Office of Public Affairs
15-05 Parklawn
HFI-1
301-594-6004 or 301-443-3819 (fax)
301-443-1130 (phone)

TO:

Elizabeth Drye
202-456-7028

FROM:

Tracey Hill

Number of pages (includes cover) 9

Message: REGO-Cancer Drugs

If this is not clear, please call and we will send another fax. Thank you.

FDA
Fact Sheet

Getting Cancer Drugs to Patients

The Food and Drug Administration is committed to providing promising drugs to cancer patients as quickly as possible through a variety of mechanisms.

Timely Marketing Approval

- In 1994 and 1995, 12 new drugs for cancer patients or new uses for existing agents were approved in the United States.
- The average time to review and approve cancer drugs has been 12.4 months between 1990 and 1995. The following is a list of FDA's most recent approvals:

1994	
Taxol	Refractory breast cancer
Navelbine	Advanced non-small-cell lung cancer
1995	
Zinecard	Chemotherapy protectant
Aredia	Bone metastases in multiple myeloma
Casodex	Advanced prostate cancer
Doxil	Kaposi's sarcoma
Vesanoid	Acute promyelocytic leukemia
Ethyol	Chemotherapy protectant
Zoladex	Advanced breast cancer
Photofrin	Esophageal cancer
Arimidex	Advanced breast cancer

Expanded Access Mechanisms

- Through expanded access mechanisms, patients can receive promising agents even before they have been completely studied or approved for marketing.
- Cancer drugs led the way in early, expanded access. In 1970, FDA developed the Group C mechanism, whereby cancer drugs under development could be made available for treatment use. Other drug classes were offered this same provision in 1982.
- Expanded access mechanisms also include Treatment Investigational New Drug protocols (Treatment INDs), as well as other open-label protocols either for small groups of patients or for one patient (referred to by some as "compassionate use" INDs).

More than 20,000 patients with cancer have received treatment under a Treatment IND since 1987.

More than 500 cancer patients, since 1990, have received one of 36 investigational agents to treat more than 50 different malignant conditions through single-patient INDs when enrollment in a formal clinical trial has not been possible or feasible ❑

FDA BACKGROUNDER

U.S. FOOD & DRUG ADMINISTRATION

Cancer Therapies: Accelerating Approval and Expanding Access

The Food and Drug Administration is undertaking four new initiatives to improve patient access to promising new cancer therapies. FDA will:

- shorten approval times for cancer treatments by recognizing that tumor shrinkage is often an early indicator of a treatment's effectiveness
- work with pharmaceutical companies to make promising cancer therapies approved by foreign countries available to cancer patients even before the product is approved in the United States
- improve the therapy review process by ensuring that all FDA cancer-therapy advisory committee meetings include an *ad hoc* member who has personal experience with the illness for which a new product is being considered
- make it easier for investigators to test new uses for cancer therapies already on the market.

Until now, FDA has usually required that a cancer therapy's sponsor demonstrate improvements in survival time or quality of life before a therapy could be approved. Based on accumulating evidence, FDA now believes it is appropriate to approve products that show evidence of tumor shrinkage for patients who have no satisfactory alternative therapy. Companies can more quickly demonstrate tumor regression than improvements in survival time or quality of life and can do so in studies that are relatively easy to carry out. Allowing companies to provide additional evidence of increased survival or improved quality of life associated with that therapy after marketing approval may, in many situations, substantially shorten (sometimes by years) the total time needed for marketing approval.

Cancer patients and their families sometimes believe that they must travel to a foreign country to receive the newest cancer therapies. While this is rarely so, FDA will make it even less likely by actively encouraging companies to submit expanded access protocols in the United States for cancer therapies that have been approved by recognized foreign regulatory authorities.

FDA advisory committees play a critical role in product review. FDA will improve the review provided by its cancer-therapy advisory committees by adding on an *ad hoc* basis patient representatives who have experience with the illness for which a therapy is under consideration.

FDA will reduce the number of investigational new drug applications filed for additional studies of already approved therapies. This change will make it easier for researchers to study new uses of already approved therapies.

FDA is undertaking these initiatives after careful consideration of suggestions and advice offered by patients and their advocates, pharmaceutical industry representatives, and physicians and researchers. FDA will continue to seek the views of these interested parties, as well as those of the agency's advisory committees and the National Cancer Institute. FDA's goal is to significantly improve patient access to promising cancer treatments. FDA recognizes that these initiatives may also apply to therapies for patients with other serious and life-threatening diseases.

HHS NEWS

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

EMBARGOED UNTIL 2:30 P.M., E.S.T
Friday, March 29, 1996

Contact: FDA Press Office
(301)-443-1130

CLINTON ADMINISTRATION ANNOUNCES PLAN TO SPEED DEVELOPMENT AND APPROVAL OF CANCER DRUGS

President Clinton today announced a major initiative to make promising new cancer therapies available sooner to American cancer patients. As part of Vice President Gore's National Performance Review, the Food and Drug Administration's "Reinventing the Regulation of Cancer Drugs" proposes to shorten development and review times for cancer products and to make it easier for many cancer drugs approved elsewhere to be made available to cancer patients in the U.S.

"Under the leadership of President Clinton, FDA is adopting a common sense approach to approving promising new cancer therapies," said Vice President Gore, who has been working on regulatory reform as part of the National Performance Review's effort to make the federal government work better and cost less. "The FDA is eliminating unnecessary and burdensome regulations while still maintaining critical public health protections. The result is safe, new cancer drug therapies that will be available to the American people in record time."

"Cancer is a terrible tragedy for many families in this country. With our actions today, we give them new hope," said HHS Secretary Donna E. Shalala, who joined the President at the White House event. "These measures will bring safe and effective therapies to cancer patients sooner."

"Our experience with accelerated approval, particularly for AIDS, leads us to believe that these initiatives may serve as a powerful stimulus to the development of new drugs to treat cancer," said FDA Commissioner David A. Kessler, M.D.

Joining the President, Vice President and Secretary Shalala at the announcement was Stacey Oller, a cancer survivor who wants to be an oral surgeon.

This cancer initiative represents another element of the Clinton Administration's efforts to streamline the regulatory process while maintaining high standards that protect patients. It was developed on the basis of suggestions and advice offered by cancer patients and their advocacy groups, representatives of the pharmaceutical industry, physicians and cancer researchers.

-more-

The initiative consists of four major proposals:

(1) Accelerated Approval for Cancer Drugs. Although FDA now measures review times for cancer drugs in months, it can take years of testing before an application to market a cancer drug even reaches FDA. To speed the availability of cancer drugs, FDA may now rely on partial response (such as measurable but incomplete shrinkage of a tumor) to a therapy, in addition to the current criteria such as a patient's survival and improved quality of life. By basing accelerated approval on surrogate markers such as tumor shrinkage, and by allowing more definitive data on survival or other criteria to be developed after marketing approval, FDA believes that many cancer therapies will reach patients sooner.

(2) Expanded Access for Drugs Approved Elsewhere. For patients with serious and life-threatening illnesses such as cancer, FDA has devised several programs that provide access to promising but unapproved therapies even as they are being studied. To make even more cancer drugs available before formal approval, FDA will encourage sponsors of experimental drugs that have been approved in certain other countries to apply for permission to distribute the drug to eligible cancer patients before final drug approval has been granted.

(3) Increased Cancer Patient Representation at FDA Advisory Committee Meetings. FDA relies on advisory committees to provide outside expertise on agency policy and product decisions. Each advisory committee typically includes one consumer member. Because cancer is not one disease but many, FDA will now include a person who has experienced the specific cancer on each cancer-therapy advisory committee.

(4) Fewer Applications for Additional Uses of Approved Cancer Drugs. Currently, many researchers ask FDA to review "supplemental" applications to study unapproved uses for the approved cancer drugs, even if they do not intend to market the drug for the new use. In many circumstances these additional applications are unnecessary. The FDA will make clear that it does not require such submissions, thereby eliminating any confusion about the necessity of the filing. Investigators can therefore devote more of their time to the challenges of cancer research.

FDA currently has the authority to carry out these initiatives, and it will begin to do so immediately.

In a related initiative, the FDA is publishing a series of five proposals designed to establish a uniformly high level of standards for mammography centers nationwide. These proposals, which cover such issues as quality assurance, equipment, facilities, and personnel, continue the successful implementation of the 1992 Mammography Quality Standards Act.

Mammography is currently the single best means of fighting breast cancer, which is expected to kill approximately 45,000 women in 1996. It is currently estimated that women in the U.S. have a one-in-nine lifetime risk of breast cancer.

# # # # #

HHS FACT SHEET

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

EMBARGOED UNTIL 2:30 P.M., E.S.T
Friday, March 29, 1996

Contact: FDA Press Office
(301)-443-1130

ACCELERATING APPROVAL AND EXPANDING ACCESS
Clinton Administration Increases Availability of Cancer Drugs

Under reforms announced today, the Clinton Administration expects to substantially cut development and review times for promising new cancer drugs. These changes, it is expected, will reduce drug development times by at least a year and will cut FDA review time for cancer drugs almost in half, from 12.4 months to 6 months.

At a White House ceremony, President Clinton, Vice President Gore and HHS Secretary Donna E. Shalala outlined this initiative to make new therapies available sooner to American patients.

The announced reforms in the regulation of cancer drugs at the Food and Drug Administration are part of the Vice President's ongoing "reinventing government" efforts. These efforts represent another example of the Clinton Administration's commitment to streamline the regulatory process while still maintaining critical public health protections.

Specific measures announced today include:

- **Accelerated Approval for Cancer Treatments:** At present, the FDA relies mainly on improvements in a patient's survival time or quality of life for marketing approval. Starting today, the FDA will begin to rely more on partial responses, such as shrinkage of a tumor, when considering drugs for accelerated approval. Through simpler clinical trials, manufacturers can more quickly demonstrate these partial responses than they can improvements in survival and quality of life. By basing accelerated approval on these partial responses, and allowing more definitive data to be developed after approval, FDA will make more cancer therapies available to patients more quickly.

-more-

- **Expanded Access to Drugs Approved Abroad:** For patients with life-threatening illnesses such as cancer, FDA has devised several programs that provide patient access to promising therapies that have not yet completed clinical evaluations. The FDA will now begin proactively soliciting sponsors of cancer drugs approved abroad to submit these drugs for use in the existing programs. This will help make experimental therapies available to patients shortly after they are approved in other countries even if they are early in their development within the United States.

- **Cancer Patient Input:** FDA relies on advisory committees to provide outside expertise on agency policy and product decisions; the recommendations of these committees often become the basis of FDA decisions. While many of the committees currently include a consumer representative, FDA will now ensure that an individual who has personal experience with the specific cancer being studied be included as an *ad hoc* member of each cancer-therapy committee.

