country a tranquilizer called Thalidomide, said to induce calm and sleep with no side effects. Described as a miracle drug, it had been on sale in Europe for two years.

Dr. Frances Kelsey of the F.D.A. was given the application to review. She was cautious because Thalidomide had an unusual chemical structure. She asked the Merrell Company, which wanted to market it, for more information.

Early in 1961 Dr. Kelsey saw in a British medical journal a doctor's letter saying that patients who had used Thalidomide for a long time developed a nerve inflammation in their fingers. She wondered whether fetuses would be similarly affected if pregnant women took the drug. She asked more questions, irritating Merrell officials.

Over the previous year or two a strange medical phenomenon had appeared in West Germany and Britain. Children were born with grotesque deformities, lacking arms and legs. No one knew the reason.

Then, in November 1961, a German doctor traced the cause to Thalidomide. Women who took the drug early in pregnancy were liable to have deformed children. Thalidomide was withdrawn from the market.

An estimated 10,000 deformed children were born in Europe and elsewhere because of Thalidomide. But except for one trial distribution, the drug was kept out of the United States — kept out by a skeptical, determined F.D.A. doctor who was denounced, Morton Mintz of The Washington Post wrote at the time, as "a bureaucratic nitpicker."

If Newt Gingrich and his supporters have their way, no F.D.A. doctor like Frances Kelsey will again be able to block distribution of a drug like Thalidomide. For the F.D.A. is a prime target of the radical Republicans.

Speaker Gingrich has described the F.D.A. as "the leading job-killer in America." That encapsulates a right-wing view that delay in approving new drugs and medical devices is hurting American manufacturers.

Mr. Gingrich and other critics say the agency kills not only jobs but people. On NBC's "Meet the Press" last month he showed a Danish cardio-pump that he said increased the survival chances of heart-attack victims "by 54 percent" but that the F.D.A. "makes illegal." In fact, recent medical studies have shown no more benefit from the device than from conventional cardiopulmonary resuscitation.

Two weeks ago the right-wing Washington Legal Foundation ran a full-page newspaper advertisement that called the F.D.A. a killer. It cited the cardio-pump (saying it could have saved "14,000 lives so far") and other equally dubious matters. It said the American Heart Association estimated that delayed approval of a heart defibrillator cost "at least 1,000 lives"; the Heart Association denied making such a claim and deplored the ad.

The tone of the attacks on the F.D.A. is uncommonly brutal. Speaker Gingrich has called its Commissioner, David A. Kessler, who was appointed by President Bush, "a thug."

In all this we can see the real nature of the radical Republican strategy. The talk is of reforming Government. The real intention is to destroy many of its important functions.

Thus there are proposals to eliminate the F.D.A., replacing it with an industry-dominated agency; or to farm out the approval process to private bodies; or to let new drugs and medical devices be sold with a warning that they have not been approved.

Reform and simplification of Federal regulations are necessary. Some have become far too detailed and burdensome. When Washington tries to regulate minutely the practices of thousands of universities all over this vast country, for example, it is as likely to do harm as good.

But there are some things that a civilized society needs government to do. One of them is to protect its citizens from untested drugs that may do terrible harm.

In 1962 President Kennedy gave an award to Dr. Kelsey of the F.D.A. for her "high ability and steadfast confidence" in saving Americans from the Thalidomide tragedy. I do not believe that Americans really want to retreat from that standard to the age of carnival elixirs — or worse. □

A cautionary tale about weakening the F.D.A.

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

04-Apr-1996 05:51pm

TO: Jonathan Winer

FROM: Elizabeth E. Drye
Domestic Policy Council

SUBJECT: FDA, of course

In walking through FDA's new section-by-section and bill language just now, I noticed two amendments not reflected in your memo to Sally. Both fix problems you and FDA had w/the bill.

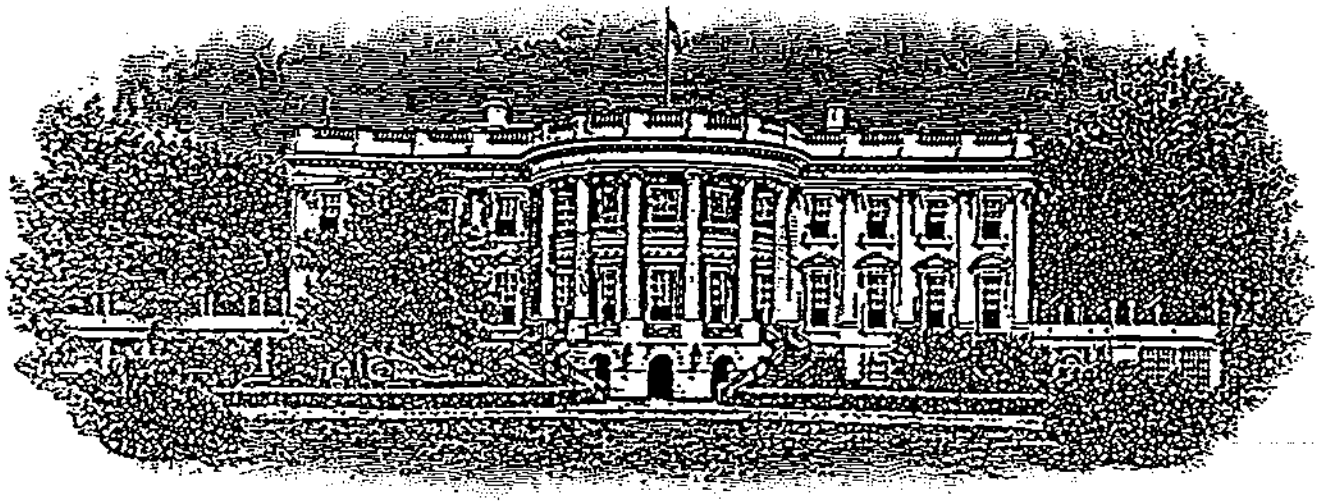
Section 410 -- Committee struck and replaced w/Kennedy amendment. See p. 11 of section-by-section, pg. 60 of bill, and pg. 3 of your memo.

Section 702(c) -- Committee accepted Kennedy amendment to give FDA discretion on what is within the "general use." See pg. 16 of section-by-section, p. 92 of bill, and p. 5 of your memo.

Also, you might want to look at changes in Kassebaum mark to Sec. 702(d) if you haven't already (p. 93 of bill; p. 16 of section-by-section).

Hope this is helpful. Thanks again for taking the time today to go over these issues, and for your great suggestion to meet outside.

The White House



DOMESTIC POLICY

FACSIMILE TRANSMISSION COVER SHEET

TO: Jonathan Winer

FAX NUMBER: 395-6974

TELEPHONE NUMBER:

FROM: Elizabeth Drye

TELEPHONE NUMBER: 6-5573

PAGES (INCLUDING COVER):

COMMENTS:

[FDA]
AP v5137 rt 3exec Revamping FDA, Bit,0800 02-19 4:55p

FDA, Critics Wrangling Over Speed of Drug Development
Eds: Also moving on general news wires.
By LAURAN NEERGAARD
Associated Press Writer

WASHINGTON (AP) - Government doctors thought they'd finally proved Americans get life-saving new medicines as fast as or faster than Europeans, but critics are insisting that's not good enough.

Afraid the good news could slow congressional efforts to revamp the Food and Drug Administration, its detractors are charging that hidden red tape forces U.S. drug makers to spend 15 years developing a single medicine.

Incensed regulators say that's just not so.

It's a question that becomes pivotal Wednesday, because which side Congress believes could determine whether it gives an overhaul or merely a face lift to the agency responsible for safeguarding medical therapy.

"We are far and away ... ahead of the world," fumed the normally imperturbable Dr. Murray Lumpkin, the FDA's drug chief.

Countered Robert Goldberg of George Washington University: "Patients are still waiting longer than necessary."

Congress begins debating legislation Wednesday to make the FDA get new therapies to patients faster.

A Senate plan would force the FDA to review new medicines under strict deadlines and streamline the time spent testing new products. The House will explore a much more radical alternative: Let private companies approve new medicines to reduce the FDA's role to that of a gatekeeper that ensures the firms are certified to work properly.

The hearings promise to be feisty and partisan: Just last week, House Republicans apologized for announcing them to FDA critics before giving Democrats the date.

Nobody disputes that FDA has worked too slowly; in 1985, it took three years on average to review a drug, but the FDA argues that it has improved on its own, averaging 18 months last year. More important, it cut in half the review time for "breakthrough" medicines, taking six months to clear drugs for killer diseases or first-of-a-kind treatments.

International drug records show that last year Americans were the first users of 10 of the world's 28 breakthrough drugs. Germany and Belgium had the next-highest rate of first approvals, with three.

The figures stunned FDA critics, and drug makers conceded the agency had improved.

The critics are giving Congress two new arguments:

-All told, the rest of the world got 18 of last year's 28 breakthrough drugs before Americans.

"I would hope the FDA would aspire to be the world's leading regulatory agency," Gerald Mossinghoff of the Pharmaceutical Research and Manufacturers Association wrote the FDA last week. "The U.S. discovered 52 percent of the important drugs marketed in industrialized countries between 1975 and 1994, yet 67 percent ... were approved abroad first."

-FDA requirements for how companies test a new medicine force drug makers to spend 15 years developing a single drug, Washington University's Goldberg charged.

"There's a great deal that can be done to improve that (development) process and streamline it, none of which puts patients at risk," said Carl Feldbaum of the Biotechnology Industry Organization.

The FDA says comparing one country to the whole world combined is unfair.

The FDA says comparing one country to the whole world combined is unfair.

And it is "absolutely untrue" that the FDA demands 15 years to develop a drug, said medical policy chief Dr. Robert Temple.

"We got a 50 percent reduction in review times - that's a miracle. Now they're complaining about development time, but 90 percent of that is the company's decision," he fumed.

A British study tracked 700 drugs in 20 countries and concluded that drug development times are equal worldwide. The study also showed drugs are tested in humans for about six years in both Britain and the United States.

Industry records show companies study medicines in the test tube and animals for three to six years, areas the FDA doesn't touch. When it's time to test people, the FDA has 30 days to object or trials start automatically. Ten percent of trials are stopped for safety concerns.

So what's the holdup? Temple cites the new blood pressure drug carvedilol, tested in 8,000 patients when the FDA asked for just 1,000. SmithKline Beecham used the extra patients to compare carvedilol to competing drugs, data the FDA doesn't use but that helps insurance companies decide which drugs they will cover, Temple explained.

But the biotechnology organization's Feldbaum counters that companies must twiddle their thumbs while FDA officials wait weeks to do something as simple as returning a phone call to restart a drug trial on hold to ensure against side effects.

(FDA)

The Washington Times ★ THURSDAY, DECEMBER 14, 1995 / PAGE A21

The FDA's snail's pace approach

By Julie DeFalco

There are lies, damned lies, statistics — and government statistics. Especially when it comes to the Food and Drug Administration.

Under increasing Congressional scrutiny, the FDA is facing charges that it kills people by taking too long to approve medical drugs and devices, and by restricting medical innovation. The FDA has responded by using dubious numbers to back up the agency's claim that the situation actually is improving. One example is a letter from James O'Hara, the FDA's Assistant Commissioner for Public Affairs, recently printed in The Washington Times.

Mr. O'Hara used a recent General Accounting Office report on medical device review times to back up his assertion that approval times for devices known as "510(k)s" have dropped in recent years. These new devices, which are "substantially equivalent" to existing devices, make up the majority of the device applications filed with the FDA. Mr. O'Hara quoted from the report, "For 510(k) applications submitted in a given fiscal year, the review time remained stable over the 3 years from 1989 to 1991, then rose sharply in 1992 and 1993 before dropping in 1994."

In short, according to Mr. O'Hara, the FDA's critics are wrong — the FDA is doing a great job, and is building on past successes. Yet all one needs to do is turn to the next page in the GAO report to realize that Mr. O'Hara is not telling the whole story.

The reality is that during 1989-1991, the median review time for medical devices was 80-90 days. By 1993, the median time for 510(k)s jumped 250 percent to 230 days. The report states, "Although the median review time showed a decline in 1994 (152 days), it remained higher than that of the initial 3 years." In short, the median approval time doubled between 1989 and 1994.

But more reliable numbers show that the FDA has been masking the agency's poor record through statistical sleight-of-hand, in this case, fuzzing the distinction between "mean" and "median" to bolster its case.

The mean is the average of a set of numbers. The median is the middle value of a set of numbers; that is, there are an equal number of values on either side of the median. "Until recently," the GAO report states, "FDA reported review time in terms of means." Now, however, the FDA reports review times in terms of medians.

Why the change? The GAO report notes, "The discrepancy between the two measures gives some indication of the distribution of the review time. When the mean is larger than the median, as in the case of the 510(k)s. . . it indicates that a group of applications required lengthy reviews." Which is what the FDA has been trying to hide.

