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001. letter	Christopher Jennings to Constituent [partial] (1 page)	12/30/1996	b(6)
002. letter	Christopher Jennings to Constituent [partial] (1 page)	12/30/1996	b(6)
003. letter	Constituent to Chris Jennings (2 pages)	12/16/1996	b(6)

COLLECTION:
Clinton Presidential Records
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FOLDER TITLE:
FDA Reform 1996 [7]

2014-0046-S
rc1405

RESTRICTION CODES

Presidential Records Act - [44 U.S.C. 2204(a)]

P1 National Security Classified Information [(a)(1) of the PRA]
P2 Relating to the appointment to Federal office [(a)(2) of the PRA]
P3 Release would violate a Federal statute [(a)(3) of the PRA]
P4 Release would disclose trade secrets or confidential commercial or financial information [(a)(4) of the PRA]
P5 Release would disclose confidential advice between the President and his advisors, or between such advisors [a)(5) of the PRA]
P6 Release would constitute a clearly unwarranted invasion of personal privacy [(a)(6) of the PRA]

C. Closed in accordance with restrictions contained in donor's deed of gift.
PRM. Personal record misfile defined in accordance with 44 U.S.C. 2201(3).
RR. Document will be reviewed upon request.

Freedom of Information Act - [5 U.S.C. 552(b)]

b(1) National security classified information [(b)(1) of the FOIA]
b(2) Release would disclose internal personnel rules and practices of an agency [(b)(2) of the FOIA]
b(3) Release would violate a Federal statute [(b)(3) of the FOIA]
b(4) Release would disclose trade secrets or confidential or financial information [(b)(4) of the FOIA]
b(6) Release would constitute a clearly unwarranted invasion of personal privacy [(b)(6) of the FOIA]
b(7) Release would disclose information compiled for law enforcement purposes [(b)(7) of the FOIA]
b(8) Release would disclose information concerning the regulation of financial institutions [(b)(8) of the FOIA]
b(9) Release would disclose geological or geophysical information concerning wells [(b)(9) of the FOIA]

R. Amendments
Gregg *

AMENDMENT NO. ____ Calendar No. ____

Purpose: To modify the food health claim provisions of the Federal Food, Drug, and Cosmetic Act relating to claim requirements and authorization for use of a claim.

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

S. 1477

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

Referred to the Committee on _____
and ordered to be printed

Ordered to lie on the table and to be printed

AMENDMENT intended to be proposed by Mr. GREGG

Viz:

On page 115, insert after line 17, the following:

SEC. 903. HEALTH CLAIMS OF FOOD PRODUCTS.

(a) AUTHORIZATION OF HEALTH CLAIMS BY AUTHORITATIVE GOVERNMENT SCIENTIFIC BODY.—Section 403(r)(3) (21 U.S.C. 343(r)(3)) is amended by adding at the end thereof the following new subparagraph:

"(C) Notwithstanding the provisions of subparagraphs (A)(i) and (B), a claim of the type described in paragraph (1)(B) which is not authorized by the Secretary

in a regulation promulgated in accordance with subparagraph (B) shall be authorized and may be made if—

"(i) an authoritative scientific body of the United States Government with official responsibility for public health protection or research directly relating to human nutrition (such as the National Institutes of Health or the Centers for Disease Control and Prevention), the National Academy of Sciences, or subdivisions of the scientific body or the National Academy of Sciences, have published statements, conclusions, or recommendations currently in effect recognizing that the relationship between the nutrient and disease or health-related condition to which the claim refers is supported by the pertinent scientific evidence; and

"(ii) the manufacturer or distributor of the food for which such claim is made has submitted to the Secretary at least 90 days before the first introduction of such food into interstate commerce a notice of claim, including a concise description of the basis upon which such manufacturer or distributor relied for determining that the requirements of clause (i) have been satisfied.".

(b) DIETARY SUPPLEMENTS.—Section 403(r)(5)(D) (21 U.S.C. 343(r)(5)(D)) is amended to read as follows:

"(D) Notwithstanding subparagraph 403(r)(6), a subparagraph (1)(B) claim made with respect to a dietary supplement within the meaning of section 201(ff) shall be subject to section 403(r)(3) to the same extent as other foods.".