- **Fewer Applications for Additional Uses of Cancer Drugs:** Currently, many researchers ask FDA to review "supplemental" applications to study unapproved uses for approved cancer drugs, even if they do not intend to market the drug for the new use. In many circumstances, these additional submissions are unnecessary. The FDA will make clear that it does not require such submissions, thereby eliminating any confusion about the necessity of the filing. Investigators can therefore devote more of their time to the challenges of cancer research.

The Clinton Administration currently has the authority to carry out all of these reforms and will begin to do so immediately.

A more detailed explanation of the initiatives announced today is available in "Reinventing the Regulation of Cancer Drugs," a report from the Vice President's National Performance Review.

Background on Cancer: In 1996, more than 1.3 million people will be diagnosed with cancer in this country. Every day, more than 1,500 Americans of all ages, races, and incomes will die because of these deadly diseases. But because of our extraordinary breakthroughs in therapies, early detection, and prevention, there are 7 million Americans today who can call themselves cancer survivors.

FDA Approval of Cancer Drugs: In 1994 and 1995, 12 new drugs for cancer patients or new uses for existing agents were approved in the United States.

- The average time to review and approve cancer drugs has been 12.4 months between 1990 and 1995. The following is a list of FDA's most recent approvals:

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Zoladex	Advanced breast cancer
Photofrin	Esophageal cancer
Arimidex	Advanced breast cancer

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URGENT

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

5/17/96

LEGISLATIVE REFERRAL MEMORANDUM

LRM NO: 4473

FILE NO: 2329

Total Page(s): 4

TO: Legislative Liaison Officer - See Distribution below:

FROM: Janet FORSGREN Janet Forsgren (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: Congressional Proposed Draft Bill on the treatment of certain dietary supplements under the Federal Food, Drug, and Cosmetic Act.

DEADLINE: Monday, May 20,1996

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: CLOSE HOLD -- sponsor is requesting the Administration's views on the attached draft legislation and possible Administration statement of support. PLEASE EXPEDITE YOUR REVIEW.

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RESPONSE TO LEGISLATIVE REFERRAL MEMORANDUM

LRM NO: **4473**

FILE NO: **2329**

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: Congressional Proposed Draft Bill on the treatment of certain dietary supplements under the Federal Food, Drug, and Cosmetic Act.

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

104TH CONGRESS
2D SESSION

S. _____

IN THE SENATE OF THE UNITED STATES

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.''.

The New York Times

Founded in 1851

ADOLPH S. OCHS, *Publisher 1896-1935*
ARTHUR HAYS SULZBERGER, *Publisher 1935-1961*
ORVIL E. DRYFOOS, *Publisher 1961-1963*
ARTHUR OCHS SULZBERGER, *Publisher 1963-1992*

Making It in New York City

Few postwar trends have devastated New York City more than the collapse of manufacturing, which has hollowed out neighborhoods and eliminated at least 700,000 jobs. In recent years, however, a contrary trend has occurred. Smaller manufacturers, often operated by immigrants, are sprouting everywhere. Mayor Rudolph Giuliani is right to try to encourage the trend by promising to cut costs for these new businesses. At the same time, his administration calls for giving big "super stores" access to some areas now set aside exclusively for manufacturing. That approach could also stimulate the economy and widen the choices for consumers.

In the early 1970's, the city tried to keep its manufacturers by barring housing and commercial enterprises from its manufacturing districts. The theory was that competing development in these areas would drive up property values and rents, forcing the manufacturers to shut down or flee.

A generation later, it is clear that the city's strategy has failed. It now makes sense to let big stores — including hardware, housewares, supermarkets and general stores like Kmart — into the city. Lobbyists for small businesses are opposed, but consumers will welcome the chance to shop in places already popular in the suburbs.

Under the Mayor's plan, stores as large as 200,000 square feet could open in areas now zoned for manufacturing without going through cumbersome approval processes, as long as they are built in areas with adequate transportation. The City Planning Commission argues that more than $3 billion in retail sales are lost because New Yorkers now go to the suburbs to find similar stores. Smaller stores may find the competition difficult, but the record in other communities is that smaller operations can survive if they offer distinctive goods or better service.

Meanwhile, even as the city looks to new uses for manufacturing districts, it is also finding that some of the smaller manufacturers can operate safely in areas now zoned for commercial, retail and residential development. Large garment manufacturers may have fled, but small specialty shops that make purses, ties or other high-quality goods have sprouted to take their place. The city's big bakeries have mostly shut down, but lots of little bakeries have opened. Small operations in the telecommunications, software and computer field have already transformed Manhattan into what some call "silicon alley." Many steps can be taken to encourage even more growth in these areas, such as lifting costly and cumbersome government regulations.

Tax relief might also help these industries, and to that end Mr. Giuliani is offering business and selective sales tax cuts. But can a city already strapped for cash afford these cuts? Some of Mr. Giuliani's other proposals may be more realistic — improving freight access to Kennedy International Airport, ending the erratic enforcement of traffic and parking restrictions, streamlining the permit process and targeting job-training funds to business sectors that promise growth. As a report by the Taub Urban Research Center at New York University points out, the city must also insure that its schools turn out a skilled work force, that its transportation links are maintained and that it continues to be a magnet for immigrants with an entrepreneurial spirit.

No one knows the long-term trend for the city's economic base, but one of New York's great assets — its reputation as a place where industrious and creative people want to live and work in close proximity with each other — will survive only if the city does not take it for granted. With these new initiatives, the city sends a signal that it will fight for its future.

THE NEW YORK TIMES
TUESDAY, MAY 28, 1996

Critical Days for Northern Ireland

The next few weeks are critical to the prospects for peace in Northern Ireland. Elections there this week will produce delegates to attend all-party peace talks that are scheduled to commence on June 10. With the help of some good will on all sides, the days ahead could bring real progress toward ending this long and tortured conflict.

There have been some hopeful signs in recent days. John Major, the British Prime Minister, cleared away one obstacle earlier this month by saying that London would not insist on the disarming of the Irish Republican Army before all-party talks could begin. It was an important concession, and not an easy one for Mr. Major to make.

Gerry Adams, the leader of Sinn Fein, the political wing of the I.R.A., followed Mr. Major's good example by formally agreeing to the principles of nonviolence contained in a report on the Irish problem prepared by an international commission headed by former Senator George Mitchell.

The next step in this encouraging sequence must be the declaration of a new cease-fire by the I.R.A. Without that, Sinn Fein will be barred from the all-party talks, and the chances of reaching a peace agreement will swiftly fade.

There is now every reason for the I.R.A. to suspend its revived terror campaign. The organization's greatest concern — that it would have to accept immediate disarmament before talks could begin — has been removed. To alleviate lingering I.R.A. concern about the conditions and timing of disarming, Mr. Major should offer a specific plan for dealing with the issue as part of the all-party peace talks.

The talks are set to unfold on three tracks. The first will deal with issues within Northern Ireland. The second — and most controversial — will address the relationship between Northern Ireland and the Irish Republic. The third will handle the relations between Britain and the North. There should be a fourth track on disarmament issues. The whole negotiating enterprise is based on the sensible principle that agreement in one area will not be valid unless the parties reach agreement in all phases of the talks.

Mr. Mitchell, who is viewed as an honest broker by all sides, should be given a central role in the peace talks, possibly chairing the plenary sessions when all the delegates meet together. Alternatively, he could direct the discussion of north-south issues, or lead disarmament negotiations.

David Trimble, who heads the Ulster Unionist Party, has threatened to bring down Mr. Major's Government — which now survives with a one-vote majority — if the Prime Minister fails to make disarmament of the I.R.A. a condition for any negotiation. Mr. Trimble is bluffing. If he were to bring down Mr. Major, which is far from certain, he could not expect a better deal from a Labor leader.

The next move is up to the I.R.A. Mr. Adams has worked hard to bring peace to his homeland, but he cannot take the next step without the help of the I.R.A. There has not been a better opportunity in a generation to settle the Irish conflict.

Don't Jeopardize Food Safety

With "mad cow" disease barely faded in the headlines, it seems an odd time for Congress to consider weakening America's food safety laws. Yet that is the threat of a package of proposals intended to "reform" the Food and Drug Administration.

The F.D.A. is responsible for insuring food safety and truth in food labeling. Among other things, the agency approves food additives, inspects food processing plants and insures that health claims on food labels are supported by "significant" scientific agreement.

In recent months, the agency has come under fire in Congress for moving too slowly. Reform proposals are making their way through the House and Senate, with the House version set for consideration by the commerce committee soon.

One of the most controversial parts of the House bill, sponsored by Representative Scott Klug, Republican of Wisconsin, would weaken the 38-year-old Delaney Clause, which absolutely prohibits manufacturers from putting cancer-causing additives in processed food. The House proposal would allow "negligible or insignificant" cancer risks in food and color additives, and drugs given to food-producing animals.

In 1993, the Clinton Administration agreed to loosen the Delaney Clause's no-risk standard relating to pesticide residues in processed foods — but only in exchange for a uniform standard that would be much tougher in limiting pesticide residues on fresh foods, where the clause does not apply. Congress, however, never took action. Now the House proposal would adopt a similar standard for food additives that are deliberately applied to foods.

The Administration, however, sensibly wants to keep Delaney in place for processed foods. It draws a distinction between directly added substances, like preservatives and food coloring, which do not need to be in the food at all, and indirectly added substances, like pesticides, which may inadvertently enter the food supply. Moreover, the Delaney Clause is a powerful regulatory club that should not lightly be given away except for some clear gain in overall safety.

In another section aimed at providing national uniformity, the House bill would pre-empt many state safety and labeling laws that are more stringent than the Federal law or that simply make sense locally. The bill could thus nullify warning labels on shellfish in states like Florida and California, date-stamping to prove freshness as required in Ohio and labeling of kosher foods in New York and other states.

The bill also sacrifices sensible uniformity on food labels achieved in the 1990 Nutrition Labeling and Education Act. That law tried to minimize false and misleading food labels by setting clear guidelines for terms like "low" or "reduced" fat. Now, Mr. Klug's bill would allow use of synonyms devised by manufacturers, like "not much" fat, that could be misconstrued.

Both the House bill, and a bill heading to the Senate floor, would privatize some F.D.A. functions by allowing third-party approvals of food additives and inspections of food plants.

The United States has a pretty good track record in keeping its food supply safe. But that record will be jeopardized unless the current Congressional proposals are significantly revised.