The median can be calculated even when some applications are still on hold. And, as the GAO report notes, "a large proportion of the applications have yet to be completed." The report points out that as these pending applications are reviewed, the mean will increase.

The FDA also knows most people will confuse the median with the mean. Since the median is smaller than the mean, this year's median time, for example, would compare favorably with other years' mean times. As Robert Higgs, Research Director at the Independent Institute in California, observes, "This is a blatant attempt to make the FDA's performance look better than it really is."

The very real regulatory delays in the United States have increasingly led U.S. medical device firms either to abandon projects, or to do research and development overseas. No matter what the FDA does to sugarcoat its record, it cannot stop this technological exodus to Europe. Dr. Higgs explains, "It is important to remember that the number of annual approvals now is less than in the 1980s because it is so much less promising to even submit an application."

Consider the situation of "breakthrough" devices — new and important devices that must go through the Pre-Market Approval (PMA) process. PMA applications dropped by half in five years, from 84 in 1989 to 43 in 1994.

At the same time, the FDA has grown. In 1988, the agency approved 46 PMAs. By 1994, after an 80 percent increase in the FDA's funding and 20 percent increase in its personnel, PMA approvals dropped to 26. This is because the increase in funding for the FDA did not spur an increase in productivity; rather, the agency diverted resources to enforcement activities.

The FDA's policies are a public health problem. The United States lags far behind the rest of the world in terms of access to state-of-the-art medical equipment, and this is directly attributable to the FDA. Because of this, says Dr. Keith Lurie of the University of Minnesota, "We don't get the equipment we need to save lives."

Spokespeople for the agency, including Commissioner David Kessler himself, continue to crow about the FDA's apparent successes, even though it is clear that the FDA's medical device approval record is a great deal worse than the agency would like the public to think. The bottom line is that the FDA is less concerned about protecting the health and safety of Americans than it is with protecting the health and safety of the agency.

Julie DeFalco is a policy analyst at the Competitive Enterprise Institute in Washington, D.C.

The Washington Times

PAGE B6 / THURSDAY, DECEMBER 14, 1995 ★

Senate bill prods FDA

A senior Republican senator yesterday introduced a bill to speed up the Food and Drug Administration's review of new drugs and medical devices. Sen. Nancy Landon Kassebaum of Kansas said the FDA is required to review applications to market new drugs and medical devices in 180 days but is taking an average of 570 to 649 days.

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TELEFAX TRANSMITTAL SHEET

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DATE: 26 March 1996

TO: Elizabeth Drye

TELEFAX NUMBER: 202-456-7028

COMMENTS: Elizabeth -- I've attached a couple of articles from our consumer magazine that explain the drug approval process. I've also attached a backgrounder that provides some details on early access to therapies. Finally I've attached a wire story on the SC AG's comments yesterday.

NUMBER OF PAGES, EXCLUDING COVER: 12

Testing in 'Real People'

by Ken Flieger

No part of the drug development process is more critical than clinical trials—testing a new drug in humans to find out whether it is really useful in fighting disease. Usually the answer is no. One major U.S. drug company says that of every 20 compounds it submits to clinical trial, only one may be sufficiently safe and effective to merit FDA approval for marketing. In drug development, unfortunately, failure is the norm.

According to an industry official involved in planning and evaluating clinical research, "Most compounds that look interesting in animal and other laboratory studies never even make it to clinical trial. They're either ineffective, too toxic, too difficult to produce in quantities sufficient for human testing (let alone marketing), or of such limited usefulness that the cost of development can't be recovered." Those that do show genuine promise in preclinical research and development face the most rigorous, costly, and time-consuming stage of drug development, evaluation first in healthy human volunteers and later—maybe—in patients who actually have the condition the drug is intended to remedy.

There's a common misconception that FDA is responsible for testing drugs before they're approved for sale. While the agency does a great deal of testing to check on the purity and potency of drugs, it's the drug sponsor—a pharmaceutical company, a research organization, a public or private agency, even an individual—that is required to initiate studies to assess drug safety and effectiveness. FDA's role is to examine the design and conduct of those studies, and, of course, the results, as part of the process of deciding whether a new drug can be approved for marketing.

Basically, FDA wants to be sure that the welfare of participants in clinical studies will be protected and that the studies will be planned and carried out by qualified experts. The method used to study the drug and the way the results are interpreted have to be scientifically valid and free of subjective bias. The investigators have to identify and analyze all their results, including those they didn't expect, and they must follow up any problems, especially those involving people who, for whatever reason, dropped out of the study.

But before an investigational drug can be given to the first patient, the sponsor has to provide FDA with the results of laboratory and animal research, plus information, if there is any, about previous use of the drug in humans in this country and abroad. The sponsor must describe in detail how the clinical trials will be conducted—how many people will be involved, how they will be selected, where the studies will be done and by whom, how the drug's safety and effectiveness will be evaluated, and what findings would require the study to be changed or halted. This material is sent to FDA in the form of an investigational new drug application, or IND. Clinical trials can begin 30 days after FDA receives an IND unless the agency approves an earlier start or orders a "clinical hold" because of questions about the request.

Normally, clinical trials are carried out in three phases involving progressively larger numbers of people. Drug sponsors arrange with physicians and hospitals to actually conduct the studies.

Clinical trials are normally done in three phases. Phase 1 trials are concerned primarily with learning more about the safety of the drug, though they may also provide some information about effectiveness. Phase 1 testing is normally done on healthy volunteers. The volunteers are usually paid for their services, which consist chiefly of submitting to a variety of tests to learn what happens to the drug in the human body—how it's absorbed, metabolized (broken down), and excreted; what effects it has on various organs and tissues; and what side effects occur as the dose is increased. Evidence of toxicity at doses too small to produce any beneficial effect is one of the chief causes of failure in phase 1 drug testing.

These initial studies are critical to the design of later clinical trials. They provide essential information about how much of the drug a patient should receive, how often it should be used, and what precautions need to be taken to make sure the drug is being used safely. Phase 1 studies usually involve fewer than 100 subjects—sometimes as few as 20—who receive the drug for a month or so. To complete this phase normally takes from six months to over a year.

If the results of phase 1 testing present no unacceptable safety problems, phase 2 trials can begin. (Actually, in some cases, phase 2 studies may begin before all the phase 1 trials are completely evaluated.) Only about 13 or 14 out of 20 drugs that enter phase 1 clinical trials go on to phase 2. This stage of clinical testing may take somewhat longer than phase 1 studies. It normally involves a few hundred patients and is designed to show whether the drug is effective in treating the disease or condition for which it's intended. Phase 2 studies also attempt to disclose short-term side effects and risks in people whose health is impaired.

(Continued on page 12)

How Experimental Drugs Are Tested in Humans

	Number of Patients	Length	Purpose	Percent of Drugs Successfully Completing*
Phase 1	**20 - 100**	**Several months**	**Mainly safety**	**67 percent**
Phase 2	**Up to several hundred**	**Several months to 2 years**	**Some short-term safety, but mainly effectiveness**	**45 percent**
Phase 3	**Several hundred to several thousand**	**1-4**	**Safety, effectiveness, dosage**	**5-10 percent**

***For example, of 20 drugs entering clinical testing, 13 or 14 will successfully complete phase 1 trials and go on to phase 2; about nine will complete phase 2 and go to phase 3; only one or two will clear phase 3 (and, on average, about one of the original 20 will ultimately be approved for marketing).**

(Continued from page 11)

Most phase 2 studies are randomized controlled trials. A group of patients receiving the drug, a "treatment" group, is matched with a group that is similar in important respects, such as age, sex, disease state, and other factors that could affect the course of their illness and the effect of the investigational drug. This latter "control" group receives a standard treatment or a placebo (an inactive substance). Comparison of the two groups tells both the investigators and FDA a great deal about the drug. Often these phase 2 studies are "blinded"—designed and carried out so that neither the patients nor the researchers know who is getting the experimental drug. Blinded studies help avoid errors in interpreting results caused by over-enthusiasm or other kinds of bias among patients and investigators.

There is some controversy over whether it is ethical to give a placebo to some patients in certain drug studies, especially when their condition is a serious or even life-threatening one, such as AIDS (acquired immune deficiency syndrome). Some people think that in such cases *all* patients should be given the experimental drug, since it offers at least *some* hope, where the placebo offers none.

But to do so would defeat the purpose of the clinical trial, making it impossible to learn whether the experimental drug does, in fact, have any more effect than no treatment at all. And that knowledge is crucial in the battle against diseases such as AIDS, allowing more lives to be saved in the long run. It is generally agreed, for example, that the clinical trials of the anti-AIDS drug zidovudine (formerly known as azidothymidine, or AZT) were actually shortened by testing it against a placebo. The studies showed dramatically better results for zidovudine, compared to a placebo, and FDA was able to approve the drug for marketing in March 1987, only four months after receiving an application from the drug's manufacturer, Burroughs Wellcome Co., of Research Triangle Park, N.C.

About 30 percent of the drugs studied in phase 2 are abandoned. Thus, of 20 drugs that enter phase 1 clinical trials, only about nine survive to go into phase 3 testing.

By the time the drug is ready for phase 3 studies, both the sponsor and FDA, which has been receiving reports on the progress and results of the clinical trials, know quite a bit about the drug's safety and effectiveness. They know by now from the results of the carefully controlled studies that the drug does have a therapeutic effect. They have a fairly good picture of its short-term side effects and adverse reactions. And they also know that the sponsor is very likely to apply to FDA for approval to put the drug on the market.

There is, however, much yet to be learned about how to use the drug properly. For example, phase 1 and phase 2 testing usually aren't designed to provide information about optimum dose rates and schedules. And, of course, scientists aren't likely to have data on long-term safety in humans. The comparatively small number of patients involved in phase 1 and 2 trials and their short duration generally mean that only the most common, frequent side effects and adverse reactions will have been seen. A more complete understanding of the drug's

(Continued on page 15)

There's a common misconception that FDA is responsible for testing drugs before they're approved for sale.

(Continued from page 12)

safety, along with verification of its usefulness in treating disease, has to await the far more extensive testing that constitutes phase 3 clinical trials.

At the end of phase 2, representatives of the drug sponsor may meet with FDA staff to discuss their plans for phase 3 studies. At that meeting, FDA might suggest changes in the design of studies or indicate additional information the sponsor should develop to clarify the drug's safety and effectiveness. FDA might ask the sponsor to arrange studies in special groups—elderly patients, people with impaired kidney function, or patients receiving other drugs that may interact with the investigational drug, for example. The object of phase 3 testing and of the joint FDA-drug sponsor meetings is to develop information that will allow the drug to be marketed and used safely.

Phase 3 clinical trials can involve as many as several thousand patients who have the condition against which the drug is effective. It's not unusual for these studies to continue for three or four years or longer. Although they are often controlled studies, phase 3 trials tend to approximate more closely the conditions of ordinary medical practice. They expand on the research carried out in phase 2 in order to clarify the drug's benefit-risk relationship, discover less common and even rare side effects and adverse reactions, and generate information that will be incorporated into the drug's professional labeling, the FDA-approved guidance to physicians and others about how to use the drug.

Occasionally, the evidence of safety and effectiveness coming out of phase 2 studies is so strong that phase 3 trials are not needed. Such was the case with the anti-AIDS drug zidovudine: During the same four- to six-month period of phase 2 testing, only one AIDS patient died while being treated with zidovudine, while 19 died while being given a placebo.

The kind of patients who participate in phase 2 and 3 clinical trials depends on the drug under investigation and how it is thought to be useful. They may or may not be hospitalized. They may already be under treatment or have a newly diagnosed condition for which treatment has not yet begun. And, of course, some of the people who take part in phase 2 and 3 drug testing, the control patients, will not receive the investigational drug at all.

Of the 20 drugs that entered clinical trials, only one or two survive the rigors of all three phases of testing. About 75 percent of those are eventually approved for marketing.

Of the 100,000 or more pages of information FDA may be called on to review in order to decide if a drug can be approved for marketing, at least 80 percent or more is information generated by clinical testing. Some industry officials think FDA's requirements for clinical testing could be reduced and the process shortened. Most recognize, however, that it takes exhaustive clinical studies to discover relatively uncommon adverse effects—the kind that may occur in only one of several hundred patients receiving the drug—and to develop the detailed information health-care practitioners need in order to prescribe a drug safely and effectively.