(c) CONFORMING AMENDMENT.—Section 403(r)(1)(B) (21 U.S.C. 343(r)(1)) is amended by inserting a period after "subparagraph (3)" and striking "or 5(D).".

#3

AMENDMENT NO. ____ Calendar No. ____

Purpose: To modify the provisions of the Federal Food, Drug, and Cosmetic Act to require the Secretary to apply a negligible or insignificant risk standard in making a safety determination on whether an animal drug, food additive, or color additive induces cancer.

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

S. 1477

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

Referred to the Committee on _____
and ordered to be printed

Ordered to lie on the table and to be printed

AMENDMENTS intended to be proposed by Mr. GREGG

Viz:

On page 114, between lines 4 and 5, insert the following:

SEC. 807. ANIMAL DRUG SAFETY.

Section 512(d)(1)(I) (21 U.S.C. 360b(d)(1)(I)) is amended by striking "if the Secretary finds that," and all that follows through "derived from the living animals;" and inserting the following: "if such drug presents, taking

into account the susceptibility of infants and children, a negligible or insignificant risk;".

On page 114, between lines 9 and 10, insert the following:

SEC. 902. FOOD AND COLOR ADDITIVES.

(a) FOOD ADDITIVE SAFETY.—Section 409(c)(3)(A) (21 U.S.C. 348(c)(3)(A)) is amended by striking "as an ingredient of feed for animals" and all that follows through "the living animal; or" and inserting "that presents, taking into account the susceptibility of infants and children, a negligible or insignificant risk; or".

(b) COLOR ADDITIVE SAFETY.—Section 721(b)(5)(B) (21 U.S.C. 379e(b)(5)(B)) is amended by striking "as an ingredient of feed for animals" and all that follows through "derived from the living animal." and inserting the following: "that presents, taking into account the susceptibility of infants and children, a negligible or insignificant risk.".

On page 114, line 10, strike "**SEC. 902.**" and insert "**SEC. 903.**".

2. Third Party Review of Food Additives

Would require FDA to contract with outside organization to review applications for approval of food additives.

This provision has several fatal flaws. First, the net effect of the provisions is to shift the burden to FDA to prove the additive should not be approved; right now, burden is on the manufacturer to prove it should be approved. Second, it precludes the FDA from looking at all relevant information by putting a cut-off date in the review process after which FDA can only consider data if submitted the applicant. Third, the system, which calls for concurrent review by FDA and the third party, with FDA paying the third party, seems inefficient at best and wasteful of scarce resources at worst. Why pay some one else to do the work (with scarce government resources) if FDA has to do it too? An interesting twist on reinventing government.

3. Preemption

Would preempt all state and local requirements relating to foods and cosmetics, with a very narrow exception if regulations are issued.

This is aimed a California labeling law, Proposition 65, and some other state labeling laws that companies do not like. It sweeps way too broadly to preempt in areas that states have filled in because FDA is too slow (Gulf coast seafood warnings) or because the consumers of a particular state want particular information (Kosher labeling (a Massachusetts requirement), freshness labeling, unit pricing). It also may preempt state tort law.

AMENDMENT NO. ____ Calendar No. ____

Purpose: To modify the provisions of the Federal Food, Drug, and Cosmetic Act to provide for an alternative approval process for use of direct food additives and color additives.

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

S. 1477

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

Referred to the Committee on _____
and ordered to be printed

Ordered to lie on the table and to be printed

AMENDMENTS intended to be proposed by Mr. GREGG

Viz:

On page 114, between lines 9 and 10, insert the following:

SEC. 902. REGULATION OF DIRECT HUMAN FOOD AND COLOR ADDITIVES PETITION REVIEW.

(a) CONTENT OF PETITION.—Section 409(b)(2) (21 U.S.C. 348(b)(2)) is amended by adding at the end thereof the following flush sentence:

"In a case in which the petition relates to a direct human food additive, the petition may also contain a request for

a third party consideration under subsections (j) through (o).".