OFFICE OF THE VICE PRESIDENT
WASHINGTON

April 16, 1996

Mr. Edward V. Fritzky
Chairman and CEO
IMMUNEX
51 University Street
Seattle, Washington 98101

Dear Mr. Fritzky:

To follow up on our May meeting last year with Betsey Wright, we wanted to make sure that you were aware that we took your concerns to heart about the need to expedite the FDA drug approval process for pharmaceuticals used to treat cancer. As you no doubt know, on Friday, March 29th, the President, the Vice President and Dr. Kessler announced a series of initiatives aimed at bringing cancer drugs to the market and to the people who need them as soon as possible.

We are enclosing a copy of the remarks the President made as he announced this initiative, as well as the remarks from Dr. Kessler and the background material for this announcement. We hope you find this information useful.

Thank you for the helpful information and support you provided to make our ongoing efforts to strengthen and improve the important work of the FDA. We look forward to working with you on this and other issues of mutual interest in the future.

Sincerely,

Greg Simon
Chief Domestic Policy Advisor
to the Vice President

Elaine C. Kamarck
Senior Policy Advisor
to the Vice President

Enclosure

bcc: Betsey Wright
Carol Rasco
Chris Jennings

OFFICE OF THE VICE PRESIDENT
WASHINGTON

April 16, 1996

Ms. Gerri Henwood
CEO
BIO-PHARM
Four Valley Square
510 Township Line Road
Blue Bell, Pennsylvania 19422

Dear Ms. Henwood:

To follow up on our May meeting last year with Betsey Wright, we wanted to make sure that you were aware that we took your concerns to heart about the need to expedite the FDA drug approval process for pharmaceuticals used to treat cancer. As you no doubt know, on Friday, March 29th, the President, the Vice President and Dr. Kessler announced a series of initiatives aimed at bringing cancer drugs to the market and to the people who need them as soon as possible.

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to the Vice President

Enclosure

bcc: Betsey Wright
Carol Rasco
Chris Jennings

OFFICE OF THE VICE PRESIDENT
WASHINGTON

April 16, 1996

Mr. David Holveck
President and CEO
Centocor, Inc.
200 Great Valley Parkway
Malvern, Pennsylvania 19355-1307

Dear Mr. Holveck:

To follow up on our May meeting last year with Betsey Wright, we wanted to make sure that you were aware that we took your concerns to heart about the need to expedite the FDA drug approval process for pharmaceuticals used to treat cancer. As you no doubt know, on Friday, March 29th, the President, the Vice President and Dr. Kessler announced a series of initiatives aimed at bringing cancer drugs to the market and to the people who need them as soon as possible.

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Senior Policy Advisor
to the Vice President

Enclosure

bcc: Betsey Wright
Carol Rasco
Chris Jennings

OFFICE OF THE VICE PRESIDENT
WASHINGTON

April 16, 1996

Mr. Patrick J. Mahaffy
President and CEO
NeXstar Pharmaceuticals, Inc.
2860 Wilderness Place
Boulder, Colorado 80301

Dear Mr. Mahaffy:

To follow up on our May meeting last year with Betsey Wright, we wanted to make sure that you were aware that we took your concerns to heart about the need to expedite the FDA drug approval process for pharmaceuticals used to treat cancer. As you no doubt know, on Friday, March 29th, the President, the Vice President and Dr. Kessler announced a series of initiatives aimed at bringing cancer drugs to the market and to the people who need them as soon as possible.

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Chief Domestic Policy Advisor
to the Vice President

Elaine C. Kamarck
Senior Policy Advisor
to the Vice President

Enclosure

bcc: Betsey Wright
Carol Rasco
Chris Jennings

OFFICE OF THE VICE PRESIDENT
WASHINGTON

April 16, 1996

Mr. Dennis J. Purcell
Managing Director
Hambrecht & Quist
230 Park Avenue
New York, New York 10169

Dear Mr. Purcell:

To follow up on our May meeting last year with Betsey Wright, we wanted to make sure that you were aware that we took your concerns to heart about the need to expedite the FDA drug approval process for pharmaceuticals used to treat cancer. As you no doubt know, on Friday, March 29th, the President, the Vice President and Dr. Kessler announced a series of initiatives aimed at bringing cancer drugs to the market and to the people who need them as soon as possible.

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Carol Rasco
Chris Jennings

OFFICE OF THE VICE PRESIDENT
WASHINGTON

April 16, 1996

Dr. Philip S. Schein
Chairman and CEO
U.S. Bioscience
One Tower Bridge
100 Front Street, Suite 400
West Conshohocken, Pennsylvania 19428

Dear Dr. Schein:

To follow up on our May meeting last year with Betsey Wright, we wanted to make sure that you were aware that we took your concerns to heart about the need to expedite the FDA drug approval process for pharmaceuticals used to treat cancer. As you no doubt know, on Friday, March 29th, the President, the Vice President and Dr. Kessler announced a series of initiatives aimed at bringing cancer drugs to the market and to the people who need them as soon as possible.

We are enclosing a copy of the remarks the President made as he announced this initiative, as well as the remarks from Dr. Kessler and the background material for this announcement. We hope you find this information useful.

Thank you for the helpful information and support you provided to make our ongoing efforts to strengthen and improve the important work of the FDA. We look forward to working with you on this and other issues of mutual interest in the future.

Sincerely,

Greg Simon
Chief Domestic Policy Advisor
to the Vice President

Elaine C. Kamarck
Senior Policy Advisor
to the Vice President

Enclosure
bcc: Betsey Wright
Carol Rasco
Chris Jennings

(Prepared remarks for David A. Kessler, MD, Commissioner of Food and Drugs, on the occassion of the White House announcement of FDA's oncology initiatives on March 29, 1996)

WHAT IT ALL MEANS

The four initiatives announced today have a single, significant meaning: American cancer patients, from now on, will have faster and easier access to more promising therapies.

Here, in a nutshell, is the importance of each of our four proposals:

First, for patients with refractory -- hard to treat -- cancer, instead of requiring evidence of clinical benefits -- such as survival -- FDA will rely on objective evidence of tumor shrinkage as a basis for initial approval. This will allow reliance on smaller, shorter studies for initial approval of drugs. This accelerated procedure, which will be followed up by further studies of clinical safety and effectiveness in larger groups of patients, should simplify and speed up the evaluation and approval of drugs for advanced stages of solid tumors.

Second, we will expedite the availability of promising medications that have been approved in certain other countries. If there is a promising drug approved in a foreign market, we will invite the manufacturer to submit to us the **same** information that made possible the approval abroad and, whenever possible, use it as basis for making such therapy available to critically ailing patients in this country. Use of similar approaches to drug evaluation, in our experience with AIDS therapies, has been a powerful stimulus to the development of new agents.

Third, we will include representatives of cancer patients in FDA's cancer-related advisory committees, and thereby make sure that their views are heard when it comes to recommending approval or non-approval of new cancer drugs.

And fourth, we will eliminate unnecessary paper work that used to delay or discourage cancer research by non-commercial clinical investigators.

Two more points about these initiatives are of importance:

- (1) they are designed to accomplish their aims without lowering FDA's high standards of drug safety and effectiveness, or reducing the amount of information available to physicians. And
- (2) they are not to be seen as one-time measures, but rather as part of a continuing FDA effort to improve the quality and availability of drugs for all people with serious and life-threatening diseases.

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, 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.

THE WASHINGTON POST
WEDNESDAY, APRIL 10, 1996

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.

Truth and Trash

THE THEME of Jerry Springer's show one day last year was "Honey, Have I Got a Surprise for You!" By this time, of course, very few things would surprise anyone on a show like Mr. Springer's, where guests confess, before a national TV audience, to odd and awful things they've been doing. In this case, however, there was quite a domestic shock: A man who had been carrying on with the family's teenage babysitter was to tell his wife about it for the first time—on the air.

The show went as planned: The husband related his escapades, the studio audience hooted, the wife came on and burst into tears at the confession, and, finally, the babysitter made an appearance to cap off the turmoil. It was only some time later that the show's producers learned the whole thing was a hoax, the work of a Toronto comedian named Jerry Gardhouse and two of his friends, who had answered the show's televised solicitation for people who'd done just what Mr. Gardhouse so convincingly confessed to. The conspirators told a reporter for the Associated Press that they had no trouble getting through the show's screening process and were coached, cajoled and misled (the woman playing the wronged wife said she was not told what would happen on camera) to produce the most dramatic confrontation possible.

The show's producer, Multimedia Entertainment Inc., filed suit in federal court, maintaining, in the words of the AP account, that the hoax "threatens the very integrity of shows like Springer's." This is, mind you, the same program on which adulterers and their girlfriends once appeared and the girlfriends took pregnancy tests during the show, announcing the results on camera; where a guest bragged of having sex with minors and subsequently was arrested, tried and sentenced to five years in prison.

The producers of these true-confession programs fear they'll lose audience if people start wondering whether the spectacles are real or acted. On the contrary, it seems to us they would gain viewers, simply because they could draw on the large number of people who'd feel better about watching these doings if they could comfort themselves all the while with the same sort of reassurances you give a child at a disturbing movie: "He's not really dead. That's only ketchup. People don't behave like this in real life."

What's News—

Business and Finance

CS HOLDING proposed a merger with Union Bank of Switzerland that would create the largest bank in Europe and one of the biggest in the world. The two have total assets of $669 billion, and a linkup would allow for significant cost-cutting, providing a combined bank greater resources to take on major U.S. and Japanese rivals. However, CS Holding — parent of Credit Suisse and CS First Boston — stressed the talks are "exploratory."

(Article on Page A3)

* * *

The chip industry's key book-to-bill ratio fell unexpectedly last month, adding to concerns about the strength of important technology markets.

Motorola reported better-than-expected quarterly profit, partly due to cost-cutting efforts. The results were posted after markets closed.

(Articles on Pages A3 and B4)

* * *

Bonuses for GM top executives were reduced last year, despite record profit at the auto maker, reflecting the fact that results fell short of aggressive targets set by the board.

(Article on Page A3)

* * *

Under proposed FCC rules, cable-TV firms could avoid rate regulation where they compete with phone companies. But the FCC is leaving open the prickly matter of what constitutes competition, an issue that will recur as the many rules necessitated by communications-law changes are crafted.

(Article on Page A4)

* * *

Some economists are brightening their short-term outlook for the economy, given the recent string of better-than-expected economic reports.

(Article on Page A2)

* * *

Netscape and a GE unit plan to jointly develop software aimed at making it easier for companies to do business with one another on-line.

(Article on Page B6)

* * *

The EEOC sued Mitsubishi Motor Manufacturing of America, saying hundreds of female workers endured harassment over several years.

(Article on Page B1)

* * *

Green Tree Financial's top executive, Lawrence Coss, received $65.1 million in compensation last year.