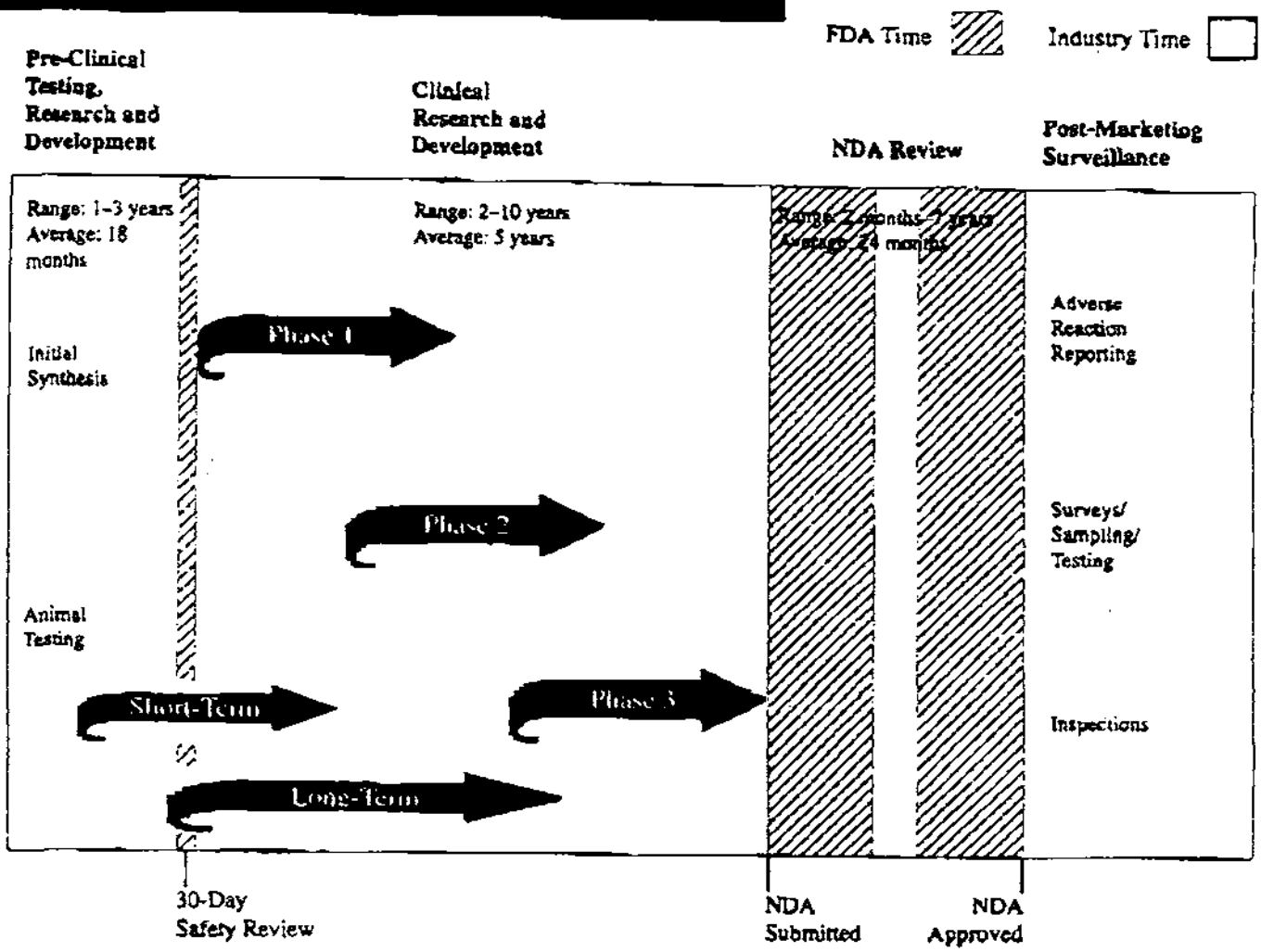
The clinical trial phase of drug development can, and frequently does, take a very long time. FDA estimates a range of two to 10 years with an average of five years. The length of clinical trials depends largely on the kind of drug being studied. A drug to treat relatively common infections that is meant to be used only for a few days or weeks may get through all three clinical trial phases in two to four years. On the other hand, a drug for high blood pressure that patients may take for decades could be in the clinical trial phase for seven to eight years or more to thoroughly assess its long-term effects.

FDA has taken steps to simplify and expedite the clinical trial stage of drug development. The agency has reduced regulatory requirements and issued guidelines that help sponsors plan clinical research. Agency officials meet with drug sponsors who want to discuss the planning and conduct of clinical research. It is doubtful, however, that the extent of clinical trials could be substantially reduced without lowering U.S. standards of safety and effectiveness, standards that are respected throughout the world. However, drug companies could avoid redundant studies and prevent other problems by consulting with FDA along the way, urges Commissioner Frank E. Young, M.D., Ph.D.

The system is not perfect. Drugs that undergo rigorous, carefully designed and conducted clinical trials and are approved for sale sometimes cause unexpected problems when they come on the market. But we learn from failures as well as successes, and the system gets better. To make new drugs available to those who need them, studies in a few thousand willing participants help pave the way for safe and effective treatment in hundreds of thousands or millions of patients. ■

Ken Flieger is a free-lance writer. He was formerly a member of FDA's Office of Health Affairs.

New Drug Development



Personal Participation

Anyone interested in participating in a clinical trial should discuss the idea with his or her physician. Doctors are generally aware of investigational drugs that might be of benefit to their patients and of clinical trials involving these drugs. They can obtain detailed information from a variety of sources, including drug sponsors.

Clinical trials are carried out at major medical research centers such as teaching hospitals, at specialized clinics for people with AIDS, Alzheimer's disease or other conditions, and even in doctors' offices. Although they often involve hospitalized patients, many clinical trials are conducted on an outpatient basis, with participants more or less going about their normal activities. The center or institution where a study is to be carried out often runs newspaper ads recruiting potential participants for clinical studies that tell readers where to call or write for further information.

Although investigational drug studies vary widely, some things should be expected by participants in virtually any clinical trial. For example, participants might have to give blood samples more often than during ordinary care. Tests to assess disease status might be more frequent. Participants are often required to keep detailed records of their symptoms and follow strict schedules.

It's also important to understand that volunteering for a clinical trial does not guarantee that an individual patient will receive the drug under investigation. Control patients may get a placebo, a drug already approved for their condition, or perhaps no treatment at all.

These and other aspects and implications of taking part in a clinical trial must be fully explained in advance by the people conducting the trial, and patients must agree to the conditions before they can participate. The hope of personally benefiting from a new drug—or the desire to take part in research that might one day benefit millions—is what makes people volunteer for clinical trials. But it shouldn't prevent them from finding out all they can about being a part of the process. ■

—K.F.

Benefit Vs. Risk:
How FDA Approves New Drugs

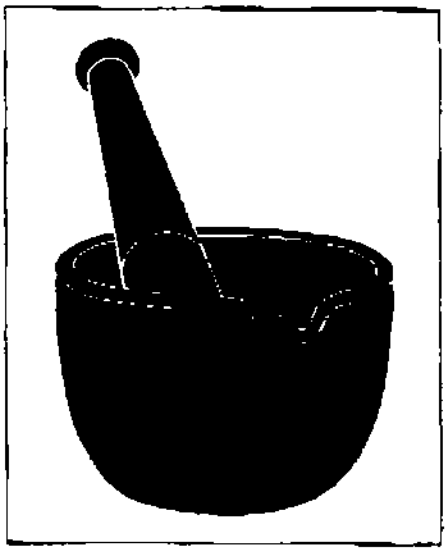
by Dixie Farley

Under current law, all new drugs need proof that they are effective, as well as safe, before they can be approved for marketing. But it's important to realize that no drug is absolutely safe. There is always some risk of an adverse reaction. It's when the benefits outweigh the risks that the Food and Drug Administration considers a drug safe enough to approve.

In fact, it was little more than 30 years ago that U.S. drug law first embraced the idea of risk vs. benefit that is now the key to new drug approval. Providing evidence of safety before marketing was first required by the Federal Food, Drug, and Cosmetic (FD&C) Act in 1938, but not until the Kefauver-Harris Drug Amendments of 1962 did firms also have to show a drug's effectiveness before marketing.

Before any drug gets on the market today, FDA decides—as quickly as a thorough evaluation allows—whether the studies submitted by the drug's sponsor (usually the manufacturer) show it to be safe *and effective* for its intended use. Here's what goes into those decisions.

"Take AZT, for example," says Robert Temple, M.D., director of the Office of Drug Evaluation I, in FDA's Center for Drug Evaluation and Research. (AZT stands for azidothymidine, the former generic name of the drug now known generally as zidovudine and marketed as Retrovir to treat AIDS.) "It has significant toxicity. If you weren't quite sure it had a benefit, it would be hard to describe it as 'safe.' But we know, from well-controlled studies, that it has a benefit. In the first large clinical study with the drug, there were 19 deaths in patients taking a



placebo (an inactive substance), but only one death in those on AZT."

Zidovudine was approved in March 1987 in a record 107 days. But no corners were cut. Indeed, FDA expended an estimated eight staff years at a cost of $600,000 on zidovudine's evaluation. That the review was so rapid was due largely to the fact that FDA was involved with the drug every step along the way from the start of clinical studies in AIDS patients.

FDA has in a number of ways taken steps to make urgently needed drugs available sooner. These are drugs for treating serious or life-threatening diseases that have no good treatment.

Under the accelerated approval rule, the agency can rely as a basis for drug approval on a reasonable "surrogate" endpoint—that is, an effect of a drug on a marker of the disease, rather than an actual effect on survival or illness. (An example of a marker would be CD4 cell counts, used to measure the strength of the immune system. Usually such a surrogate can be assessed much sooner than such an endpoint as survival.) In accelerated approval, FDA approves the drug on condition that the sponsor study the actual clinical benefit of the drug.

According to FDA Commissioner David A. Kessler, M.D., "We cannot wait for all the evidence when people are suffering and dying from a devastating disease. But, we must ensure that all the evidence we need eventually does get collected."

Promising Experimental Drugs

Today's policies also allow broader use of some investigational drugs even before they are approved for marketing.

These new policies include the Treatment IND (IND stands for investigational new drug application) and the parallel track mechanism. (See "A Drug Review Glossary," page 28, and "FDA Finds New Ways to Speed Treatments to Patients," page 19.)

Both allow promising drugs, not yet approved for marketing, to be used in "expanded access" protocols—relatively unrestricted studies in which the intent is not only to learn more about the drug, especially about its safety, but also to provide treatment for people with no real alternative. But these expanded access protocols also require researchers to formally investigate the drug in well-controlled studies and to supply some evidence that the drug is likely to be helpful.

"This expanded access does not represent just 'giving the drug out,'" Temple

says. "The sponsor has the obligation to develop the drug properly, so we will know whether it really is useful."

FDA participates actively in the drug development process, seeking to provide clear standards and expectations. Sponsors are encouraged to meet with FDA, Temple says, at an "end of phase 2 conference" before carrying out the large-scale controlled clinical trials. (For information about the various phases of drug study, see "Testing Drugs in People," page 6.) At this conference, FDA gives advice about the design of the sponsor's study plan to ensure that the trials will be acceptable.

As Temple puts it: "We try to find and eliminate flaws in the individual studies and overall development plan that we know will give us trouble later on in the NDA review. We don't want people to carry out a large study that has no chance of being considered adequate and well-controlled."

FDA also provides advice, he says, in the form of guidelines on how to study particular classes of drugs and on how to submit and analyze data in a marketing application.

In addition, to ensure that institutional review boards meet FDA's rules for the protection of the rights and welfare of research subjects, the agency routinely inspects the boards every five years. "We may go more often, if there are problems," says Frances O. Kelsey, Ph.D., M.D., director of FDA's division of scientific investigations.

FDA routinely inspects animal laboratories every two years, or more often, Kelsey says, "if a review division has a question about a specific animal study."

Reviewing NDAs

The documentation required in an NDA is supposed to tell the drug's whole story, including: what happened during the clinical tests; how the drug is constituted—its components and composition; results of the animal studies; how the drug behaves in the body; and how it's manufactured, processed and packaged, especially the quality controls. FDA also requires samples of the drug and its labels.

Full reports of a drug's studies must be submitted so that FDA can evaluate the data. The controlled clinical trials are especially important because they provide the only basis, under law, for demonstrating effectiveness. They answer the question, "Does this drug work for the proposed use?" The whole data bank is used to look for adverse effects. From analyses of the data, FDA reviewers assess the benefit-to-risk relationship. (See "The Review Team.")

The human studies also generate information that will be in the drug's professional labeling, the guidance approved by FDA on how to use the drug. This is the package insert that accompanies a drug in all shipments to physicians and pharmacies.

Whenever an NDA is submitted to FDA, the agency lists it in a computer database, and the division of scientific investigations learns of that NDA by routinely checking the database.

According to Alan Lisook, M.D., who works in the division with Kelsey, "After determining the important studies supporting approval, we send assignments to the field to make on-site inspections of the investigators who did the work, to verify that it was valid." The division may also participate in the inspections.