(b) NOTICE OF REGULATION.—Section 409(b)(5) (21 U.S.C. 348(b)(5)) is amended to read as follows:

"(5) Notice of the regulation proposed by the petitioner shall be published in general terms by the Secretary within 30 days after the filing of a petition. The notice shall include the name of the food additive, the intended use of the additive, and if applicable, shall provide that the petition shall be reviewed pursuant to third party consideration procedures.".

(c) THIRD PARTY CONSIDERATION.—

(1) PETITION.—Section 409(b) (21 U.S.C. 348(b)) is amended by adding at the end thereof the following new paragraph:

"(6) Upon request of the petitioner set forth in the petition for a direct human food additive under paragraph (2), the Secretary shall accept the petition for third party consideration and the petition shall be subject to the procedures set forth in subsections (j) through (o).".

(2) PROCEDURES.—Section 409 (21 U.S.C. 348) is amended by adding at the end thereof the following new subsections:

"Third Party Consideration

"(j)(1) Upon the publication of a notice of filing of a petition for a food additive that includes a notification that the petition shall be reviewed pursuant to third party consideration procedures, the Secretary shall promptly, but not later than 30 days after the publication of the notice of filing, place on public display in a location maintained for the examination of public documents a complete copy of the data and information (except for data and information that are trade secrets or confidential commercial information) included in the petition that relate to the safety and functionality of the additive.

"(2) Upon the publication of a notice of filing of a petition for a food additive that includes a notification that the petition shall be reviewed pursuant to third party consideration procedures, the Secretary shall promptly, but not later than 30 days after the publication of the notice of filing, provide a complete copy of the data and information contained in the petition that relate to the safety and functionality of the additive to an independent review organization with which the Secretary has entered into an agreement under subsection (o). The Secretary shall determine which organization shall conduct the review.

"(3)(A) The Secretary and the independent review organization shall review the petition for a period not to exceed 6 months from the notice of filing.

"(B) During the 6-month review period described in subparagraph (A), the Secretary and the independent review organization may communicate with each other or with the petitioner in person or in writing. A complete record of all such communications and the responses of the petitioner shall be maintained by the Secretary.

"(C) Within the 6-month period provided for review of the petition, the Secretary and the independent review organization shall advise the petitioner in writing of all significant issues relevant to the evaluation of the petition.

"(D) In evaluating a petition under this subsection, neither the Secretary nor the independent review organization may consider any data or information that is not filed with the Secretary within 6 months of the notice of filing or presented at a public meeting under subsection (k), unless such data and information were provided by the petitioner.

"Public Meetings Relating to Third Party Petition Reviews

"(k)(1) Within 60 days of the expiration of the 6-month review period described in subsection (j)(3), or the

Secretary and the independent review organization shall convene a public meeting to consider the petition.

"(2) The petitioner shall have the right to appear and to present testimony and to respond to questions. Members of the public shall have the right to appear and present testimony concerning the safety and functionality of the additive.

"(3) A verbatim record of the hearing shall be maintained. The meeting shall be chaired by a representative of the independent review organization.

"Recommendations Relating to Third Party Petition Reviews

"(l)(1)(A) Within 60 days of the completion of the public meeting convened under subsection (k), the independent review organization shall provide to the Secretary a report and recommendations, together with a statement of the reasons or basis for the recommendations. The independent review organization shall recommend that the petition be approved if a fair evaluation of the data and information before the independent review organization establishes that the proposed use of the additive under the conditions of use to be specified in the regulation will be safe within the meaning of section 201(u).

"(B) Not later than 30 days after the date of the receipt of a report and recommendations under this para-

graph, the Secretary shall provide a copy of the report and recommendations to the petitioner and shall place a copy of the report and recommendations on public display in a location maintained by the Secretary for the examination of public documents, except that trade secret and confidential commercial data and information shall not be disclosed.

"(2) The independent review organization may defer submission of the report and recommendations required under paragraph (1) for up to 180 days with the agreement of the petitioner.