(Article on Page A2)

* * *

Former Disney executive Jeffrey Katzenberg filed a suit seeking over $250 million in a contract dispute.

(Article on Page B1)

* * *

An ex-fiancee of a former Philip Morris researcher turned over boxes of documents to lawyers in the big Castano lawsuit against tobacco firms.

(Article on Page B8)

* * *

FASB has proposed an accounting rule that would boost per-share earnings, in practice, by trimming the dilutive effect of options and warrants.

(Article on Page C1)

* * *

World-Wide

THE U.S. BEGAN evacuating its citizens as fighting raged in Liberia's capital.

The first U.S. helicopters arrived in Monrovia to begin to take the 470 Americans to Sierra Leone, where transport planes and about 100 special-forces troops were waiting. More than 15,000 people have crowded into the U.S. Embassy compound in Monrovia to escape the fighting between government troops and Ulimo rebels. Hundreds of civilians and West African peacekeeping troops have been taken hostage by the rebels.

The fighting that broke out Saturday is the worst since 1993. A six-year civil war in Liberia has killed 150,000 people and left half the population homeless.

* * *

ROSTENKOWSKI PLEADED GUILTY to two mail-fraud counts and will go to jail.

The former chairman of the powerful House Ways and Means Committee will serve 17 months and pay a fine of $100,000 in the plea agreement with federal prosecutors. In return, 11 other charges will be dropped from a 1994 indictment. At a hearing yesterday, a U.S. judge told the Chicago Democrat, "You have shamelessly abused your position." (Article on Page A4)

Rostenkowski turned down at least one previous offer of a deal. It would have involved pleading guilty to one felony count and a six-month prison term.

* * *

A Pulitzer Prize was awarded to Wall Street Journal reporter Alix M. Freedman for national-affairs coverage of the tobacco industry and its secrets. The New York Times won three awards, while Newsday of Long Island, N.Y., won two. Richard Ford won the fiction prize for his novel "Independence Day." (Article on Page A2)

* * *

Chief Justice Rehnquist said federal judges shouldn't be threatened with impeachment over their rulings. The nation's top judge told an American University audience such threats undermine the independence of the judiciary. The White House last month threatened to ask a judge to resign over his ruling in a New York drug case.

* * *

Federal agents continued to build a case against the Unabomber suspect. Justice Department officials said documents found in Theodore John Kaczynski's Montana cabin referred to categories of targets consistent with the Unabomber's. Agents also turned up evidence that Kaczynski may have crossed paths with four victims.

* * *

A key prosecution witness admitted he gave incorrect testimony in federal court in 1994, when he pleaded guilty to Whitewater charges. At that time, he testified he hadn't benefited from fraudulent loans, but under cross-examination yesterday he admitted he had. David Hale said the inconsistency resulted from being "scared to death."

* * *

Clinton signed the line-item veto, giving presidents the power to slash specific spending items from bills while allowing the rest of the legislation to survive. The new law, which represents a significant shift of power from the legislative to the executive branch, takes effect next year. Court challenges to the law's constitutionality are expected.

* * *

Israel's Peres said he won't be pushed into a hasty response to rocket attacks by Lebanon-based Hezbollah guerrillas that wounded 36 people in northern Israel. Protests forced the prime minister to cancel a visit to a town where most of the damage occurred. Separately, Israeli troops broke up a big demonstration at Hebron University.

* * *

Oklahoma City suspects appeared for pretrial motions for the first time since the bombing case was shifted to Denver. The defense sought government files on terrorist groups, hoping to show a wide conspiracy behind the bombing. Prosecutors said they have evidence to support such a theory.

* * *

Austrian police handed over a Bosnian Croat prison-camp commander, charged with crimes against Serbs, to the U.N. war-crimes tribunal. Separately, Bosnian Serbs released three Muslim prisoners of war in an effort to gain admittance to a reconstruction conference this week.

* * *

Researchers urged pregnant women to take more calcium, which they say prevents high blood pressure and cuts the risk of a complication known as preeclampsia. Those conditions are among the leading causes of death during pregnancy, the report in the AMA's journal said. (Article on Page B6)

* * *

Died: James W. Rouse, 81, developer of retail attractions such as New York's South Street Seaport and Boston's Faneuil Hall, in Columbia, Md., of Lou Gehrig's disease.

Intellectual-property piracy in China continues to expand, according to an industry alliance, despite Beijing's pledge to crack down on makers of illicit CDs and other material.

(Article on Page A9)

* * *

ITT's talks to acquire Bally Entertainment have stalled, partly over an effort to ensure that Bally holders get a minimum price in a stock swap.

(Article on Page B2)

* * *

Markets—

Stocks: Volume 421,196,100 shares. Dow Jones industrials 5560.41, off 33.96; transportation 2171.23, up 3.29; utilities 209.89, up 1.88.

Bonds: Lehman Brothers Treasury index 6153.22, up 23.71.

Commodities: Oil $23.08 a barrel, up 5 cents. Dow Jones futures index 151.17, off 0.72; spot index 150.07, off 0.12.

Dollar: 108.32 yen, up 0.64; 1.4985 marks, up 0.0170.

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104TH CONGRESS
2D SESSION

H. R. 3201

To amend the Federal Food, Drug, and Cosmetic Act to facilitate the development, clearance, and use of devices to maintain and improve the public health and quality of life of the citizens of the United States.

IN THE HOUSE OF REPRESENTATIVES

MARCH 29, 1996

Mr. BARTON of Texas (for himself, Mr. GREENWOOD, Mr. RICHARDSON, Mr. BILIRAKIS, Mr. HALL of Texas, Mr. GORDON, Mr. BURR, Ms. ESHOO, Mr. COBURN, Mr. BREWSTER, Mr. KLUG, Mr. DOOLEY of California, Mr. GANSKE, Mr. MCHALE, Mr. BILBRAY, Mr. PAYNE of Virginia, Mr. OXLEY, Mr. HOLDEN, Mr. FIELDS of Texas, Mr. PAXON, Mr. SCHAEFER, Mr. TAUZIN, Mr. FOX of Pennsylvania, Mr. UPTON, Mr. CAMPBELL, Mr. MCINTOSH, Mr. COX of California, Mr. DREIER, Mr. HEINEMAN, Mr. FUNDERBURK, Mr. WELDON of Florida, Mr. HOSTETTLER, Mr. SHAYS, Mr. HASTERT, Mr. NORWOOD, Mr. BURTON of Indiana, Mr. FRAZER, Mr. STEARNS, Mr. FRISA, Mr. RAMSTAD, Mr. MARTINI, and Ms. DUNN of Washington) introduced the following bill; which was referred to the Committee on Commerce

---

A BILL

To amend the Federal Food, Drug, and Cosmetic Act to facilitate the development, clearance, and use of devices to maintain and improve the public health and quality of life of the citizens of the United States.

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

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104TH CONGRESS
2D SESSION

H. R. 3200

To amend the Federal Food, Drug, and Cosmetic Act to increase access to nutritional information about foods, to increase the availability of safe food products, and for other purposes.

IN THE HOUSE OF REPRESENTATIVES

MARCH 29, 1996

Mr. KLUG (for himself, Mr. GREENWOOD, Mr. TOWNS, Mr. BILIRAKIS, Mr. RICHARDSON, Mr. BURR, Mr. HALL of Texas, Mr. BARTON of Texas, Mr. GORDON, Mr. UPTON, Mr. BREWSTER, Mr. BILBRAY, Mr. PAYNE of Virginia, Mr. COBURN, Mr. DOOLEY of California, Mr. GANSKE, Mr. MCHALE, Mr. OXLEY, Mr. HOLDEN, Mr. FIELDS of Texas, Mr. PAXON, Mr. WHITFIELD, Mr. SCHAEFER, Mr. TAUZIN, Mr. FOX of Pennsylvania, Mr. CAMPBELL, Mr. MCINTOSH, Mr. COX of California, Mr. DREIER, Mr. HEINEMAN, Mr. FUNDERBURK, Mr. WELDON of Florida, Mr. SHAYS, Mr. HASTERT, Mr. NORWOOD, Mr. FRAZER, Mr. STEARNS, Mr. FRISA, Mr. RAMSTAD, Mr. MARTINI, and Ms. DUNN of Washington) introduced the following bill; which was referred to the Committee on Commerce

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A BILL

To amend the Federal Food, Drug, and Cosmetic Act to increase access to nutritional information about foods, to increase the availability of safe food products, and for other purposes.

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

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104TH CONGRESS
2D SESSION

H. R. 3199

To amend the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act to facilitate the development and approval of new drugs and biological products, and for other purposes.

IN THE HOUSE OF REPRESENTATIVES

MARCH 29, 1996

Mr. BURR (for himself, Mr. GREENWOOD, Mr. RICHARDSON, Mr. BILIRAKIS, Mr. TOWNS, Mr. BARTON of Texas, Mr. HALL of Texas, Mr. KLUG, Ms. ESHOO, Mr. UPTON, Mr. GORDON, Mr. BILBRAY, Mr. BREWSTER, Mr. COBURN, Mr. DOOLEY of California, Mr. GANSKE, Mr. MCHALE, Mr. OXLEY, Mr. PAYNE of Virginia, Mr. FIELDS of Texas, Mr. ROSE, Mr. PAXON, Mr. HOLDEN, Mr. TAUZIN, Mr. SCHAEFER, Mr. FOX of Pennsylvania, Mr. FUNDERBURK, Mr. CAMPBELL, Mr. MCINTOSH, Mr. COX of California, Mr. DREIER, Mr. HEINEMAN, Mr. WELDON of Florida, Mr. SHAYS, Mr. HASTERT, Mr. NORWOOD, Mr. BURTON of Indiana, Mr. FRAZER, Mr. STEARNS, Mr. FRISA, Mr. RAMSTAD, Mr. MARTINI, and Ms. DUNN of Washington) introduced the following bill; which was referred to the Committee on Commerce

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A BILL

To amend the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act to facilitate the development and approval of new drugs and biological products, and for other purposes.

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

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

27-Mar-1996 10:53am

TO: Carol H. Rasco

FROM: Christopher C. Jennings
Domestic Policy Council

SUBJECT: FDA/Texas case

You may remember that FDA/cancer drug case in which Ross Perot expressed at least some passing interest. It involved a doctor in Texas named Burzynski who was prescribing alternative cancer treatments.

Burzynski was complaining that FDA was making it difficult to impossible for him to prescribe and give out (and be reimbursed for) medications that he felt were helpful in treating cancer. (Burzynski has a number of strong patient/family supporters who believe his treatments are making the difference between life and death and backed him up on his criticisms of FDA.) FDA countered that the doctor could treat his patients if they followed their prescribed treatment and study protocal for an investigational new drug (IND). They believe that all patients who feel they need this drug can get it if the doctor follows their guidelines. (They charge that Burzynski simply has not.)