Since more and more foreign studies are being accepted as primary evidence for drug approval, the agency has been doing a larger number of foreign inspections, Lisook says, "the same as we do here. We compare the data submitted with those data available on site." The sponsor makes sure FDA has access to the research, he says.

If FDA's evaluation of studies reveals major deficiencies, substantially more work by the sponsor may be needed, ranging from further analyses to the conduct of new studies—in either case thereby extending the evaluation time and delaying approval.

"It's particularly important," Temple says, "that sponsors use the opportunities FDA offers during the IND to discuss the critical studies and overall plans, so that they know what we expect with respect to study design, conduct and analysis. This can greatly reduce the chance that the application will 'recycle.'"

FDA has undertaken various ways to re-

The Review Team

The members of the FDA review team simultaneously bring their special technical expertise to the review of an NDA.

- Chemists focus on how the drug is made, and whether the manufacturing, controls and packaging are adequate to ensure the identity, strength, quality, and purity of the product.
- Pharmacologists examine the effects of the drug on laboratory animals in short-term and long-term studies.
- Physicians [illegible] the drug's benefits—its therapeutic effects—and whether the proposed labeling correctly describes the effects of the drug.
- Pharmacokinetics investigate the rate and extent to which the drug's active ingredient is made available to the body and the way it is distributed, metabolized and eliminated.
- Statisticians evaluate the designs for each controlled study and the analyses and conclusions drawn from the data.
- Microbiologists evaluate the data on anti-infective drugs (antibiotics, antivirals and antifungals). These drugs differ from others in that they're intended to attack the workings of microbes inside the body. Reviewers need to know how the drug acts on these microorganisms, which ones it affects, the resistance to the drug, and clinical laboratory methods needed to evaluate the drug's effectiveness. Microbiologists also are concerned with ensuring that injectable drugs are free of organisms.

duce drug review time, which during the past several years has averaged (median) about two years, down from about two-and-one-half years.

For example, funds provided by the Prescription Drug User Fee Act of 1992 (see "User Fees to Fund Faster Reviews," page 50) allow the agency to hire several hundred additional reviewers and support staff and expedite its move to accepting computerized NDAs.

Writing to Congress in September 1992, Commissioner Kessler listed FDA's goals for using the additional resources, including the following five-year goals for review and approval time frames for new prescription drugs:

- Within six months of an NDA's submission date, review and act on complete applications for "priority" drugs (those appearing to represent an advance over available therapy).
- Within 12 months, review and act on NDAs for "standard" drugs (those appearing to have therapeutic qualities similar to those of an already marketed drug).

(In both classifications, major amendments received within three months of the action due date extend a time frame three months.)

- Within six months, review and act on supplements not requiring clinical data review.
- Within 12 months, review and act on supplements requiring clinical data review.
- Within six months, review and act on complete applications resubmitted after receipt of a "not approvable" letter (which describes deficiencies that preclude approval unless corrected).

Review Priorities

FDA classifies investigational new drug applications (INDs) and new drug applications (NDAs) to assign review priority on the basis of the drug's chemical type and potential benefit.

Chemical Type

1. New molecular entity, or NME: An active ingredient that has never been marketed in this country.

2. New derivative: A chemical derived from an active ingredient already marketed (a "parent" drug).

3. New formulation: A new dosage form or new formulation of an active ingredient already on the market.

4. New combination: A drug that contains two or more compounds, the combination of which has not been marketed together in a product.

5. Already marketed drug product, but a new manufacturer: A product that duplicates another firm's already marketed drug product: same active ingredient, formulation, or combination.

6. Already marketed drug product, but a new use: A new use for a drug product already marketed by a different firm.

Treatment Potential

P. Priority review drug: A drug that appears to represent an advance over available therapy.

S. Standard review drug: A drug that appears to have therapeutic qualities similar to those of an already marketed drug.

Other Designations
(may apply simultaneously)

AA. AIDS drug: A drug indicated for treating AIDS or other HIV-related disease.

E. Subpart E drug: A drug developed or evaluated under special procedures for drugs to treat life-threatening or severely debilitating illnesses. (The name refers to Title 21 of the *Code of Federal Regulations*, Part 312, Subpart E, which governs this classification. Also see, "The Evolution of U.S. Drug Law," page 26.)

V. Designated orphan drug: A drug for which the sponsor received orphan designation under the Orphan Drug Act. Such a sponsor is eligible for tax credits and exclusive marketing rights for the drug. ■

Priorities

The order in which applications are looked at is determined with the aid of a classification system. (See "Review Priorities.") The idea is to give priority to drugs with the greatest potential benefit. For example, all AIDS drugs receive the highest priority, and all drugs that offer a significant medical advance over existing therapies for any disease are considered "priority drugs."

Which of FDA's review staffs gets an NDA depends on the drug. For example, cancer treatments go to the division of oncology and pulmonary drug products, and contraceptive drugs go to the division of metabolism and endocrine drug products. Generic drugs go to a different office, the Office of Generic Drugs.

FDA frequently seeks advice from its 17 standing advisory committees on drugs. (See "Getting Outside Advice for 'Close Calls'," page 30.) This is especially true when an approval decision is a "close call."

To be sure approval decisions reflect the most recent safety data, FDA requires safety updates four months after the NDA is submitted, again after it sends the firm an "approvable letter," and at other times if necessary. Updates must report new adverse reactions and important changes in the frequency or severity of effects that are known.

After FDA primary reviewers finish their evaluation, additional review is given by supervisory personnel. "In general," says the agency's Leah Ripper, "office directors take final action on new molecular entities, switches from prescription to OTC status, and other impor-

(continued on page 29)

available under "parallel track" protocols while the controlled clinical trials essential to establish the safety and effectiveness of new drugs are carried out. The system established by this policy is designed to make the drugs more widely available to patients with these illnesses who have no therapeutic alternatives and who cannot participate in the controlled clinical trials.

Pharmacology: The science that deals with the effect of drugs on living organisms.

Post-Marketing Surveillance: FDA's ongoing safety monitoring of marketed drugs.

Preclinical Studies: Studies that test a drug on animals and other nonhuman test systems. They must comply with FDA's good laboratory practices. Data about a drug's activities and effects in animals help establish boundaries for safe use of the drug in subsequent human testing (clinical studies). Also, because animals have a much shorter lifespan than humans, valuable information can be gained about a drug's possible toxic effects over an animal's life cycle and on offspring.

Raw Data: Researcher's records of patients, such as patient charts, hospital records, x-rays, and attending physician's notes. These records may or may not accompany an NDA, but must be kept in the researcher's file. FDA may request their submission or may audit them at the researcher's office.

Safety: No drug is completely safe or without the potential for side effects. Before a drug may be approved for marketing, the law requires the submission of results of tests adequate to show the drug is safe under the conditions of use in the proposed labeling. Thus, "safety" is determined case by case and reflects the drug's risk-vs.-benefit relationship.

Safety Update Reports: Reports that an NDA sponsor must submit to FDA about any new safety information that may affect the use for which the drug will be approved, or draft labeling statements about contraindications, warnings, precautions, and adverse reactions. Safety update reports are required four months after the application is submitted, after the applicant receives an approvable letter, and at other times upon FDA request.

Supplement: A marketing application submitted for changes in a product that already has an approved NDA. FDA must approve all important NDA changes (in packaging or ingredients, for instance) to ensure that the conditions originally set for the product are not adversely affected.

Surrogate Endpoint: A laboratory finding or physical sign that may not, in itself, be a direct measurement of how a patient feels, functions or survives, but nevertheless is considered likely to predict therapeutic benefit. An example would be CD4 cell counts, used to measure the strength of the immune system.

Treatment IND: A mechanism that allows promising investigational drugs to be used in "expanded access" protocols—relatively unrestricted studies in which the intent is both to learn more about the drugs, especially their safety, and to provide treatment for people with immediately life-threatening or otherwise serious diseases for which there is no real alternative. But these expanded access protocols also require researchers to formally investigate the drugs in well-controlled studies and to supply some evidence that the drugs are likely to be helpful. The drugs cannot expose patients to unreasonable risk.

User Fees: Charges to drug firms for certain NDAs, drug products, and manufacturing establishments. FDA uses these fees to hire more application reviewers and to accelerate reviews through the use of computer technology. ■

tant actions, such as a major new use of a drug. Other approval decisions are made at the division level." Ripper is special assistant to the director of the Office of Drug Evaluation II.

Final Actions

In the final analysis, FDA's decision whether to approve a new drug for marketing boils down to two questions:

- Do the results of well-controlled studies provide substantial evidence of effectiveness?
- Do the results show the product is safe under the conditions of use in the proposed labeling? Safe, in this context, means that the benefits of the drug appear to outweigh its risks.

When the review is complete, FDA writes to the applicant to say the drug is either approved for marketing, is "approvable," provided minor changes are made, or is not approvable because of major problems. In the last case, the applicant can then amend or withdraw the NDA or ask for a hearing. Once its NDA is approved, a drug is on the market as soon as the firm gets its production and distribution systems going.

As reflected by the innovations of accelerated approval, the Treatment IND, and the parallel track mechanism, the need for effective treatments for serious illnesses has been so great that it has called for changing the drug approval process.

"The riskiest thing we can do when it comes to life-threatening diseases," says Commissioner Kessler, "is to be unwilling to take risks. But when we take risks, we have to follow through."

Thus, while change is inevitable and often desirable, there are some constants at FDA. Safety and effectiveness, risk vs. benefit, remain the pivotal issues in FDA drug review. ■

Dixie Farley is a staff writer for FDA Consumer.

FDA BACKGROUNDER

U.S. FOOD & DRUG ADMINISTRATION

FDA Mission: Protect Public Health

The American people expect and rely on a safe and wholesome food supply, and access to safe and effective drugs and medical devices. To meet those expectations, FDA inspects and oversees almost 95,000 establishments that produce:

- $487 billion worth of food
- $107 billion worth of drugs—prescription and over-the-counter—and biologics
- $350 billion worth of medical devices and radiation-emitting products
- $3 billion worth of animal drugs and medicated feed
- $39 billion worth of cosmetics and toiletries.

In addition to overseeing the production of safe foods and the manufacture of safe and effective drugs and medical devices, FDA has responsibility for:

- protecting the rights and safety of patients in the clinical trials of investigational medical products
- reviewing and approving in a timely manner the safety and efficacy of new drugs, biologics, medical devices, and animal drugs
- monitoring the safety and effectiveness of new medical products after they are marketed and acting on the information collected.

As the nation's oldest consumer protection agency, FDA is also responsible for seeing that the public has access to truthful and non-misleading product information by:

- monitoring the promotional activities of drug and device manufacturers
- regulating the labeling of all packaged foods.

FDA's public health mission also encompasses efforts to assure:

- the safety of the nation's blood supply
- the safety of all imported FDA-regulated products.

Making New Therapies Available

FDA has instituted a number of ways by which patients can receive promising therapies before they receive final approval. These policies are aimed at helping patients have access to promising therapies while not compromising the scientific integrity of formal clinical testing and the review process. One of the most important such policies, the treatment IND, has been used to give patients early access to products since 1987.

- More than 75,000 patients have received access to therapies under this policy.

- Specific examples include:
  - 22,000 received ddI for AIDS.
  - 13,000 received d4T for AIDS.
  - 2,000 received paclitaxel for ovarian cancer.
  - 11,400 received colfosceril palmitate for respiratory distress syndrome.
- There are other therapies that are just beginning to enroll patients under this policy. For example, gemcitabine hydrochloride was recently approved for treatment IND status for patients with advanced or metastatic pancreatic cancer.

Several drugs have been approved under accelerated approval, a process that is aimed at making life-saving therapies available to patients as soon as possible in the development process without sacrificing the rigor of a thorough review of the data. Examples include:

- Didanosine for AIDS
- Zalcitabine for AIDS
- Stavudine for AIDS
- Clarithromycin for an AIDS-related opportunistic infection
- Interferon beta-1B for multiple sclerosis
- DNase for cystic fibrosis.

Improving Performance

In 1992, the U.S. Congress passed the Prescription Drug User Fee Act. This legislation provided additional resources for FDA through user fees paid by the pharmaceutical industry, and the agency committed to significant performance goals in the review and approval of prescription drugs. The goal is to reduce significantly the time needed for review of new drugs: from the historic average of about 27 months in the late 1980s to 12 months for routine drugs and six months for significant new therapies by 1997. That FDA is meeting the challenge of improved performance is shown by the most recently compiled review and approval times in 1994:

- 10.4 months was the median time for the review and approval of new drugs with important therapeutic uses under the user fee program.
- 13.5 months was the median time for the review and approval of all user fee drugs.
- 17.5 months was the median time for the review and approval of new drugs being marketed in the United States for the first time—down from 23 months in 1993.
- 19 months was the median time for the review and approval of all new drugs approved in 1994—21 percent less time than in 1993.
- 12.2 months was the median time for the review and approval of vaccines and other biological products—almost 50 percent less time than in 1993.