"(3) A report and recommendations from the independent review organization that conclude that an additive has been demonstrated to be safe shall create a presumption of approvability.

"Action on the Recommendations Relating to Third Party Petition Reviews

"(m) Not later than 90 days after the receipt by the Secretary of a report and recommendations under subsection (l), the Secretary shall either—

"(1) issue a regulation providing for the use of the additive under the conditions of use found by the independent review organization to be safe; or

"(2) reject the report and recommendations if there is substantial evidence to demonstrate that the

additive has not been shown to be safe under the intended conditions of use.

The decision of the Secretary to reject the report and recommendations of the independent review organization shall set forth the evidence on which the Secretary relies and the basis and rationale for the decision. A copy of the decision of the Secretary to reject the report and recommendations shall, prior to the expiration of the 90-day period described in this paragraph, be provided to the petitioner and independent review organization and placed on public display in a location maintained by the Secretary for the examination of public documents.

"Judicial Review for Third Party Petition Reviews

"(n) Upon an issuance by the Secretary of a regulation under subsection (m)(1)(A), a rejection under subsection (m)(1)(B), or the failure of the Secretary to act within 90 days of receipt of a report and recommendations under subsection (l), any person adversely affected by such action of the Secretary, and without regard to the provisions of subsection (f), may obtain judicial review in accordance with subsection (g).

"Independent Review Organization

"(o)(1) The Secretary shall enter into an agreement with at least 3 organizations qualified to evaluate petitions seeking approval for the use of food and color additives

to review such petitions and to make reports and recommendations on such petitions. In assessing the qualifications of any such organization, the Secretary shall consider, among other relevant factors—

"(A) the scientific and technical capabilities of the organization and the persons employed by the organization;

"(B) the experience of the organization in evaluating petitions or similar applications for approval, or data of the type typically contained in petitions;

"(C) the ability of the organization to protect the confidentiality of trade secret and confidential commercial information;

"(D) the ability of the organization to conduct balanced and objective reviews of petitions and to be free of bias; and

"(E) the ability of the organization to conduct competent and timely reviews of petitions.

"(2) The agreement between the Secretary and an independent review organization shall require the organization to conduct its reviews in accordance with the provisions of this section and regulations issued by the Secretary to implement this section. In performing its responsibilities under an agreement with the Secretary, such or-

ganization shall not be subject to the provisions of the Federal Advisory Committee Act (5 U.S.C. App. 2).

"(3) The Secretary shall publish annually the fee schedule in effect for each independent review organization for the review of petitions in the 12-month period succeeding the notice of the fee schedule. The Secretary shall also prescribe appropriate terms for payment by a petitioner to a independent review organization, including terms to ensure that the independent review organization completes the tasks required under this section within the time periods required by this section and that payments by the petitioner are contingent upon completion of such tasks within the required time periods.".

(d) COLORS.—Section 721 (21 U.S.C. 379e) is amended by adding at the end thereof the following new subsection:

"Third Party Consideration of Petitions

"(g) Notwithstanding any provision to the contrary in this section or any other provision of this Act, any person may file with the Secretary a petition that requests the issuance of a regulation authorizing the use of a color in or on a food, drug, device, or cosmetic and that includes a request for a third party consideration under section 409(b)(2)(F). Upon the acceptance for filing of any such

petition, the provisions of section 409 (j) through (o) with respect to third party consideration shall apply.".

On page 114, line 10, strike "**SEC. 902**" and insert "**SEC. 903**".

On page 114, line 11, strike "is" and all that follows through "amended" on line 12 and insert ", as amended by section 903(c)(3)(B), is further amended".

On page 114, line 14, strike "ALTERNATIVE APPROVAL PROCEDURE" and insert "ALTERNATIVE APPROVAL PROCEDURE FOR INDIRECT FOOD ADDITIVES".

On page 114, line 15, strike "(j)(1)" and insert "(p)(1)".

5. 5 Year Market Exclusivity for Food Additives

Would grant 5 years monopoly to any one with approval of a direct food additive (i.e., a food ingredient).