We checked into it and solicited the advice of White House General Counsel's Office -- Chris Cerf -- about whether or not we should look into this matter. Their strong advice was to stay away because of pending Justice Dept indictments of Burzynski. We followed their advice, although we did notify FDA that this issue was getting more and more public/media attention.)

Subsequently, there have been print and broadcast stories on this matter. For the most part, the media has been fairly sympathetic to the position FDA is taking.

Yesterday and today, Burzynski and his followers have held press conferences on Capitol Hill attempting to raise their plight again, against the backdrop of the FDA reform legislative developments in the Congress. Moreover,they are saying that the Justice Department and the FDA is going to force Burzynski to shut down and not give out any additional medications out to many needy patients. FDA disputes this and says that all needy patients who want this drug will have access to it through the IND process they set up with Burzynski. The Justice Dept. apparently feels even

Justice and Interior are working to analyze this decision. It literally came out this morning, so they are just today getting copies of the 200+ page decision. They will get us a better analysis of this decision sometime next week, but in the meantime I wanted to pass this on to you FYI.

I will also alert Harold's shop, Marcia Hale, and Political affairs.

April 19, 1996

DRAFT DRAFT DRAFT

H.R. 3199
"DRUG AND BIOLOGIC PRODUCTS REFORM ACT OF 1996"[1]

SEC. 1 SHORT TITLE, REFERENCE, AND TABLE OF CONTENTS

SEC. 2 FDA MISSION AND ANNUAL REPORT

- Section 2(a), the mission statement establishes efficient review and approval and global harmonization as primary FDA goals.

  The agency's core mission is not to "approve" products, but rather to thoroughly and fairly evaluate them and render impartial decisions about their safety and effectiveness. The mission statement should include protecting the public from products that do not have the requisite approval prior to marketing -- i.e., products that have not been shown to be safe and effective.

- Section 2(b) requires FDA to, simultaneously with the submission of an annual budget, submit to the Commerce Committee in the House and the Committee on Labor and Human Resources in the Senate, an annual report that (1) reviews its performance in meeting its mission and developing policies to meets its mission; (2) reviews its performance in meetings its own performance standards (including meeting statutory deadlines); (3) describes its staffing and lists third parties that have been accredited to perform product reviews and GMP inspections and to conduct investigations; (4) describes its harmonizations activities and accomplishments; and (5) compares FDA's performance in approving innovative products with that of the most "successful" agency performing similar functions in other countries and compares the resources used by such agencies.

  The agency does not disagree with the principle that the agency must be held accountable. The concern is that some of the requirements set forth in this provision are not clearly defines and/or possibly not feasible. For example, the requirement that FDA compare its performance with that of the most "successful" agency performing

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[1] H.R. 3199 includes a number of supportable concepts. The emphasis of this section-by-section analysis, however, is on the problematic provisions in the bill.

similar functions in other countries is vague and may be difficult, if not impossible, to meet. The term "successful" is not one that provides much guidance. Moreover, it is uncertain whether such data are available from other countries or if such data are available, whether a comparison is possible.

SEC.3 STREAMLINING CLINICAL RESEARCH ON DRUGS AND BIOLOGICAL PRODUCTS

- Section 3 provides that a clinical investigation of a new drug may begin 21 days after the Secretary has received a submission that contains adequate reports of basic information necessary to assess the drug's safety and adequate information on the chemistry, manufacturing, controls, and primary data tabulations for the drug from animal or human studies, except that for phase I or II clinical investigations, detailed information shall not be required unless the office director makes a written request within 21 days.

  The effect of section 3 is to reduce (from 30 days to 21 days) the amount of time FDA has to place a clinical hold before the investigation of a new drug begins. The shortened timeframe is even more difficult to meet because, as set forth below, it does not permit a telephone call. (Moreover, the written notification that is required must set forth the reasons for the clinical hold.) CDER alone received 1972 INDs in FY 1995. The problem is that studies may be allowed to proceed without FDA being able to assess the risk. The reduced time frame in the bill shaves LITTLE time from the total drug development process, but a LARGE fraction of the time available to FDA for the protection of human subjects. Patients enrolled in these clinical trials will suffer the consequences of FDA being unable to meet the timeframes.

  This provision does not seem to require the sponsor to submit information on the study design. If this is the intent of the provision, that is problematic.

  The provision exempts Phase I and II studies from requiring the inclusion of detailed information on chemistry, manufacturing, controlled, and data tabulations unless the office director makes a written request within 21 days. Because this is the stage of the clinical investigation where FDA is deciding whether to allow a drug to be administered to human subjects, this is the stage where FDA needs certain detailed information. [If a request for detailed information is made, can the investigation proceed or does the agency have to couple

the written request for detailed information with a clinical hold?]

- FDA cannot place a trial on clinical hold unless the Secretary demonstrates "based on specific information available to the Secretary" that the drug presents an unreasonable risk to the safety of the subjects taking into account the trial design, the conditions for which the drug will be studied and the health status of the subjects. The clinical hold must be in writing and must specify the basis for the clinical hold. The Secretary may issue a clinical hold upon a demonstration that the drug to be investigated represents an unreasonable risk to the safety of the persons who are the subject of the clinical investigation, taking into account the design of the clinical investigation, the condition for which the drug is to be investigated, and the health status of the subjects involved. If the sponsor requests that the hold be removed, the Secretary must provide a decision in writing within 15 days or the clinical hold shall be deemed withdrawn.

  Because the notification may not have to include the design of the trial or the health status of the subject, FDA may not have the information necessary to make the requisite finding. Moreover, even if FDA had the requisite information, it would not have enough time to make the finding.

  The provision restricts FDA's ability to place a trial on clinical hold to instances when the drug to be investigated represents an unreasonable risk to the safety of the persons who are the subject of the clinical investigation, taking into account the design of the clinical investigation, the condition for which the drug is to be investigated, and the health status of the subjects involved. Under current law, FDA can place a trial on clinical hold for a number of other reasons. For example, a Phase I, II, or II clinical trial can be placed on hold if the clinical investigators are not qualified to conduct the investigation; the information the sponsor has given to the investigators about the drug and its pharmacological and toxicological effects, and what is known about the safety and effectiveness of the drug in humans is misleading, erroneous, or materially incomplete; or the IND does not contain sufficient information to assess the risks to subjects. A Phase III trial can also be placed on hold if the plan or protocol for the investigation is clearly deficient in design to meet its stated objectives. See 21 CFR 312.42(a); see also 21 CFR 312.55, 312.23(a)(5).

  The provision requires review of a response to a clinical hold within 15 days. This is unrealistic. Pursuant to REGO, FDA has proposed to complete such a response within 30 days.

- As an alternative procedure, a Phase I or Phase II clinical investigation may begin after an accredited institution has approved the investigation and the Secretary has been notified by the sponsor. The notification need only set forth the name and address of the sponsor and the uses of the drug that the sponsor intends to investigate.

  This provision is problematic re: Phase II clinical investigations because for certain drugs, such as AIDs drugs, the investigation does not proceed beyond phase II trials. This provision would permit sponsors to begin the studies without submitting data to FDA. FDA would have a difficult time issuing a clinical hold because it would not have access to the detailed information about the study. (It is not clear that the notification requirements set forth above apply -- and even if they do, Phase I and II are exempt from submitting detailed information.)

  It would be very difficult for local IRBs to include among their members or consultants all of the expertise needed to assess the risks to patients with various diseases. The scheme set forth in the bill increases the possibility that patients would exposed to an unreasonable risk.

- Section 3 also gives FDA exclusive jurisdiction over the regulation of new drugs in clinical investigations.

  This eliminates duplication by NIH (i.e., for drugs (including biotechnology drugs) being study under HHS-funded research.

SEC.4 THE CONTENT AND REVIEW OF A NEW DRUG APPLICATION

- Section 4 permits sponsors of new drug application to submit summary data. Primary data may be requested by the office director. Such request must be in writing and must specify the reasons for the request for a particular application.

  This provision will compromise the credibility of FDA's review process. Summary reports sometimes contain errors that can be discovered only by reviewing primary data. Moreover, summary data has been screened, processed and interpreted by the sponsor. Companies often just do not see the shortcomings of their drugs. Someone other than a company official should be taking a hard look at the underlying data. Primary data are essential to verify the interpretation of summary data. Problems associated with a drug may be visible through an examination of the raw data that are not visible

from a summary. For example, deaths and discontinuations of study subjects may be attributed to causes other than the drug but review of the raw data may show adverse reactions associated with the drug itself. The submission of primary data is essential to discovering and discouraging the submission of fraudulent data.

Even hints of information found in patient reports can reveal or lead to critical information. For example, then a CDER reviewer reviewed the patient data for xxx, she (not the company) noticed that three of the subjects suffered from xxx while on the experimental drug. Based on her knowledge of this class of drugs, and the fact that no other drugs of this type caused this type of side effect, she decide to look further. She consulted with the company, which took a look at data available from the other countries where the drug had already been approved. the company found not merely xxx, but also deaths due to the drug. Based on this careful observation by an FDA reviewer, the drug was not approved in the United States, and it was removed from the market in xx, xx, and xx. the House proposes to eliminate FDA's ability to find the next case of xxx.

- Section 4 also requires FDA to meet with product sponsors within 30 days of a request for a meeting. FDA advice provided in writing and made a part of the administrative record cannot be changed after testing begins unless the sponsor agrees or the office director determines, after an informal hearing, that such a change is needed to protect the public health.

  FDA makes every effort to hold meetings promptly in response to any reasonable request. It may not always be possible to do it within 30 days.

- Written review decisions on scientific and medical matters on a new drug will be binding on field and compliance staff.

- Action on an application cannot be delayed because of the unavailability of information from or action by field personnel.

  This provision would require the agency to approve products before allegations of fraud, misconduct in a clinical trial, manufacturing problems etc. could be investigated. This could allow an unscrupulous sponsor to deliberately delay an inspection so that information would not be available from the field personnel, and the approval decision would have to proceed without this information.

SEC.5 EFFECTIVENESS DETERMINATION

- Section 5 provides that "one or more" clinical investigations may be needed to show effectiveness. It also provides that a well-controlled investigation "shall include only methods of control that are appropriate to the disease or condition for which a drug is intended as prescribed, recommended, or suggested in its labeling."

  The addition of "one or more" before "clinical investigations" is problematic only if it would not permit the agency to require more than one clinical investigation where appropriate. [There are differences of opinion within FDA as to whether the bill language might so this.]