In areas not covered by user fees, the agency is also reducing review and approval times:

- 24 months was the median time for the review and approval of generic drugs—26 percent less time than in 1993.
- The backlog of medical device premarket notifications—510(k)'s—has been reduced by almost 80 percent—from 1,824 in January 1994 to 371 in January 1995.
- 98.5 days was the median time for the review of 510(k) devices as of January 1995, down from a median of 160.5 days as of January 1994. (The slowest 5 percent still take more than 500 days.)

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BC-CLINTON-SMOKING-HNS
CLINTON AND STATE OFFICIALS VOW CRACKDOWN ON TEEN TOBACCO USE
(For use by New York Times News Service clients.)
By STEWART M. POWELL
c.1996 Hearst Newspapers

WASHINGTON - President Clinton and a bipartisan group of state attorneys general vowed Monday to crack down on tobacco sales to minors to shatter the illusion that "glamour and grit' lie in packs of cigarettes.

But the cooperative spirit of a non-partisan summit between the president and 40 attorneys general quickly gave way to election-year politics.

South Carolina Attorney General Charles M. Condon, a Republican serving as head of the state presidential campaign of Sen. Bob Dole, R-Kan., said after the White House meeting that he had personally questioned Clinton for spending time on what Condon said was a secondary issue.

"The president of the United States is using his good office to talk about what? Tobacco use," Condon told reporters as he left the White House meeting. "This is bizarre, my friends."

City streets four blocks from the White House are "not safe to walk" and the Clinton administration is "losing the war on drugs," Condon said, adding: "I think these are the issues that the average American is concerned about. The idea of emphasizing tobacco use I find very, very bizarre."

South Carolina is the nation's fourth largest producer of tobacco, with the cash crop worth $172 million and 17,218 jobs tied to the industry, according to the Tobacco Institute. The port of Charleston, S.C., is the fourth busiest leaf export facility in the nation, generating another $117 million for the South Carolina economy.

Condon said that Clinton's emphasis on curbing minors' tobacco use stemmed from a political calculation.

"It's obviously an issue I think that his pollsters have told him will help him with the middle 20 percent in this country so he's emphasizing it today," said Condon, elected in 1994 as the

health of Americans. But in terms of issues to emphasize, the president of the United States should emphasize making America safe once again."

White House officials had no immediate comment.

Rhode Island Attorney General Jeffrey B. Pine, also a Republican, appealed for a non-partisan approach.

School violence, guns, crimes in the street, domestic violence and youths' illegal access to tobacco "cross party lines" to afflict "rich and poor, black and white, Republican and Democrat," Pine declared. "That's where our focus should be as attorneys general and... I think it would serve others well to follow our lead, frankly."

New Mexico Attorney General Tom Udall, a Democrat serving as president of the National Association of Attorneys General, said Clinton was "appealing to us as Democrats and Republicans to help assist him in his efforts," adding: "This is not a partisan issue."

Clinton urged the law enforcement officials to enforce existing regulations restricting the sale and distribution of cigarettes and chewing tobacco to minors - or risk a reduction of federal block grants for substance abuse and treatment.

The linkage dates from a provision of the Public Health Service Act of 1992 named for the late Rep. Mike Synar, D-Okla., an anti-smoking crusader.

Clinton, in remarks to the law enforcement officials, conceded that it will be an uphill battle to persuade teenagers to avoid the use of tobacco.

"No matter how hard we work... I'm convinced that it won't be enough," Clinton warned. "Young people are barraged constantly by messages that glamour and grit can be found in a package of cigarettes."

(STORY CAN END HERE -- OPTIONAL MATERIAL FOLLOWS)

Tom Lauria, a spokesman for the Tobacco Institute, the cigarette manufacturers' lobbying organization in Washington, D.C., said the tobacco industry favors efforts to "police the sales counter better to keep cigarettes out of the hands of kids."

But Lauria said cigarette manufacturers continue to oppose Clinton's effort to have the Food and Drug Administration (FDA) regulate nicotine in tobacco - a move that he said could claim 92,000 jobs nationwide.

Lauria also voiced opposition to Clinton's proposed restrictions on tobacco advertising, saying: "We do not believe that by censoring advertising we can effectively address youth smoking."

Clinton has taken a hard line against tobacco use by minors, ordering the FDA last August to regulate nicotine as a drug. Clinton offered to ease the offensive if Congress and the tobacco industry adopted 16 measures to impede tobacco companies' ability to reach minors.

The FDA is studying public comments on the proposal and is expected to issue a final rule later this year.

Clinton proposed measures that included proof of age to purchase tobacco products, bans on 400,000 unattended cigarette vending machines and prohibitions on color advertising for tobacco products in publications aimed at the young, outdoor tobacco advertising within 1,000 feet of schools or playgrounds, giveaways with tobacco company logos and tobacco company sponsorship of sporting events.

Some 3.1 million American teenagers smoke an estimated 5½ million packs of cigarettes each year. An estimated 1.1 million teenagers join the ranks of the nation's 40 million regular smokers each year.

Federal authorities estimate that smoking trims between 12 and

FDA
TALK PAPER

FOOD AND DRUG ADMINISTRATION
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T95-57
Oct. 19, 1995

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Fiscal Year 1995 Medical Devices Update

Faster reviews of most medical devices, more and speedier approvals for clinical studies of medical devices, and the near elimination of a backlog of devices awaiting review marked the fiscal year 1995 (FY 95) performance of the Food and Drug Administration's Center for Devices and Radiological Health (CDRH).

The CDRH achievements continued a trend begun two years ago with the introduction of several management initiatives, including an expedited review process for life-saving devices and an abbreviated review process for low-risk devices.

The most striking acceleration of CDRH processes last year was achieved in the category of so-called 510(k)s. These devices, which are identified by the manufacturer as similar to already existing products, include more than 90 percent of medical devices marketed in the United States.

The average review time for 510(k)s was reduced by more than 24 percent, from 182 days in FY 94 to 138 days in FY 95. It is

-More-

important to note, moreover, that one half of these devices were reviewed in 91 days or less.

The backlog of 510(k)s under review for more than 90 days was reduced to nine from 500 in October 1994. The elimination of these overdue applications will enable CDRH to start reviewing new 510(k) submissions soon after they come in, without relegating them to a protracted queue.

The average review time for premarket applications (PMAs) for new uses and new types of devices was reduced from 21.5 months in FY 94 to 20 months in FY 95.

The 27 PMAs approved last year included the use of a catheter system through which electric current destroys heart cells causing abnormally fast heart beats, and a mechanical blood vessel support inserted by a catheter to allow bloodflow to bypass a diseased liver, thus possibly avoiding major surgery.

Other approved devices regarded as a unique advance in diagnosis or treatment technology are lasers for smoothing corneas for some types of eye disease; a new way to use ultrasound to help broken bones heal faster; and a computerized pattern recognition device designed to improve quality control of PAP smear readings.

By the end of last fiscal year, CDRH also cut by half the number of overdue PMA supplements -- applications for

modifications of PMA devices -- despite a 34 percent increase in this type of submission over FY 94.

The proportion of Investigational Device Exemptions (IDEs) -- applications for proposed clinical studies of new devices -- approved within 30 days of receipt increased from 30 percent in FY 94 to 65 percent in the second half of FY 95. In addition to speedier processing of IDEs, FDA also cooperated in the development of an important new regulation that will provide Medicare coverage for patients in most device clinical trials.

In the coming year, the Center will focus its efforts on further reducing the review time for PMAs and PMA supplements while maintaining its performance on 510(k)s and IDEs.

###

- Scale up and Post Approval Changes

FDA
Center for Drug Evaluation and Research
Comments on GMP in HR 3199

There are actually three tiers of manufacturing changes, none of which change the qualitative or quantitative formulation or specifications. However, each tier represents a different risk for adversely affecting the safety, purity, potency or effectiveness of the final product and, therefore, requires different reporting requirements.

A qualitative change in formulation is a change in the specific materials used in the final product (e.g., replacement of one material for another, addition of a new material, deletion of a material).

A quantitative change in formulation is a change in how much of a particular material is used. There are no changes in the specific materials, only in their amounts.

Tier 1: "minimal, if any, potential to have an adverse effect..."

Example 1: Change in Batch Size

Imagine a tablet formulation in which a drug is mixed with a lubricant to make a powder that smoothly flows into a tablet machine to punch out tablets.

In a small batch, for example to make 100,000 tablets, the drug is to be mixed in a uniform way with the lubricant in a large mixing bowl. Let's say the lubricant is magnesium stearate. The powder can be mixed up without a lot of effort and it flows smoothly into the tablet machine. As a result, the tablets that are punched out are all the same and they dissolve quickly.

Now, let's say a company scales up or increases the batch size 20-fold to make enough powder to punch out 2 million tablets. Well, to mix together this much drug and this much lubricant, the size of the mixing bowl must be increased and the force, called shear force, to mix the ingredients up must be increased also. But, by scaling up 20-fold, the forces needed to mix the ingredients also cause the magnesium stearate powder to change. The changes which occur in the crystals of magnesium stearate are like a deck of cards in which the increasing mixing force causes the cards, one by one, to be sheared off. The sheared crystals then coat the drug crystals in a waterproof jacket. This prevents the tablets that are made from dissolving quickly. As a result, the drug may not be absorbed and there may be problems in its effectiveness.

For this reason, SUPAC-IR lets a firm scale-up their batch sizes only up to 10-fold, and allows that to be reported in an annual report. The limit of ten-fold increases minimize the chances that the magnesium crystals will waterproof the drug crystals.

Example 2:

A firm manufactures an approved product at a specific amount (scale). The firm wishes to "scale-up" the manufacturing of this product to manufacture a larger amount of the drug in one production cycle. A certain amount of scale-up can reasonably be performed without affecting the final formulation of the product. The Center considers scaling up 10-fold to be a minimal change, which must be reported in an annual report, but not pre-approved.

Tier 2: "moderate (possible, but not likely) potential to have an adverse effect..."

Example:

A firm manufactures 100,000 birth control pills in a single batch. They wish to scale-up production to make 3,000,000 birth control pills in a single batch. This has the potential to had an adverse effect on the quality of the final product, if appropriate process adjustments are not made. An analogy can be made to baking a cake, the recipe which, for example, can often be doubled without affecting the resulting consistency or flavor. If, however, the cake recipe is multiplied 20 times, without processing equipment adjustments, clumping of ingredients may occur resulting in a different blend of ingredients than originally intended. While this scale-up may make no important difference in the context of cake-baking, in drug production, the amount of active ingredient(s) is extremely important. For example, for birth control pills, the amount of drug present in the final product determines the effectiveness of the birth control pill. The U.S.P. specifications require testing of only 10-30 pills out of a batch of 3 million. Therefore, some sub-potent pills may be distributed from batches that meet U.S.P. specifications.

Tier 3: "substantial (possible, and likely) potential to have an adverse effect..."

Example:

In the manufacturing of an approved product, the active ingredient is dissolved in a solvent. The solvent/active ingredient solution is then sprayed onto an inactive ingredient (for example, starch). The entire mixture is then heated so that the solvent is dissolved. The specifications for testing the quality of the final product are designed to detect any residue which might be left from the solvent but the solvent is not part of the formulation because it is not supposed to be in the finished product. The manufacturer changes the process to use a different solvent to dissolve the active ingredient. Again, the solvent is dissolved through a heating process, again, possibly leaving a residue. However, the specifications for testing of the final product are not designed to detect residues left by the new solvent, resulting in potential contamination. Although not a change to the formulation of the product and not detectable by the specifications, this manufacturing change could significantly impact the safety of the final product because some solvents are carcinogenic or otherwise unsafe. Such a

change would require submission of a manufacturing supplement to the FDA for approval prior to implementation. The FDA would review the proposed change to ensure the continued safety of the final product.

p. 93 Med Device Modernization / p. 16 ... Sec 702(d) improved but still a two-step problem for FDA

3/21/96

FDA REFORM – KASSEBAUM BILL
SERIOUS CONCERNS ABOUT S. 1477 AND POSSIBLE COMPROMISE POSITIONS

Device modifications. Section 702(d) would eliminate FDA's role in assuring that changes made to a product do not adversely affect its safety and effectiveness. Under the bill, unless the manufacturer's own data shows the safety and effectiveness were to diminish, FDA could not require data on the modified product. The provision raises serious safety concerns.

- shall not require add'l 510(k) if modification ... can be shown to not adversely affect the safety or effectiveness of the device.

> **Compromise language could ensure that FDA is not prevented from seeking a 510(k) when a change or modification could affect the safety or effectiveness of the device -- regardless of whether the effect is adverse.**

- change validated in accordance w/ 520 f good manufacturing practices;
- data maintained and made available to Secty upon request.