This provision has not been the subject of any discussion, debate or hearings. As we read it, this provision would provide greater protection then a patent protection, since it seems to apply to substances that can't be patented. If industry can make a case -- which they have not yet done -- that they should have some patent term restoration due to premarket clearance requirements, that would be the time to consider the issue.

AMENDMENT NO. ____ Calendar No. ____

Purpose: To provide for research and development of direct human food additives and color additives.

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

S. 1477

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

Referred to the Committee on _____
and ordered to be printed

Ordered to lie on the table and to be printed

AMENDMENT intended to be proposed by Mr. GREGG

Viz:

On page 115, insert after line 17, the following:

SEC. 903. RESEARCH AND DEVELOPMENT FOR DIRECT HUMAN FOOD ADDITIVES AND FOR COLOR ADDITIVES.

Section 409(c) (21 U.S.C. 348(c)) is amended by adding at the end thereof the following new paragraph:

"(6) Effective for 5 years following the publication in the Federal Register of an order or regulation permitting the use of a direct human food additive under this section or a color additive under section 721, no person

(other than the person who submitted the petition for the order or regulation) may introduce or deliver for introduction into interstate commerce the additive unless—

"(A) such person submits its own petition for the additive supported by data and information from investigations conducted by or on behalf of such person and obtains an order or regulation for the additive; or

"(B) the original petitioner agrees in writing that such person may introduce the additive or deliver the additive for introduction into interstate commerce.".

Talking Points Against Preemption of State Authority

- The Food, Drug, and Cosmetic Act currently honors the doctrine of federalism by permitting state governments to establish food labeling rules for the protection of their citizens.

- The Gregg "national uniformity" amendment would remove this authority from the states and centralize control of food labeling regulation in the hands of the FDA.

- It is ironic that it would do so without honoring the principles supported by the Republican leadership in S.1629 which would put in place procedural safeguards that Congress should honor before preempting state laws. For example, this committee has held no hearings on these preemption provisions, which would be required under S.1629. Indeed, the National Conference of State Legislatures has come out against the uniformity amendemnts.

- The Gregg amendment would void a number of essential state food labeling laws that fill in major gaps in FDA regulation. Such laws include:

  Louisiana requirements for warning labels on raw shellfish (to warn against a deadly virus);

  Massachusetts and New York requirements for the labeling of Kosher foods (more than 20 states have kosher food labeling) ;

  Michigan requirements for the labeling of recycled bottles;

  Maryland requirements for unit pricing of foods;

  Vermont requirements for the labeling of dairy products produced by milk cows treated with BST;

  California requirements for the labeling of organic foods;

  Washington state requirements for the labeling of "previously frozen" fish;

  Minnesota requirements for freshness dating of foods.

- These state laws provide consumers with important protections in areas where the FDA has insufficient resources to act and represent a legitimate exercise of state authority.

- Transferring authority from the states to the FDA is especially inappropriate in an era of declining federal resources. The Gregg amendment is also ironic given that many members of Congress are trying to reduce the role of the federal government and return more power to the states.

AMENDMENT NO. ____ Calendar No. ____

Purpose: To provide for national uniformity in the regulation of adulterated and misbranded foods and cosmetics.

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

S. 1477

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

Referred to the Committee on _____
and ordered to be printed

Ordered to lie on the table and to be printed

AMENDMENT intended to be proposed by Mr. GREGG

Viz:

On page 115, insert after line 17 the following:

SEC. 903. NATIONAL UNIFORMITY RELATING TO THE ADULTERATION AND MISBRANDING OF FOODS AND COSMETICS.

Chapter IV (21 U.S.C. 341 et seq.) is amended by adding at the end the following new section:

"SEC. 414. NATIONAL UNIFORMITY RELATING TO THE ADULTERATION AND MISBRANDING OF FOODS.