  [what does this mean?]

- Section 5 also provides that an application for a new drug for a serious or life-threatening condition shall be considered to have substantial evidence if it could fairly and responsibly be concluded by experts that there is a reasonable likelihood that the drug will be effective in a significant number of patients and that the risk from the disease is no greater than the risk from the condition.

  This provision, which allows approval of a new product without adequate and well-controlled trials, undercuts the efficacy standard and shifts the risk analysis away from risk/benefit.

- Section 5 also would permit the approval of a new use of a previously approved drug on the basis of a demonstration that the new use is common among clinicians experienced in the field and represents reasonable clinical practice based upon reliable clinical experience and confirmatory information.

  This would establish a new process for approving new uses of existing drugs and devices that would significantly lower approval standards. It would establish a procedure for recognizing new uses based on clinical practice.

  A drug may come into common use for a condition because current theory, and experience understood in light of that theory, suggests that the drug would be reasonably expected to have the desired effect, but testing such a hypothesis against data in a controlled trial can expose new aspects of the system and may demonstrate that the drug is not acting as it had been predicted to act. Clinical experience cannot be depended upon to bring such new findings to light because it contains too many uncontrolled differences among cases and observers.

This provision moves us away from the accepted scientific standard of evidence and could perpetuate inappropriate, unproven, and ultimately unprovable medical practices.

- Section 5 provides that the determination of effectiveness cannot include the evaluation of relative effectiveness unless the effectiveness of the drug is explicitly compared in the labeling to that of another drug.

  There are public health implications if FDA is not allowed to consider relative effectiveness for products that involve serious or life-threatening illness or which involve public health transmittal risks. For example, FDA requires a 95 percent efficacy rate for gonococcal eradication for products intended to treat GC. This is an efficacy rate products can meet today. It would not be in the public interest to have products available that are less effective in treating a public health epidemic. The same is true for illnesses that are life-threatening. Lesser efficacy than that which other products have established represents a threat to public health.

  In addition, there are instances when the testing of a new product involves testing versus another treatment rather than versus a placebo. Use of a placebo would be unethical. Here relative effectiveness is the only thing that can be considered.

- Section 5 also provides that the determination of effectiveness cannot include the evaluation of any use not explicitly included in the labeling.

  This appears to prohibit FDA from including, in the labeling, warnings about indications for which a product is dangerous or known not to be effective.

- Section 5 provides that the determination of effectiveness cannot include the evaluation of cost effectiveness, unless the labeling references such.

  This is FDA's current practice.

SEC.6 SCIENTIFIC ADVISORY PANELS

- Section 6 requires advisory committees to include non-voting industry and public representatives.

  Is there a problem with non-voting members attending closed meetings and or receiving confidential information?

- Section 6 provides sponsors direct contact with advisory committee members.

  This provision would allow sponsors to lobby advisory committee members.

- Section 6 requires advisory committees to meet at least 6 times a year -- three of those meeting must be face to face.

  Current advisory committee members already have problems with time commitments.

- Section 6 requires FDA to make a final determination within 30 days of an advisory committee recommendation.

  The timeframe for action on a panel recommendation is one half that required by S. 1477. Moreover, the provision assumes that all matters presented to advisory committees are susceptible to "final" determination. This is not always true. A better approach would be to require FDA to make a determination within __ days or to notify the affected persons of the reason why a decision has not been made and the timetable by which a decision will be made.

SEC.7 MARKETING APPROVAL

- Section 7 provides for third party review of new drug applications. It defines the scope of review responsibilities of accredited persons to include the review of applications to determine whether there is a "reasonable assurance" that a drug is safe and effective. Prior to 60 days before the end of the review period, the third party shall submit a report to FDA of its review and recommendation as to whether the application should be approved or denied. The recommendation of the accredited person shall be deemed to be approved by the Secretary unless the Secretary finds that there is a reasonable probability that the drug is not safe or effective. [What if the third party finds that the product application should be denied?] The Secretary shall evaluate the recommendation within 60 of receipt and in the event that the Secretary makes a finding that the drug is not safe or effective, the Secretary shall provide a detailed basis of the difference.

  FDA has no authority to decide whether third party review is appropriate under the circumstances. Even the most complicated types of reviews could go third parties if the sponsor so chooses. The third party's lack of experience and institutional knowledge in a given area (i.e., a new technology) will not prevent it from performing the review.

Unsafe and or ineffective products could therefore reach the market.

The provision is confusing re: the approval standard. It indicates that reviews shall be conducted under the standards and requirements of the Act, but it also appears to suggest a somewhat different approval standard for accredited reviews -- i.e., a "reasonable assurance" of safety and effectiveness. In addition, it is shifting the burden to FDA. It is requiring FDA to show a scientific "negative" -- this is a difficult burden for the agency to meet and would not adequately protect the public from potential harm.

The provision appears to be saying that if a third party recommends approval of an application, it is deemed approved unless FDA finds that there is a reasonable probability that the drug is not safe or effective. It further says that FDA has 60 days to make this finding and, if it does, it must provide a detailed basis for it. Sixty days is little time for the agency to thoroughly and thoughtfully review a recommendation.

SEC.8 ACCREDITATION OF THIRD PARTIES

- Subsection (a) requires the Secretary to promulgate regulations to establish procedures for accrediting third parties to review new drug applications and perform GMP inspections.

  This section does not establish how the third parties are compensated for services.

  Contracting out may slow rather than speed approval times -- for example, it will take time to train the third party reviewers; third parties do not now have the institutional knowledge needed to adequately review applications.

  Third party review raises safety issues. Because third parties lack institutional knowledge they will not be able to spot the problems that an experienced reviewer might see; FDA's in-house expertise will be lost. The end result may result in unsafe or ineffective products on the market.

  Other issues: what about tort liability? Will third parties still be in business?

- Subsection (a) further requires the Secretary to provide for accreditation through government or qualified non-government entities. This paragraph also establishes certain criteria for accreditation of third parties relating to conflict of interest, competency, and protection of information.

  From this section, it appears that the intention is not to have the Secretary accredit any particular entity, but rather to have the Secretary designate agencies or organizations who will then perform the accreditation process. It would help if FDA could add qualifications.

  The provision does not sufficiently address conflict of interest issues. What employment restriction will be imposed regarding future/past employment with a sponsor or a sponsor's competitor? Lack of clarity on conflict of interest issues could result in questionable reviews.

- Subsection (b) amends the prohibited acts section of the FDC Act to add a new section relating to actions by accredited third parties. Under proposed 301(w), a third party would violate this section if it submitted a materially false or misleading report, disclosed trade secret confidential commercial information, or accepted a bribe or performed any other corrupt act in connection with its delegated responsibility.

SEC.9 DISPUTE RESOLUTION

- Section 9 permits drug sponsors to seek dispute resolution before an advisory committee or a special government employee or a nongovernmental person who is qualified to mediate or arbitrate and who is acceptable to FDA and the applicant whenever an "impasse" exists in the review of an application with respect to any specific issue. It requires FDA to refer the dispute to an advisory committee or third party on receipt of a notification from the applicant that a dispute exists. Within 30 days of receiving the panel or third party recommendation, the Secretary must, in writing, confirm or modify the panel or third party recommendation providing reasons and reference to data before the committee or third party for any modification. The panel or third party recommendation automatically becomes FDA's unless FDA acts within 30 days of receipt of the recommendation.

  The section duplicates existing dispute resolution procedures. It has the potential for inundating the agency with requests for advisory panel meetings, which have significant resource implications.

SEC.10 GOOD MANUFACTURING PRACTICE INSPECTIONS

- Paragraph (a) amends section 704 of the FDC Act to permit third parties to conduct GMP inspections. It also amends the section to require a 10 day waiting period after any inspection (whether by a third party or FDA ?) to give the subject an opportunity to respond to any observations. The agency may not take any regulatory action following an inspection until it has reviewed a timely response from the subject of the inspection, unless there is a reasonable probability that a drug would cause serious, adverse health consequences or death or could present an unreasonable and substantial risk of injury or illness to the public health. The Secretary must also provide a detailed assessment of the response submitted by the subject of the inspection within 30 days.

  In general, requiring a 10 waiting day period, a review of the manufacturer's response, and a detailed response in 30 days may have a significant impact on agency workload. Because a warning letter is considered regulatory action, this provision would stop FDA from issuing one until this process is complete. This may not significantly slow down current time frames for issuing warning letters, but it has the potential to hamper agency action.

- A third party performing a GMP inspection does not submit a copy of its observations to the Secretary. However, if the findings indicate a serious problem, the third party must immediately notify the Secretary unless the person subject to the inspection immediately ceases distribution, notifies health professionals and drug user facilities, and undertakes all corrections identified by the third party. When such compliance is completed, the third party provides a certification of compliance, a copy of which is provided to the Secretary. The Secretary may not perform another gmp inspection for 2 years after the date of the certification unless justified by good cause.

  As it is drafted, the agency never becomes involved in compliance matters when a third party has undertaken the original inspection. The third party oversees corrections and certifies to the Secretary that the company is in compliance. The Secretary may not conduct a GMP inspection for 2 years after the date of this certification, "unless justified by good cause."

  The two year prohibition poses additional problems. Conditions can change: a change in ownership or internal management may change manufacturing conditions, or personnel may simply drift into bad habits. This is more likely if companies know that FDA may not reinspect for two years. Awareness that FDA can inspect at any time reinforces vigilance.

SEC.11 GOOD MANUFACTURING PRACTICES

- Section 11 states that all chemistry, manufacturing, and controls that comply with an approved NDA or with the opinion of an appropriate FDA official responsible for review of chemistry, manufacturing, or controls and which is reduced to writing and made part of the record shall be deemed to comply with GMPs.

ADD

- Section 11 further states that FDA cannot take action to delay or prevent the manufacture or marketing of a drug for failure to conform to gmps unless there is a reasonable probability of actual harm to public health or the Secretary determines in writing after a formal hearing that the drug is not bioequivalent, deviates from drug specifications, lacks adequate assurance that it will meet represented sterility, or has been rendered unsafe or ineffective.

ADD

SEC.12 PILOT AND SMALL SCALE MANUFACTURE

- Section 12 provides that a new drug manufactured in a pilot or other small facility may be used to demonstrate the safety and effectiveness of the product and to obtain approval prior to scaling up to a larger facility unless FDA demonstrates in writing specifying in detail the reasons, after an informal hearing, that a full scale production facility is necessary to assure safety and effectiveness.