Substantial equivalence determinations. Section 702(c) would recognize any use "included within a general use for a predicate device" as an approved use for 510(k) devices. This would allow a device originally marketed for one clinical indication to later be marketed for other indications, with only the submission of an abbreviated application (510(k)) that would not document the product's effectiveness for the new indication. The provision's effect is to virtually eliminate approval of devices for specific uses and thus, eliminate the requirement to show that these uses are safe and effective.

> **Compromise language could allow a new use of a device that is substantially similar to the use of the predicate device to be deemed a legally marketed use of the predicate device for purposes of section 510(k) premarket notifications. Such language would have to be drafted in a way that would not permit devices with significantly different uses to be marketed without first submitting safety and efficacy data.** current law.

702(a) Automatic exemption of all class I devices. Section 702(a) exempts all class I devices from premarket notification. FDA has already exempted 572 class I devices. Many of the 216 devices that FDA has not exempted, were not exempted for public health reasons.

> **Compromise language could permit FDA to not exempt certain class I devices that have serious public health concerns. Alternatively, compromise language could simplify and expedite reclassification of the most problematic class I device into Class II.**

The Device Approval Standard. Section 703 would require the agency to accept retrospective or historical clinical data as a control or for determining the effectiveness of a device if sufficient valid data are available and the effects of the device are clearly defined and well understood. The provision indicates a preference for a lower quality of evidence.

Compromise language could set forth the concept that retrospective or historical clinical data are acceptable if they are sufficient to demonstrate an assurance of effectiveness and that FDA can require concurrent clinical trials when the effects of the device are not clearly defined or well understood, when the retrospective or historical clinical data do not meet the statutes standards, or when there is a compelling health reason.

Device Performance Standards. Section 708 requires FDA to recognize performance standards of certain standard setting organizations.

The concept of greater regulatory use of consensus standards is supportable. However, FDA should have the authority to decertify any standard setting organization and to decide which standards it will recognize. FDA also should have authority to decide whether it is appropriate for companies to self-certify compliance with recognized standards.

Sound medical practice. Section 407 would establish a procedure for approving new uses of previously approved drugs and devices based on sound medical practice (i.e., a use that has existed for five years, is "common" among experienced clinicians, and is reasonably based on experience and other confirmatory evidence). This provision, which would create a standard for permitting new uses that completely bypasses the approval process and could result in marketing for unsafe or ineffective uses, is not acceptable.

As an alternative to this provision, legislative concepts designed to improve FDA's performance in reviewing and approving efficacy supplements could be adopted. The concepts would require FDA:

(1) to have performance goals for efficacy supplements;

(2) to create a small office that would be responsible for working with companies and the centers on expediting efficacy supplements, working to identify off label uses/studies that might be the basis for efficacy supplements, and working with outside scientific experts to identify new indications that might be studied; and

(3) to issue guidance to industry that reflects the presumption that the safety data required for efficacy supplements is often not as extensive as that required for NDAs and that if the new indication is related to an approved indication, developing the protocol should be easier.

The concepts further suggest that FDA could be required to report back to Congress after a reasonable period on the success of these efforts.

Off-label promotion. Section 407 would allow companies to distribute journal articles and other types of information (such as textbooks, continuing medical education materials, etc.) to promote unapproved uses. This provision allows manufacturers to promote uses that have not been proven safe and effective. Moreover, it reduces the incentive for companies to do the scientific research and have the new uses reviewed by FDA (in fact, there would be a disincentive because FDA might determine that the new use is not supported by the evidence).

A proposed compromise would be to tie the distribution of articles to the submission of efficacy supplements. Under this approach, a manufacturer would be permitted to disseminate journal articles etc. (as set forth in section 407) 90 days after an efficacy supplement has been submitted to FDA for review. FDA should be allowed to disclose information in its possession about the safety or efficacy of a product regardless of the source. This compromise approach addresses FDA's concern that the safety and efficacy of these off label uses will never be known and gives FDA the opportunity to prevent the dissemination of articles, etc. if such dissemination raises public health concerns. There also could be a provision directing an IOM study on the issue of whether there are specific areas where the compromise position does not go far enough.

Shortened Review Times Without Additional Resources. Without providing new resources, S.1477 would require FDA to meet extremely short deadlines (e.g., 4-6 months for drugs). Moreover, it imposes a substantial number of burdensome requirements (e.g., FDA must meet with sponsors at defined time periods and prior to such meeting must provide the sponsor written information regarding application deficiencies and steps towards approval (see sections 404 and 707)). The requirements would have the effect of further shortening the time periods (e.g., in order to provide the written information FDA would have to substantially complete its review of the application prior to the meetings). As a result of the shortened timeframes, reviewers may have to approve drugs, devices, or food additives based on less information, with fewer analyses and much greater uncertainty about the products' safety and efficacy. The agency also may have to strip away all work other than product approval reviews. This will adversely impact other programs (e.g., blood safety, product tampering, mammography).

As to timeframes, a compromise should include the Prescription Drug Use Fee Act (PDUFA) times for drugs and biologics. Anything else undercuts the progress FDA has made under PDUFA. Other statutory timeframes should be changed so that they are realistic. A compromise to sections 404 and 707 could require one pre-submission meeting, one post submission meeting (to be held at a time that is meaningful) and consultation throughout the time period for application review. The compromise language should also make the requirements for FDA's "deficiency" letters more reasonable -- e.g., letters would include deficiencies identified to date (thus not cutting the short deadlines even further).

Third Party Reviews Section 403(a) permits FDA to contract for outside review to evaluate parts or all of applications or petitions. Section 403(b) appears to require FDA to contract out all applications, notifications, and conditions if certain (quite loose) conditions are met.

A proposed compromise would be to add language to ensure that the section 403(b) language is discretionary. Alternatively, the language could be revised to limit and tighten the conditions under which contracting out would be required.

The Drug Approval Standard. Section 602 states that substantial evidence may consist of data from one well-controlled clinical investigation and confirmatory evidence. This may lower the effectiveness requirement from two adequate and well-controlled studies to, at most, one. Although FDA often accepts data from one adequate and well-controlled trial, this should not be the standard. Section 410 provides that for efficacy supplements, the data may consist entirely of information published in medical literature if the proposed condition of use relates to treatment of a life-threatening disease. This suggests that information other than from adequate and well-controlled studies would be acceptable. Moreover, although FDA has, on occasion, relied on reports of adequate and well-controlled studies published in journal articles to approve an efficacy supplement, this is not and should not be the general rule.

Re: section 602: A compromise position could include minor changes to the provision that would (1) add the phrase "adequate and" before the term "well-controlled" (to make the term consistent with its prior use in the statute) and (2) add the phrase "if appropriate" to ensure that while FDA may accept one trial, one trial is not the presumption.

Re: section 410: The concerns regarding efficacy supplements that this provision is trying to address are dealt with in the concepts being proposed as a compromise to the sound medical practice provision. If it is felt, however, that this provision needs to stay in the bill, it should be clarified to provide that the information in the literature is about one or more adequate and well controlled studies.

Limits FDA's Review of Safety and Efficacy. Section 408 provides that the review of an application cannot include the evaluation of any use not included in the labeling. Section 408 appears to prohibit FDA from including, in the labeling, warnings concerning indications for which a product is known not to be effective.

A proposed compromise would be to change section 408 so that it would not permit FDA to deny an application based on any potential use not included in the labeling. This change would permit FDA, where appropriate, to include in the labeling a warning that the product is not effective for a certain use.

Animal Drug Approval Standard. Section 802(a) amends the Act to redefine the "substantial evidence" criteria that currently must be met to establish effectiveness. The requirement for adequate and well controlled studies would be changed to "scientifically sound studies." Section 802 also replaces the requirement that the studies fairly and reasonably show effectiveness to a requirement that there is a reasonable assurance of effectiveness.

A compromise position would be to revise the current standard to clarify that one study may be enough to establish effectiveness and that field investigations will only be required where appropriate.

Pediatric Studies Marketing Exclusivity. Section 411 provides a 6 month marketing exclusivity for approved applications with pediatric studies submitted by an applicant.

It is important to provide incentives for conducting pediatric studies. However, there are concerns about whether the provision is sufficiently tailored so that it applies to important new uses and as to whether the incentive is too generous in light of the fact that these trials often are very inexpensive.

Statutory Hammers. The bill includes a number of statutory hammers. Section 404 requires FDA to contract for outside review if in any fiscal year it fails to meet the statutory time frame for 95% of the applications in a particular category. It also requires FDA to give special priority to applications, notifications, or petitions for products that have been approved in the EU or UK if by July 1, 1998, FDA fails to meet a time period for action on an application, notification, or petition for approval or clearance of a new drug, biologic, device, or animal drug that is a significant improvement over existing products or of a food additive that has the potential to make foods more wholesome and contribute to a healthier diet.

The understanding is that these hammer provisions will be deleted from the bill. If left in the bill, however, they would present serious concerns in that they undermine the statute's primary objective that FDA find that drugs and devices be proven safe and effective and that food additives be proven safe before they can be marketed.

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There are a number of additional technical and substantive changes throughout the bill that are important, but in general, are not likely to be controversial.

NDA New Drug Application

PDUFA Prescription Drug User Fee Act of 1992

"Treatment IND"
before approval but after clinical trials

Medical Device Expanded Pilot Review Program (RSEQ II)
- $24 M shortfall; 200 staff per mos.
- manufacturer demonstrates device is "substantially equivalent" to device already on the market
- FDA promises 10 categories of devices; 100-400 applications annually will be reviewed by outside reviewers accredited by FDA
- manufacturer funded

Devices 3 classes,
2 processes (1) 510(k) process (premarket notification) Avg.
- FDA must determine whether a device is "substantially equivalent" to a legally marketed device.
- If "subs equiv" the manufacturer may market and comply with good manufacturing practices (GMP) requirements

(2) Pre market approval process (PMA)

Drugs
- Tested first in animals then in humans
- data reviewed by FDA scientists in a New Drug Application (NDA)

Biologics - vaccines, blood products, biotech drugs
- before marketing, sponsor must submit for FDA approval a Product License Application which presents safety and efficacy data, and the facility must submit an Establishment License Application showing safe manuf.
- approves changes, e.g. to ingredients, by reviewing a "supplement" to original application

GAO study

FDA review and approval times were faster than in U.K. Met PDUFA deadlines

FDA Study

"Timely Access to New Drugs in the 1990's An International Comparison"

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

05-Apr-1996 08:10am

TO: Sally Katzen

FROM: Jonathan Winer
Office of Mgmt and Budget, OIRA

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SUBJECT: FDA ANNOUNCES PILOT INITIATIVES TO IMPROVE MEDICAL DEVICE RE

FDA ANNOUNCES PILOT INITIATIVES TO IMPROVE MEDICAL DEVICE REVIEW PROCESS
The Food and Drug Administration April 3 announced plans to implement initiatives designed to streamline regulation of medical devices (61 FR 14786, 14789, 14922).
One initiative is a pilot program to assess whether reviews by third-party organizations will improve the efficiency of FDA's medical device review process and conserve resources. The pilot program will run for two years, beginning Aug. 1, according to the Federal Register notice.
Besides studying whether third-party organizations can safely and efficiently complete reviews of new devices, FDA will evaluate whether conflict-of-interest rules can be maintained in a third-party review process. The pilot project will be limited to reviews of low- and moderate-risk medical devices--electronic thermometers and surgical gloves, for example--for which no clinical safety and effectiveness data is required. Manufacturers of these products submit premarket notifications, also known as 510 (k)s, in order to show that their products are substantially equivalent in safety and efficacy to existing approved products. HHS estimated that FDA receives approximately 1,500 510(k)s each year.
The third-party pilot program will operate on a voluntary basis--manufacturers can request third-party review or leave the process to FDA. According to HHS, companies opting for third-party review will be able to choose from among the FDA-certified companies to review 510(k) applications under the pilot program.
The third-party company will review the product, submitting the marketing application, the results of its review, and its recommendations to FDA for assessment. FDA will make a decision on the application within 30 days. This would eliminate the first phase of FDA's traditional review process, HHS said.
Proposals Test Public Health Protections
FDA has been sharply criticized by members of Congress and industry groups for the lengthiness of its medical device review process and provisions addressing the issue appear in FDA reform legislation introduced in both the House and Senate (S 1477, HR 3201).
In a statement issued by the Department of Health and Human Services, FDA Commissioner David A. Kessler commented, ``The test for any reform is whether it protects the public health. Our proposal will test whether this speeds up