"(a) IN GENERAL.—Except as provided in subsection (c), no State or political subdivision of a State may directly or indirectly establish or continue in effect under any authority any requirement (including a prohibition) for a food for human use of the type authorized or required under the adulteration or misbranding provisions of this Act, and the administrative implementation thereunder that is not identical to a requirement imposed under the authority of this Act.

"(b) NOTIFICATION REQUIREMENT.—

"(1) IN GENERAL.—Except as provided in subsection (c), no State or political subdivision of a State may directly or indirectly establish or continue in effect under any authority any notification requirement for a food that—

"(A) provides for disclosure of the constituents, source, or method of production or processing of the food; or

"(B) provides for a warning concerning the safety of the food or of any component or packaging thereof,

unless such a notification requirement has been prescribed under authority of this Act and the notifica-

tion requirement prescribed by the State or political subdivision is identical in all respects to the notification requirement prescribed under this Act.

"(2) DEFINITIONS.—

"(A) NOTIFICATION REQUIREMENT.—As used in this subsection, the term 'notification requirement' includes any requirement relating to the dissemination of information about a food in any manner, such as by labels, labeling, posters, public notices, advertising, or other means of communication.

"(B) WARNING.—As used in this subsection, the term 'warning' means any statement, vignette, or other representation that indicates, directly or by implication, that the food presents or may present a hazard to human health or safety.

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

"(1) is justified by compelling and unique local conditions;

"(2) protects an important public interest that would otherwise be unprotected;

"(3) would not cause any food to be in violation of any applicable requirement or prohibition under Federal law; and

"(4) would not unduly burden interstate commerce.".

TITLE X—COSMETICS

SEC. 1001. NATIONAL UNIFORMITY RELATING TO THE ADULTERATION AND MISBRANDING OF COSMETICS.

Chapter VI (21 U.S.C. 361 et seq.) is amended by adding at the end thereof the following new section:

"SEC. 604. NATIONAL UNIFORMITY TO THE ADULTERATION AND MISBRANDING OF COSMETICS.

"(a) IN GENERAL.—Except as provided in subsection (c), no State or political subdivision of a State may directly or indirectly establish or continue in effect under any authority any requirement (including a prohibition) for a cosmetic of the type authorized or required under the adulteration or misbranding provisions of this Act, and the administrative implementation thereunder, that is not identical to a requirement imposed under the authority of this Act.

"(b) NOTIFICATION REQUIREMENT.—

"(1) IN GENERAL.—Except as provided in subsection (e), no State or political subdivision of a State may directly or indirectly establish or continue in effect under any authority any notification requirement for a cosmetic that—

"(A) provides for disclosure of the constituents, source; or

"(B) method of production or processing of the cosmetic, or provides for a warning concerning the safety of the cosmetic or of any component or packaging thereof,

unless such a notification requirement has been prescribed under authority of this Act and the notification requirement prescribed by the State or political subdivision is identical in all respects to the notification requirement prescribed under this Act.

"(2) DEFINITIONS.—

"(A) NOTIFICATION REQUIREMENT.—As used in this subsection, the term 'notification requirement' includes any requirement relating to the dissemination of information about a cosmetic in any manner, such as by labels, labeling, posters, public notices, advertising, or other means of communication.

"(B) WARNING.—As used in this subsection, the term 'warning' means any statement, vignette or other representation that indicates, directly or by implication, that the cosmetic presents or may present a hazard to human health or safety.

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

"(1) is justified by compelling and unique local conditions;

"(2) protects an important public interest that would otherwise be unprotected;

"(3) would not cause any cosmetic to be in violation of any applicable requirement or prohibition under Federal law; and

"(4) would not unduly burden interstate commerce.".

AMENDMENT NO. ____ Calendar No. ____

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

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

S. 1477

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

Referred to the Committee on _____
and ordered to be printed

Ordered to lie on the table and to be printed

AMENDMENT intended to be proposed by Mr. GREGG

Viz:

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

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

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

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

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

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

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

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

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

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

4. Health Claims

Would open up the Nutrition Education and Labeling Act's provision on health claims, which now must be approved by FDA. Would let companies put claims on label that have been recommended by other government bodies.