  For most drugs, this is currently permitted by CDER and, in fact, is explicitly defined/allowed in a guideline that has been harmonized in the US, EU and Japan in the ICH process. However, it is not acceptable if it pertains to sterile drug products. Adequate sterility assurance is built into a drug or product during the manufacturing process. End-product testing (i.e., compendial sterility tests) and specifications cannot adequately provide sterility assurance. Change from a pilot plan to a larger facility often involves changes in the processes and monitoring systems used to control microbial contamination, changes in the methods and controls used to sterilize equipment, and, in some cases, changes in the processes and controls used to render the product itself sterile. Non-sterility of an injectable drug product, for example, can have severe adverse consequences for patients, including death.

For biologics, under REGO, FDA has issued guidance to clarify its policy on licensing small-scale and pilot facilities.

SEC.13 MANUFACTURING CHANGES

- Section 13 permits manufacturers of drugs and most biologics to make many changes in manufacturing without prior approval as long as there is not a resulting change in formulation or release specifications and the changes are validated and records are made available to FDA during inspections.

  Changes that do not affect formulations or release specifications, however, can still change the safety and effectiveness of a product. For example,

  (1) In the infamous "Cutter" incident with Salk polio vaccine, the company simply changed the type of filter used during manufacturing of the vaccine. No change in formulation or release specifications resulted, but the change in filter led to live virus in the product. Eleven people died and about two hundred more got polio.

  (2) A change of the method of growing cells that a biotech heart drug is made from resulted in a change in the fine structure of the drug molecule that resulted in an ineffective dose not detectable by final product testing.

  (3) Without submitting a supplement, a firm substituted an unapproved source of bulk drug for an approved source of carbamazepine, a seizure medication. The drug from the unapproved source caused the tablets to dissolve more slowly than did the product made from the approved source. The slower dissolution could result in patients absorbing the drug more slowly and thus getting smaller doses. FDA received reports of problems that may have been related to this unapproved change.

  There are additional examples of changes that the bill would allow to be made without FDA review that could raise significant safety concerns. For example, under the bill, a company could change the strain of a virus used for a vaccine such as oral polio vaccine, which could result in increased number of cases of vaccine associated polio. Similarly, a manufacturer could change the method of viral inactivation in a blood product used to treat hemophilia, which could result in a

product that could transmit hepatitis or HIV.

FDA already has undertaken to reduce the number of manufacturing changes that require pre-approval.

CDER is working diligently with industry to delineate a series of science-based recommendations for the tests and filing requirements when change occurs in the manufacture of an approved new drug. The first of this series is a guidance termed SUPAC-IR, which is intended to provide guidance for immediate release (IR) solid oral dosage forms. Further guidance documents are planned for other types of new drug dosage forms, including extended release solid oral dosage forms, liquids and semisolids, and certain biotechnology products.

CBER has created a reporting process tailored to the severity and complexity of manufacturing changes. Less stringent reporting requirements will apply when changes do not pose a substantial risk of adverse effects on product purity, potency, or safety.

CVM is taking steps towards revising its regulations to ease the process of submitting and reviewing manufacturing changes by better categorizing the types of manufacturing changes, better characterizing the procedures for handling changes, and more appropriately correlating submission and review procedures with the particular categories of changes.

SEC.14 INSULIN AND ANTIBIOTICS

- Section 14 repeals requirements for lot and batch verification.

  This is consistent with REGO.

SEC.15 NONPRESCRIPTION DRUGS

- Section 15 provides that all applications for Rx to OTC switches shall be reviewed by a single office in CDER. That office is to report directly to the Center Director.

  The result of this provision will be that reviewers who have worked on the product's NDA and have expertise in the area will not be responsible for reviewing the switch applications.

SEC.16 INFORMATION SYSTEMS

- Section 16 requires FDA to establish a system to track the status and progress of each application. The system must permit access by the applicant.

  This section raises concerns re: protecting the confidentiality of applicant information. In addition, there are resource implications re: set-up and maintenance.

SEC.17 ENVIRONMENTAL IMPACT REVIEW

- Section 17 eliminates the requirement to prepare an environmental analyses unless the Secretary demonstrates that because of extraordinary circumstances, the action will have a significant effect on the human environment and the consideration of such significant effect will directly affect the Secretary's decision and on the action.

  This is similar to Sec. 406 of the Senate bill, but the House version makes it harder to require an environmental impact review because it requires the Secretary to demonstrate that the action "will have a significant effect on the human environment."

SEC.18 APPLICATION OF STATE AND FEDERAL LAW TO THE PRACTICE OF PHARMACY COMPOUNDING

- Section 18 (1) exempts drugs that are compounded by pharmacists on the order of a licensed physician from the drug and device provisions of the Act, and (2) exempts bulk drug products or other drugs intended for use by pharmacists for compounding from all of the Act's provisions, except those that relate directly to identity, purity, or quality.

  The exemption has no constraints on the volume of compounding. This is likely to encourage large-scale manufacturing under the guise of pharmacy compounding.

  The exemption would allow bulk drug suppliers or drug manufacturers to circumvent the approval requirements of the Act by shipping bulk drug substances to pharmacies for reconstituting or other processing. A shadow industry of unapproved generic drugs will develop.

  Some might argue that the gmp requirements do not apply because they do not relate directly to the purity, quality, or identity of the drug

substance. FDA would disagree.

The exemption would allow potentially dangerous compounding. For example, sterile drugs could be compounded (even on a large scale) without regard to CGMPs for sterile products. Improperly compounded sterile products could result in serious adverse effects, including death.

SEC.19 HARMONIZATION

- Provides that the Secretary shall participate in meetings with other countries to discuss methods and approaches to reduce the burden of regulation, to harmonize regulatory requirements, and to seek appropriate reciprocal arrangements. Within 180 days of enactment the Secretary must make public a plan that establishes a framework for achieving mutual recognition of gmps. The Secretary must provide 60 day notice to the Committee before executing any agreements with foreign countries.

SEC.20 USE OF SCIENTIFIC AND MEDICAL INFORMATION

- This section amends 502 (f) to make it legal to disseminate medical texts, journal articles, and government information, and to make presentation at medical and scientific meetings about off-label uses. These activities would not constitute misbranding and would not trigger the need to file a new drug application unless the person "in addition" encourages the unapproved use of a legally marketed device through labeling, advertising,or other means of promotion. The provision also establishes that knowledge of an off-label use would not trigger any obligation for the manufacturer to change the labeling or amend a marketing application. The section also makes it permissible for sponsors of INDs and their agent to disseminate materials, make presentations, and display investigational devices at trade shows so long as the sponsor or agent does not "encourage the use of the drug".

  This section assumes that the various activities it permits are not promotion and do not encourage off-label uses or uses of investigational products. The provision will make it possible for sponsors to promote off-label uses and investigational products without filing marketing applications or INDs. The provision affirmatively eliminates incentives for manufacturers to conduct studies needed to demonstrate the safety and effectiveness of new uses and to go through the regulatory process to have off-label uses reviewed.

SEC.21 INFORMAL AGENCY STATEMENTS

- This section prohibits the Secretary from relying on policy statements, guidance documents, and similar statements to require any action to satisfy a provision of the FDC Act. It also requires the Secretary to publish notice of availability of such statements and to make them accessible electronically.

  FDA's position is that guidance documents are not binding on the agency or the public. FDA recently issued a Federal Register notice that affirms this position and has agreed to take steps to ensure that the agency and the public know and understand this principle. To the extent that this provision is reaffirming that position it is not problematic. To the extent that it is saying that FDA cannot issue guidance that explains how it believes compliance with the Act may be accomplished, it is problematic -- particularly for the industry. FDA will no longer be able to provide guidance and there is a risk of non-uniformity in the application of the laws and regulations that FDA is tasked with implementing.

SEC.22 RESEARCH AND EDUCATION; PRACTICE OF MEDICINE

- New section 908(a) requires FDA to train and educate its employees.

  FDA currently does this through staff colleges etc.

- New section 908(b) limits FDA's research activities to research directly related to the implementation of the FDC Act.

- New section 909 states that nothing in the FDC Act shall limit or interfere with a health care practitioner's authority to prescribe or administer legally marketed drugs or devices.

  Although generally FDA does not wish to interfere with the "practice of medicine," there have been instances in which the agency has taken action against physicians (e.g., where there was a concern for patients' safety, approved products were being promoted by the physicians for unapproved uses, failure to comply with the requirements for conducting clinical investigations). New section 909 could hamper FDA's ability to act in these circumstances.

SEC.23 DELEGATION OF AUTHORITY

- Section 23 provides that the authority granted under the provisions relating to the request for primary data, changes to testing protocols, IND submission requirements, and establishment of advisory panels may not be delegated.

SEC.24. JUDICIAL REVIEW

- Section 24 provides for judicial review of any written decision respecting any aspect of an investigational new drug or any written decision respecting any aspect of an application, petition, or notification for marketing review or approval for a drug.

  This provision could paralyze the agency. Current section 505(h) limits judicial review to decisions refusing to approve or withdrawing application approvals after notice to the applicant and an opportunity for a hearing. It is unclear whether this provision eliminates or retains the requirements for final agency action/exhaustion of administrative remedies -- i.e., new section 505(h)(1) appears to permit virtually unfettered judicial review but new section 505(h)(3) appears to limit the court's jurisdiction in accordance with Title 5, Chapter 7 of the U.S. Code (judicial Review -- final agency action, exhaustion of administrative remedies, etc.)

SEC. 25 PUBLICATION OF NOTICE OF DEVIATION

- Section 25 prevents the Secretary from making public or communicating to any person outside of FDA any information regarding a notice that informs a regulated person of a purported deviation from a requirement of the Act until after the Secretary has completed the investigation of such deviation.

  It is unclear what is meant by "after the Secretary has completed the investigation of the deviation." Does it mean after FDA completes a particular inspection and issues a 483? If so, the provision changes nothing in the way FDA currently does business.

  If, however the intent is that there be no disclosure until after FDA determines that further regulatory action is not indicated or until FDA closes the matter out, this is a problem. It could interfere with FDA enforcement actions because FDA would be unable to disclose, to DOJ or a court, the inspectional observations. Moreover, it would call into question the agency's long-standing practice of making 483s, warning

letters, and correspondence with regulated industry available to the public. Such a radical change in FDA's public information procedures and regulations could hamper the agency's ability to carry out its public health mission effectively. The difficulty the agency currently has with respect to prohibitions on public disclosure of information contained in marketing applications would extend to disclosure of information about observed violations and enforcement initiatives.

SEC.26 BIOLOGICAL PRODUCTS

- Section 26 establishes distinct product categories for (1) biological products, (2) blood and blood components, and (3) tissue. Each is discussed separately.