the process and if the integrity of the review can be maintained.''
HHS Secretary Donna E. Shalala described the initiatives as ``another example of FDA's innovative regulatory strategy for the 21st century.''
``It explores how the agency can best review low-hazard products while enabling the agency to target its resources where risks are high,'' she added.
These initiatives also respond to goals set out in the National Performance Review's Reinventing Government effort headed by Vice President Gore, which aims to improve the way the federal government works while reducing costs.
Comments on the FDA's proposal to implement a third-party review test program, Docket No. 96N-0025, should be submitted by June 3 to the Dockets Management Branch (HFA-305), FDA, 12420 Parklawn Dr., Room 1-23, Rockville, Md. 20857.
Companies interested in applying for recognition as a third-party reviewer should send applications to the Division of Small Manufacturers Assistance (HFZ-220), Attn: Third-Party Recognition, Center for Devices and Radiological Health, FDA, 1350 Piccard Dr., Rockville, Md. 20850.
To help prospective third-party reviewers prepare their applications, FDA will hold an informational briefing April 15. Registration forms for the briefing are available by fax from CDRH's Facts on Demand, (800) 899-0381 or (301) 827-0111. The registration forms are found on FDA's home page, http://www.fda.gov, under the Medical Devices and Radiological Health category, Third Party Review option.
Manufacturers who want to submit 510(k)s for review by third party firms should send their applications to the Document Mail Center (HFZ-401), Attn: Third Party Review, CDRH, FDA, 9200 Corporate Blvd., Rockville, Md. 20850.
Inspection Procedure Changes
FDA's second initiative, which was developed in conjunction with a task force of medical device industry representatives, would apply to manufacturers having a good history of compliance with FDA regulations.
The initiative proposes changing FDA's inspection process to:
o Give manufacturers advance notification of inspections, rather than conducting unannounced inspections;
o Allow firms to note on official inspection reports any previous violative findings that were corrected immediately; and
o Require FDA to issue a letter to companies informing them they successfully passed the inspection.
The inspection initiative will be implemented immediately and last throughout 1996. Although FDA initially is limiting the pilot inspection program to medical device companies, it will be expanded to other product areas, if it is found to be effective after evaluation.
According to the Federal Register, medical device inspections currently done under contract by California, Colorado, and Texas will not be included in the pilot program.
Comments on the proposed inspection pilot program, Docket No. 96N-0086, should be submitted to the Dockets Management Branch at the address noted above.
FDA also is proposing to streamline requirements that medical device manufacturers must meet under the National Environmental Policy Act. According to HHS, the proposal will apply to all FDA-regulated products and is designed to reduce the number of environmental assessments industries must prepare and submit to FDA. This change could result in yearly savings of approximately $15 million for medical device manufacturers and save FDA $1 million as well, HHS said.
PMA Approval Process Suspensions

Meanwhile, under a final rule scheduled to appear in the April 5 Federal Register, FDA has established procedures for temporarily suspending approval of a premarket approval application (PMA) or PMA supplement.

FDA received new authority to halt temporarily the PMA process from the Safe Medical Devices Act of 1990 (PL 101-629). Under SMDA, FDA can take action after an informal hearing if ``there is reasonable probability that continued distribution of a device would cause serious, adverse health consequences or death.'' After temporarily suspending the PMA, FDA has 60 days to permanently withdraw the approval of the PMA or PMA supplement.

The final rule becomes effective 30 days after publication of the notice in the Federal Register. For more information, contact Lisa A. Rooney, CDRH (HFZ-84), FDA, 2094 Gaither Rd., Rockville, Md. 20850; (301) 594-4765, extension 164.

Hazardous Materials

FDA Chief Warns Against Some Parts of Overhaul Legislation

By John Schwartz
Washington Post Staff Writer

Congressional efforts to reform the Food and Drug Administration geared up again yesterday, as a Senate committee considered a bill that would force the agency to approve new drugs and devices faster.

But FDA Commissioner David A. Kessler told members of the Senate Labor and Human Resources Committee that the agency he has headed since 1990 was already doing a good job of reforming itself. He suggested that some of the provisions of the bill, sponsored by committee Chairman Sen. Nancy Landon Kassebaum (R-Kan.), could compromise public health.

Kessler said the agency's harshest critics threaten, "intentionally or not, to undermine the real progress that has been made."

The Kassebaum bill would require the FDA to act within four months on applications for new drugs to treat life-threatening diseases or other disorders with no approved treatment. The agency would be required to act within six months on applications for all other FDA-regulated products. The bill contains a "hammer" provision that would force the FDA to meet the deadlines by 1998 or cede parts of the approval process to private companies.

Federal law already requires that the agency act on applications within six months, but the FDA has historically taken much longer. A 1992 law created a user-fee system for drug companies and set deadlines for the agency to shorten its review times. Kessler said the FDA was three years ahead of schedule in meeting those goals, and that most new drug reviews now take 12 months. He cited statistics showing that his agency is currently approving new drugs for AIDS and other life-threatening diseases in less time than the Kassebaum bill would require, adding that many new drugs reach Americans before they are approved in other nations.

But Kessler said there are limits to how fast the FDA can act. "One day we are going to make a mistake," he said, predicting that when something goes tragically wrong with a rapidly approved drug, he would be back before a congressional committee to answer the question, "Where was FDA?"

Sen. Dan Coats (R-Ind.) accused the agency of having "a Ralph Nader mentality," mistrusting the companies it regulates and refusing to tolerate the slightest risk. Despite what he called Kessler's "fancy talk" about improvement in drug review times, Coats said, "We are faced with an agency . . . way behind the times."

Yesterday's session was the first of several scheduled hearings on FDA reform in both Houses. Today, the Labor and Human Resources Committee will take up a portion of the Kassebaum bill that would allow companies to provide doctors with the results of scientific studies of unapproved uses of approved drugs—so-called "off-label" uses. The FDA currently outlaws such activities, saying that companies must prove to the agency that their products are effective for such uses before advertising them.

In an interview yesterday, Sen. Connie Mack (R-Fla.), sponsor of the provision, said the agency's attitude "implies that peer-reviewed data is inadequate unless it receives Washington's approval. I find that troubling."

Next week the House will hold hearings on its FDA reform bills. Instead of one umbrella bill, House members are expected to introduce as many as three bills, including one to speed the approval process for the medical device industry.

The new crop of proposals come after a significant loss of momentum for the FDA reform effort in Congress. Kenneth Reid, who publishes three FDA-related newsletters through his Washington Information Source Co., predicted that the combination of continuing wrangling over the budget and the upcoming election "is going to keep FDA reform from really going anywhere" this year.

But Alan H. Magazine, president of the Health Industry Manufacturers Association, said that Sen. Robert J. Dole (R-Kan.) told him last week in Manchester, N.H., that if Kassebaum could get her bill voted out of her committee in March, he would find floor time for it in April.

Magazine called the Kassebaum bill "a good first step," but added, "We want it to go further."

Yesterday's hearing was replete with the eye-glazing minutiae that accompanies any discussion of the FDA's inner workings. There were flashes of humor, however. After Kessler's statement, Kassebaum noted that, uncharacteristically, the commissioner had not used up his allotted 10 minutes.

"We're learning how to accelerate the process," Kessler told her.

DRAFT

- This section, as drafted would require FDA to provide an opportunity for affected individuals to participate in the development of most guidance before it is implemented. Under present and expected future budget constraints, FDA would have to choose between: (1) shifting resources from consumer protection programs and product review to developing policy under the procedures required in this section or (2) not expending resources to develop policy including that designed to facilitate marketing of new products. FDA anticipates, and believes that industry would agree, that not all guidance warrants the same amount of public input before implementation. This could delay policy decisions.

Sec. 107 Scientific Review Groups

- The provision restricts FDA flexibility in its use of advisory committees (e.g., requires (rather than recommends) that chair have X amount of experience).

- Section 904(c)(1) (Scope) permits advisory committees to set their own agendas. However, FDA must have the ability to put specific issues of concern before advisory committees.

- Section 904(c)(2) (Nonvoting Members) requires advisory committees to include non-voting industry and public representatives. Non-voting members should not attend closed meetings and should not receive confidential information.

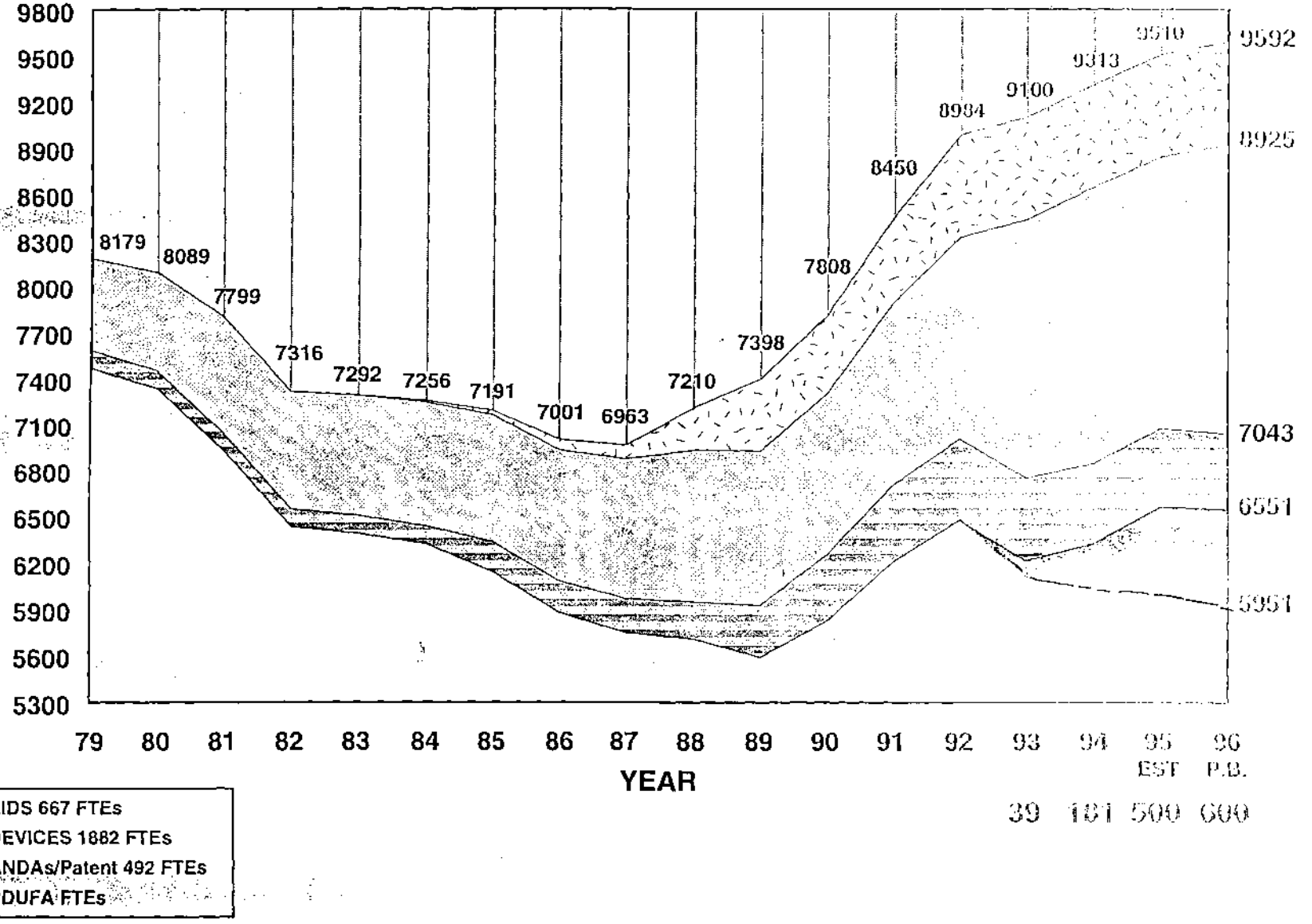
- Section 904(d)(1) requires FDA to provide advisory committee materials to the affected sponsor. That material often consists of other sponsor information, which is confidential. Therefore, FDA would no longer be able to give that information to an advisory committee.

- Section 904(e) (FDA Actions) requires FDA to make a final determination within 60 days of an advisory committee recommendation. This assumes that all matters presented to advisory committees are susceptible to "final" determination. This is not always true. A better approach might be to require an update letter from the relevant FDA division within 60 days of the advisory committee meeting.

Sec. 108. Appeals within the FDA *

- Section 107 requires FDA to establish, by regulation, an appeals system. It

FDA Staffing Including New Workloads



Report: Too Early to Tell if U.S. Should Reform FDA in Europe's Mold

WASHINGTON (AP) - Though critics are clamoring for the United States to copy the way Europe approves new medical devices, Congress should wait for more proof that Americans would be helped, a government report concludes.

The General Accounting Office, Congress' investigation arm, compared the new European Union medical system with the U.S. Food and Drug Administration.

"In contrast to FDA's almost 20 years of experience ... the EU system is quite new," so there are questions about whether it works, said the GAO report released Friday.

The FDA is under fire because it takes about 20 months to decide whether high-risk, but often life-saving, medical devices are safe and effective.