There's a kernel of sense in this proposal, but it is not properly fleshed out. While it makes sense to say that FDA should consider or react to other-science based government agencies' recommendations about health claims, FDA's expertise is needed in making sure that the risks and benefits of the claim are properly considered before the claim is allowed on food. The other agencies, such as NIH or CDC, are not charged with this responsibility and experience shows that their recommendations cannot and should not go right into the market place.

A good example is a claim FDA just approved for with folic acid which has been shown to reduce neural tube birth defects. CDC began recommending in 1992 that women of child bearing age consume adequate amounts of folic acid in order to reduce the risk of certain birth defects. When the FDA began considering to allow health claims for foods containing folic acid, it noted that over consumption of this nutrient could mask the symptoms of anemia in persons with a vitamin B-12 deficiency, thus permitting irreversible neurological damage in certain individuals to progress unknowingly. This factor was not considered fully by CDC when it issued their recommendation. FDA authorized health claims for folic acid only after determining steps that could be taken to avoid this situation from occurring. Had food companies been permitted to make health claims for folic acid based on the CDC findings alone, serious public health consequences could have resulted.

We have a counter-proposal that would trigger FDA action.

Gregg Health Claims Amendments

Background:

- The Nutrition Labeling and Education Act (NLEA) requires that claims on food labels such as "This cereal is high and fiber and can help reduce the risk of cancer" be pre-cleared by the FDA and be used only for products that meet guidelines for a healthful diet. The NLEA was passed by Congress with widespread bi-partisan support and signed into law in 1990 by President Bush.

- Since the NLEA became effective, the FDA has approved a variety of legitimate health claims that help consumers maintain proper dietary practices. These claims now appear on the labels of food industry including: Campbell Soup, Pillsbury, Kellogg, and Quaker Oats (see Attachment One). Furthermore, the FDA is considering additional health claims for sugar-free foods, dairy products, and cereal grains such as oats.

- In brief, the NLEA is working. Numerous health claims on food labels have been approved by FDA while misleading claims have been eliminated from the marketplace.

Talking Points:

- Provisions in the Gregg amendments that would allow food companies to base health claims on the findings of government agencies other than the FDA are unworkable and unwise. Two example demonstrate how unworkable this provision will be.

- **Folic Acid Claim:** The CDC began recommending in 1992 that women of child bearing age consume adequate amounts of folic acid in order to reduce the risk of certain birth defects. When the FDA began considering to allow health claims for foods containing folic acid, it noted that over consumption of this nutrient could mask the symptoms of anemia in persons with a vitamin B-12 deficiency, thus permitting irreversible neurological damage in certain individuals to progress unknowingly. This factor was not considered fully by the CDC. FDA authorized health claims for folic acid only after determining steps that could be taken to avoid this situation from occurring. Had food companies been permitted to make health claims for folic acid based on the CDC findings alone, serious public health consequences could have resulted.

- **High Fiber/High sodium**: In the 1980s, the National Cancer Institute began promoting the benefits of consuming a high fiber, low fat diet that could reduce the risk of colon cancer. In 1987, the Campbell Soup company began citing these NCI findings in ads for certain canned soups that were high in fiber and low in fat. The soups, however, were also high in sodium, and high sodium diets can increase the risk of high blood pressure and heart attack. The NCI urged the company to drop the claim, but the company refused. The NCI has no regulatory authority so it could not take any action against Campbell Soup. A coalition of state attorney generals, acting under state law, finally halted the ads in 1989.

- Case studies like these demonstrate that permitting food companies to base health claims on the scientific findings of other government agencies is unworkable and could endanger the public's health.

- Since the NLEA became effective, the FDA has approved a variety of legitimate health claims that help consumers maintain proper dietary practices. These claims now appear on the labels of food industry

including: Campbell Soup, Pillsbury, Kellogg, and Quaker Oats (see Attachment One). Furthermore, the FDA is considering additional health claims for sugar-free foods, dairy products, and cereal grains such as oats.

- In brief, the NLEA is working. Numerous health claims on food labels have been approved by FDA while misleading claims have been eliminated from the marketplace.