Biological Products

- Section 26(a) adds a definition of "biological product" to the FDC Act. The definition excludes blood, blood components, organs, eyes, milk, or human tissue. (It includes a derivative or blood and blood components.) A biological product is a drug within the meaning of paragraph (g) but is not a new drug within the meaning of paragraph (p)

  The definition uses the FDC Act language "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of a disease . . . in man" instead of the PHS Act language "applicable to the prevention, treatment, or cure of diseases or injuries." It also adds "or physiologic condition" after the word "disease."

  The provision would prohibit the regulation of immune milk as a biologic product.

  Because a biologic is not a "new drug" within the meaning of 201(p), the new drug provisions of the FDC Act (primarily section 505) do not automatically apply. However, section 26(b) (discussed below) sets forth a premarket approval scheme that incorporates many of the section 505 provisions.

- Section 26(b) adds new section 506, entitled "Biological Products." New section 506 provides that biological products cannot be introduced or delivered for introduction into interstate commerce unless an approved product license application is effective. The section 505 new drug procedures (except for those relating to patents, generics, and the release of safety and effectiveness data) apply. Section 506(b) requires the Secretary to harmonize PLA regulations with the NDA and GMP regulations within 2 years.

By taking the regulation of biologics out of the PHS Act, the bill is eliminating the flexibility that FDA now has to tailor the information in an application to new and emerging technologies.

There is no apparent justification for barring generic competition for this class of products.

The provision also prevents FDA from getting establishment information on vaccines.

New section 506(b)(5) provides that in the case of a derivative of blood and blood components, a product license will apply to all facilities of the applicant that are licensed under subsection (c).

New section 506(c), however, applies to blood and blood components, which by definition are not biologics. It provides that blood and blood components may be obtained and processed only in licensed facilities. The meaning of this section is therefore unclear. It may mean that blood derivative products can only be manufactured from blood source material that is obtained and processed in appropriately licensed facilities, as specified in the blood derivative product license application. This is what FDA currently requires. If this is the intent of the provision, then it should be clarified. Alternatively, it may mean that a product license for a derivative cannot be limited to products made from source materials obtained or processed only at facilities specified in the product license -- i.e., the product may be obtained or processed at any facility that is licensed. The problem with this approach is that just because a facility is licensed for blood or blood components does not mean that those blood or blood component products are appropriate for purposes of manufacturing blood derivatives -- i.e., not all plasma is an appropriate source for blood derivatives. FDA needs to know that the source material for a blood derivatives is appropriate -- otherwise the dependability of blood derivatives (such as Factor VIII for hemophiliacs) cannot be guaranteed.

Blood and Blood Components

- New section 506(c)(1) provides that blood and blood components that are introduced or delivered for introduction into interstate commerce require approval of a product license application. Blood and blood components intended for use in the diagnosis, cure, mitigation, treatment, or prevention of

a disease or physiologic condition in man are subject to (A) performance standards for safety, purity, and where applicable, potency, (B) gmps, and (C) labeling established by regulation and shall be obtained and processed only in facilities licensed by the Secretary.

It appears that both product and establishment licenses are required for blood and blood components when interstate commerce is involved, Apparently without interstate commerce, only a facility license is required.

[Note, the regulation of blood and blood components [and tissue] is under a provision entitled "biological Products" -- even though the definition of biological products does not include blood or blood components [or tissue].

- New section 506(c)(2) provides that licensed establishments are subject to FDA inspection, which may be conducted by nonprofit membership organizations that meet the requirements that the Secretary establishes for the accreditation of third parties.

  This provision may restrict third party inspections of blood establishments to "nonprofit" organizations. This is somewhat narrower than the broader eligibility requirements for other organizations under section 712. The provision may be read to mean that, unlike members of other industries, members of the blood industry may be inspected by the organizations that they themselves constitute -- a situation that would otherwise be read to be inherently impermissible under the terms of section 712 (because they have an organizational affiliation with the inspected entity under section 712(b)(3)). It also seems to rule out third party inspections of blood facilities by for-profit organizations, which would be permitted for other industries.

- New section 506(c)(3) directs the Secretary to establish licensing requirements for blood and blood component facilities and an application for such a license must be granted or denied within 90 days.

  This time period is much shorter than the PDUFA timeframes for drugs and biologics.

- New section 506(c)(3)(C) permits the Secretary to immediately suspend a license, with an informal hearing to follow, if the identified deficiencies constitute an immediate danger of serious adverse health consequences or death.

The standard for suspension is raised from the current "danger to health" standard.

- Before revoking a license, the Secretary must provide a written list of deficiencies and provide 30 days for a written response and for correction of the deficiencies. If the facility fails to provide an adequate response or makes corrections, the Secretary shall provide an opportunity for an informal hearing (within 30 days of receipt of the written response).

  The requirement for a hearing within 30 days of receipt of a written response is much shorter than that for any other FDA-regulated product category.

- The revocation or suspension of a license shall not prevent the continued use of blood or blood components that have left the control of the licensee unless the Secretary determines, as part of the revocation or suspension order, that such use represents actual harm to the public health.

  This means that FDA cannot prevent the use of products that have left the control of the licensee unless someone has actually been harmed. Even an extremely high risk of death would not permit FDA to prevent the use of such products.

Human Tissue

- Section 26(a) defines the term "human tissue" to mean a collection of human cells that are intended for use in the diagnoses, cure, mitigation, treatment, or prevention of a disease or physiological condition in man or for the augmentation of a natural bodily function. It may be combined with biologically inactive substances and subjected to any form of processing before use subject to operating standards established under section 506(a)(2)(A) [should say 506(d)(2)(A)]. Human tissue achieves its primary intended purpose through structural support or cellular function and not systemic action. It is not a drug or device and does not include blood, blood components, organs, or milk.

  The definition would include cellular and gene therapies which should be subject to the drug controls because they require safety and efficacy determinations. This may also be true of future technologies.

- Pursuant to section 26(b), which adds new section 506(d), the Secretary may regulate human tissue only if the Secretary demonstrates, in writing published in the Federal Register and after a hearing before the Commissioner, that

voluntary regulation under generally accepted standards is inadequate to protect the public health with respect to any particular type of human tissue or human tissue generally. If such a determination is made, the Secretary may establish, by regulation, operating standards for the safety of human tissue and may require human tissue to be processed only in an establishment registered in accordance with the procedures for drug establishment registration.

> The voluntary standards that are in place have not been working. There have been a number of cases where people have been harmed by contaminated tissue. **[add]** FDA has already made the determination that regulation of human tissue is necessary. This provision requires FDA to revisit the issue. This is unjustified and a waste of resources.
>
> FDA would have no recourse if a tissue bank failed to follow voluntary generally accepted scientific standards.

- Pursuant to new section 506(d)(2), any operating standards that FDA would develop must be limited to the following general requirements for the recovery, processing, storage, and shipment of human tissue: (i) requirements for universal infection control designs to prevent disease transmission; (ii) good processing practices that assure the safety, maintenance of structure, and preservation of original cellular function; and (iii) labeling requirements for identification of the type of tissue, the addition of any foreign substance, and information needed to permit tracing.

- New section 506(d)(2)(C) provides that registered establishments are subject to FDA inspection, which may be conducted by nonprofit membership organizations that meet the requirements that the Secretary establishes for the accreditation of third parties.

> This provision may restrict third party inspections of tissue establishments to "nonprofit" organizations. This is somewhat narrower than the broader eligibility requirements for other organizations under section 712. The provision may be read to mean that, unlike members of other industries, members of the tissue industry may be inspected by the organizations that they themselves constitute -- a situation that would otherwise be read to be inherently impermissible under the terms of section 712 (because they have an organizational affiliation with the inspected entity under section 712(b)(3)). It also seems to rule out third party inspections of tissue establishments by for-profit organizations, which would be permitted for other industries.

- The requirements for human tissue shall not apply to human tissue not stored for a significant period of time or not significantly processed.

- Section 26(c) provides that the requirements of the interim tissue regulation would remain in effect for a period of 18 months so that the Secretary has an opportunity to establish general controls for tissue pursuant to new section 506(d)(1), but that the Secretary shall not regulate eyes until the Secretary finds that voluntary regulation is inadequate.

  Is 18 months enough time? If not, there will be a time period during which tissue will not be regulated. There would be a significant risk of disease transmission during this time.

Enforcement Provisions

New section 506(e) provides that the Secretary may take action to enforce the requirements of gmps for blood and blood components and good operating standards for human tissue in the same manner as is done for drugs.

Re: tissue -- is this meant to say "good processing practices" or "operating standards" -- both terms used in new section 506(d)(2)(B). Good processing practices would be a type of operating standards.

- Section 26(d) amends section 301(d) and (e) to make introducing unapproved biologics and failing to keep records or reports required for biologics prohibited acts.

  Section 304, which authorizes seizure actions, has not been amended to specifically include unapproved biologics or blood products in violation of new section 506.

- Section 26(d) amends section 501 -- apparently intending to make biological products, blood, and blood components, adulterated under section 501 if they do not comply with the new section 506 requirements.

  Because section 501 begins with the phrase "a drug or device shall be deemed adulterated" and blood and blood components are not drugs or devices, they arguably could not be seized. (Unless violation of blood gmps could lead to seizure under new section 506(e)).

- The provision in current section 351 of the PHS Act, which prohibits false labeling of a biological product whether or not interstate commerce is involved has been deleted.

- There does not appear to be express statutory authority to order the recall of dangerous blood.

Other Products

- "Organs" are excluded from the definitions of biologic products and human tissue.

  Organs could be either human or animal. Accordingly, animal organs (such as baboon hearts), which could raise serious infectious disease or other safety and effectiveness concerns, would be unregulated (unless the device provisions apply).

- Computer software developed by, modified by, and used in a human tissue establishment shall not be subject to premarket clearance, but shall be validated to demonstrate that it achieves its intended purpose and shall be subject to gmps.

- Computer software developed by, modified by, and used in a blood or blood component establishment shall not be subject to premarket clearance, but shall be validated to demonstrate that it achieves its intended purpose and shall be subject to gmps.

  The latter two provisions undermine FDA's effort to improve the quality of computer software used in these setting. Such software can be critical to donor screening and testing and can result in major public health risks (e.g., HIV and hepatitis) if not adequately demonstrated to work.

- Blood components and derivatives of blood and blood components intended for use as a blood test or in the diagnosis of diseases are devices and are not drugs, biological products, or human tissue.

  If "blood tests" includes tests to screen blood for infectious agents, then it could be argued that some blood screening tests would not require product license applications (as currently is the case) but only 510(k)'s. For example, if viral antibodies or antigens isolated from blood were considered blood "derivatives" instead of "viruses" and were used to make blood screening tests (e.g., HIV antibody or antigen tests) then only the device authorities would apply.