Manufacturers want Congress to speed their devices to market by copying Europe, where private companies decide when everything from eye lasers to heart valves are safe enough to sell. European governments certify the companies are competent, and device makers then pay the companies for the review.

Consumer advocates say device makers will shop around for the easiest review and criticize that Europe, unlike the FDA, doesn't require that devices work well, just that they're safe.

As Congress debates what to do, Sen. Nancy Kassebaum, R-Kan., asked the GAO to compare the systems.

It concluded the European system is too new to tell if it's significantly faster than FDA and questioned whether it is as rigorous.

The Health Industry Manufacturers Associated criticized the GAO, saying it ignored a recent European study that found high-risk medical devices were approved in just eight months.

And a letter from the European Commission, the EU's policy-making body, to the GAO argued that for the riskiest devices, Europe and the FDA are equally strict.

But the GAO said most European devices are approved when the review firm decides the company has enough quality control to guarantee they are manufactured properly. However, Europe sometimes tests risky devices to see how they work in patients, the report said.

The FDA requires both quality control and evidence that devices work effectively, the GAO said.

The GAO also questioned European conflicts of interest. While the private review firms "carry out a regulatory function ... the manufacturers whose devices they review are also their clients," the GAO wrote.

[FDA]

"(2) INCREASED EFFICIENCY AND EXPERTISE THROUGH CONTRACTS.—The Secretary, acting through the Commissioner, shall use the ~~under the~~ authority granted in paragraph (1) to ~~ensure~~—

"(A) improve the efficiency, timeliness, and quality of the review of applications, petitions, and notifications for the approval or clearance of ~~new drugs, new animal drugs, biological products,~~ devices, and food additives; or

~~"(C) the efficiency, timeliness, and quality of the review of applications and notifications for the approval of new uses for approved new drugs, biological products.~~ devices

"(B) ensure that the agency has the scientific and technical expertise available to the agency necessary to be keep informed of emerging new therapies and technologies posing significant new scientific and technical issues, and for the review of indirect food additive petitions and submissions under subsection 701(k).

The Secretary shall retain full authority to make determinations with respect to the approval or disapproval a product.

OPTIONAL FORM 99 (7-90)

FAX TRANSMITTAL # of pages ▶ 1

To Elizabeth Drye	From
Dept./Agency	Phone #
Fax #	Fax #

NSN 7540-01-317-7368 5099-101 GENERAL SERVICES ADMINISTRATION

22 New York Times Saturday, Apr. 16, 1996

Streamlining the F.D.A., Safely

The Clinton Administration is making it easier for cancer patients to get promising drugs that have not been fully tested. By loosening some of the Food and Drug Administration's rules to accelerate access to experimental drugs, the White House may defuse more sweeping and dangerous reforms under consideration by Congress.

The F.D.A.'s job is to insure that drugs and medical devices are safe and effective and that food additives are risk-free. The agency gives approval only after lengthy clinical trials by the manufacturer. But many companies complain that the F.D.A. is slow to respond, escalating costs. In addition, some groups representing AIDS and cancer patients say that its bureaucracy denies them faster access to promising remedies.

Congress, the companies and the agency are now struggling to get drugs and medical devices to needy patients as quickly as possible without jeopardizing public health or sacrificing the standards of safety and efficacy that give consumers confidence in F.D.A.-approved products.

The Clinton Administration proposes faster approval for cancer-fighting drugs. Previously, the F.D.A. asked for proof that an experimental drug would help a patient's chances for survival or improve that patient's quality of life. Under the new rules, a drug can be approved based on a "partial" positive response, like shrinkage of a tumor. In addition, companies making experimental drugs that have already been approved overseas can seek permission to distribute those drugs to American cancer patients even before the F.D.A. has given final approval. These measures, which need no further approval, will take effect immediately and could apply to about 100 drugs under study.

The new initiatives are welcome but unlikely to appease Congress, which is pressing for more sweeping F.D.A. reform. Last month the Senate Labor and Human Resources Committee approved a bill sponsored by Nancy Kassebaum, Republican of Kansas, that calls on the agency to expedite clinical investigations of new drugs, devices and biological products as well as breakthrough drugs for life-threatening diseases. If the agency fails to review most applications within six months, the product sponsors could force it to contract with outside experts to complete the process.

Similarly, a bill being pushed on behalf of the House G.O.P. by James Greenwood of Pennsylvania sets tight approval deadlines and would turn over some F.D.A. review authority to third parties.

The F.D.A. would retain a supervisory role. But the outside experts and "third parties" envisioned in both the Senate and House bills could, under the guise of regulatory reform, lead to the privatization of many of the F.D.A.'s functions and undermine its role as an independent government protector of public health.

The drive to reform the F.D.A. comes at a time when the agency has been improving its performance. In 1994, 96 percent of new drug applications were approved within the 12 months allotted under current law, and the agency has been streamlining many of its internal procedures. Important life-enhancing drugs and medical devices should obviously get to consumers as quickly as possible. That is what the Administration's new cancer drug initiative aims to do. But safety and effectiveness should not be sacrificed for efficiency. At the moment, the Administration seems more mindful of that than Congress.

into account the susceptibility of infants and children, a negligible or insignificant risk;".

On page 114, between lines 9 and 10, insert the following:

SEC. 902. FOOD AND COLOR ADDITIVES.

(a) FOOD ADDITIVE SAFETY.—Section 409(c)(3)(A) (21 U.S.C. 348(c)(3)(A)) is amended by striking "as an ingredient of feed for animals" and all that follows through "the living animal; or" and inserting "that presents, taking into account the susceptibility of infants and children, a negligible or insignificant risk; or".

(b) COLOR ADDITIVE SAFETY.—Section 721(b)(5)(B) (21 U.S.C. 379e(b)(5)(B)) is amended by striking "as an ingredient of feed for animals" and all that follows through "derived from the living animal." and inserting the following: "that presents, taking into account the susceptibility of infants and children, a negligible or insignificant risk.".

On page 114, line 10, strike "**SEC. 902.**" and insert "**SEC. 903.**".

2. Third Party Review of Food Additives

Would require FDA to contract with outside organization to review applications for approval of food additives.

This provision has several fatal flaws. First, the net effect of the provisions is to shift the burden to FDA to prove the additive should not be approved; right now, burden is on the manufacturer to prove it should be approved. Second, it precludes the FDA from looking at all relevant information by putting a cut-off date in the review process after which FDA can only consider data if submitted the applicant. Third, the system, which calls for concurrent review by FDA and the third party, with FDA paying the third party, seems inefficient at best and wasteful of scarce resources at worst. Why pay some one else to do the work (with scarce government resources) if FDA has to do it too? An interesting twist on reinventing government.

3. Preemption

Would preempt all state and local requirements relating to foods and cosmetics, with a very narrow exception if regulations are issued.

This is aimed a California labeling law, Proposition 65, and some other state labeling laws that companies do not like. It sweeps way too broadly to preempt in areas that states have filled in because FDA is too slow (Gulf coast seafood warnings) or because the consumers of a particular state want particular information (Kosher labeling (a Massachusetts requirement), freshness labeling, unit pricing). It also may preempt state tort law.

Hold - will work out

AMENDMENT NO 19 Calendar No____

Purpose: To improve the regulation of food and cosmetics.

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

An Amendment to the amendment offered by Senator Kassebaum to S. 1477

To amend the Federal Food, Drug, and Cosmetic Act and Public Health Service Act to impeove 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

AMENDMENTS intended to be proposed by Senator KENNEDY

Section 604 Manufacturing Changes is amended striking page 78 line 9. following "(b) Drug and Biological Product." through page 80 line 12 anc inserting the following:

"(b)(1) Before distributing a product made using a change in the manufacture of the product (including, if the Secretary determines it is appropriate, facilities and personnel) from that established in the approved new drug application, license application, or new animal drug

application, the applicant must validate the effect on the safety, purity, potency, and effectiveness of the product.

"(2) The applicant must report such changes to the Secretary and may distribute products as follows:

"(i) If the change is of a type that the Secretary has determined has substantial potential to have an adverse effect on the safety, purity, potency, or effectiveness of the product, the applicant must submit a supplemental application to the Secretary and receive approval of the supplement before distribution of the product.

"(ii) If the change is of a type that the Secretary has determined has moderate potential to have an adverse effect on the safety, purity, potency, or effectiveness of the product, the applicant must notify the Secretary at least 30 days before distribution of the product. Unless the Secretary notifies the applicant within 30 days not to distribute the product, the applicant may proceed with distribution.

"(iii) If the change is of a type that the Secretary has determined has minimal potential to have an adverse effect on the safety purity, potency, or effectiveness of the product, the applicant must report the change in a annual report. The applicant may distribute the product without prior notification to or approval by the Secretary."

Kennedy - Corrective Amendment to Info. Systems NOT Offered

AMENDMENT NO._____ Calendar No.____

Purpose: To provide access to critical public health information.

IN THE SENATE OF THE UNITED STATE--104th Cong., 2d Sess.

An Amendment to the amendment offered by Mrs. Kassebaum to S. 1477

To amend the Federal Food, Drug, and Cosmetic Act and 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

AMENDMENTS intended to be proposed by Mr. Kennedy

On page 10, line 12 insert after the period: "Notwithstanding any other provision of law, and only to the extent the Secretary determines that dissemination of information regarding the status of clinical investigations and review of applications for product approval or clearance and safety and effectiveness of a product would enhance the public health, summaries of such information shall be made available to the public.

Sections that changed — Pre-mark-up to compare to Mark-up Version

and technology professionals, and the regulated industries, shall publish in the Federal Register quantifiable performance standards for action by the Administration on—

"(i) applications or submissions (including petitions, notifications, or any other similar form of request) for review of a protocol, a product investigation, a product approval, a new use approval, a manufacturing change, a change in labeling, or any other form of regulatory action relating to the review of a product that is a new drug, biological product, new animal drug, device, food additive, or color additive and that is subject to premarket review or approval under this Act; Sec. 103

"(ii) letters, telephone calls, requests for meetings, and the scheduling of requested meetings relating to the applications and submissions described in clause (i); and impossible micromanagement deleted

"(iii) the scheduling of advisory committee meetings, and the action taken following an advisory committee recommenda-

SEC. 705. POSTMARKET SURVEILLANCE.

Section 522 (21 U.S.C. 360l) is amended to read as follows:

"SEC. 522. POSTMARKET SURVEILLANCE.

"(a) IN GENERAL.—The Secretary may require a manufacturer to conduct postmarket surveillance for any device ~~of the manufacturer first introduced or delivered for introduction into interstate commerce after January 1, 1991, that~~ that

"(1) is a permanent implant the failure of which may cause serious, adverse health consequences or death;

"(2) is intended for a use in supporting or sustaining human life; or

"(3) potentially presents a serious risk to human health.

"(b) SURVEILLANCE APPROVAL.—Each manufacturer required to conduct a surveillance of a device under subsection (a) shall, within 30 days of receiving notice from the Secretary that the manufacturer is required under this section to conduct the surveillance, submit for the approval of the Secretary, a protocol for the required surveillance. The Secretary, within 60 days of the date of the receipt of the protocol, shall determine if the principal investigator proposed to be used in the surveillance has sufficient qualifications and experience to conduct the sur-

veillance and if the protocol will result in collection of useful data or other information necessary to protect the public health and to provide safety and effectiveness information for the device. The Secretary may not approve the protocol until the protocol has been reviewed by a qualified scientific and technical review committee established by the Secretary.".

SEC. 706. DEVICE DISTRIBUTOR REPORTING.

Section 519 (21 U.S.C. 360i) is amended—

(1) ~~by striking ", importer, or distributor" each place it appears and inserting "or importer"~~;

~~(2)~~ in subsection (a)—

~~(A) in paragraph (8), by striking ", and" and inserting a period, and~~

~~(B)~~ by striking paragraph (9); and replacing it as follows: (9) shall not impose adverse event reporting requirements on distributors who are not importers.

~~(3) by striking subsection (f).~~

SEC. 707. PREMARKET APPROVAL.

(a) ACTION ON APPLICATION.—Section 515(d) (21 U.S.C. 360e(d)) is amended— (2) in subsection (d) by striking the words "importer, and distributor and "importer or distributor each time they appear and inserting ", or importer"

(1) in paragraph (1)(A), by striking "paragraph (2) of this subsection" each place it appears and inserting "paragraph (4)";

(2) in paragraph (1)(B), by adding at the end thereof the following new clause:

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DOCUMENT NO. AND TYPE	SUBJECT/TITLE	DATE	RESTRICTION
001. contract	re: personal (4 pages)	12/28/1995	Personal Misfile

COLLECTION:
Clinton Presidential Records
Domestic Policy Council
Elizabeth Drye
OA/Box Number: 10452

FOLDER TITLE:
FDA Reform 1996 [1]

2014-0046-S
rc1401

RESTRICTION CODES

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

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

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

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

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