- The Gregg amendment is opposed by a coalition of 20 public health, consumer and medical organizations including the American Heart Association, the American Cancer Society, the American Association of Retired Persons and Consumers Union.

- The FDA reform bill hearings held by the Senate Labor and Human Resources Committee did not examine this matter and the Committee should not entertain such controversial amendments that have not been the focus of hearings.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

OFFICE OF THE ASSISTANT SECRETARY FOR LEGISLATION
OFFICE OF HEALTH LEGISLATION

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FDA letter for 4PM markup

TO OMB

DRAFT LETTER TO SEN. KASSEBAUM AND KENNEDY

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

Privatizing all device review through a mandatory "pilot" project

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

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

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

this so-called pilot project the expertise and knowledge base of the device review program could very well be damaged.

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

Unreasonable review time periods guarantee that critical public health protection activities will be privatized

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

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

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

Eliminating FDA's MedGuide Program

Finally, the bill stops the FDA's MedGuide program. This program is our effort to work with private companies to ensure that consumers get accurate information about prescription drugs --

information about how to take the drug, side effects, and dangerous interactions with foods or other drugs. Misuse of prescription drugs accounts for many injuries and deaths and costs about $20 billion in health care costs per year. Since drug companies are permitted to promote prescription drugs, FDA should be permitted to require that consumers receive accurate information.

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

Sincerely,

David A. Kessler, M.D.

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

09-Dec-1996 02:18pm

TO: Sally Katzen
TO: Jonathan D. Winer
TO: Elizabeth E. Drye
TO: John F. Morrall III

FROM: Daniel J. Chenok
Office of Mgmt and Budget, OIRA

SUBJECT: Reform Efforts, Drug User Fees Could Be Affected By Resignat

Reform Efforts, Drug User Fees Could Be Affected By Resignation
Members of the 105th Congress are expected to consider reauthorization of the Prescription Drug User Fee Act as well as reanimate the Food and Drug Administration reform debate, but it is unclear what impact FDA Commissioner David A. Kessler's plans to resign will affect these issues, sources told BNA.
The resignation announcement will make an already busy year even busier, Carl B. Feldbaum, president of the Biotechnology Industry Organization (BIO), told BNA Dec. 5, but appeared optimistic about the prospects for the user fee reauthorization and possible reform bills, which he characterized as FDA modernization vehicles.
Kessler announced his intention to resign on Nov. 25, citing a desire to return to private life as soon as his successor can be chosen.
According to Feldbaum, BIO, FDA, and the Pharmaceutical Research and Manufacturers of America currently are meeting to discuss the conditions under which phase two of the user fee act will proceed. All three parties want to see the act continued, so discussion is focusing on establishing an enforceable mechanism for reducing both drug review times and overall drug development times, he said. Adding the element of reduced development times would satisfy some concerns raised by industry and Congress during last year's reform debate.
The original act aimed to reduce the time FDA took to complete its review of drug applications and, according to Kessler, FDA has achieved the review goals before the statutory deadlines. Since industry will contribute $88 million in fiscal 1996 to support full-time employees FDA needs to meet its obligations under the user fee act, the agency is interested in reaching agreement, Feldbaum said.
Once the user fee act is addressed, Congress need only take up legislation on a few other issues, such as clarifying off-label use and export reform from the bill (S 1477) sponsored by retiring Sen. Nancy L. Kassebaum (R-Kan), Feldbaum said. He also reported that FDA might be crafting its own reform proposal.
Reform-Minded Nominee Needed
Kessler's successor needs to be a person of stature, character, and credibility, who can withstand the scrutiny of high-profile confirmation hearings and ``stare down the ideologues in Congress and the theologians at

FDA,'' Feldbaum said. Candidates from inside the agency should not be dismissed automatically, he said, but a new commissioner should have a scientific and managerial background and be reform-minded. Someone with a mixture of FDA, industry, and academic experience would be ideal, provided he or she can hit the ground running, according to Feldbaum.

The importance to industry of a candidate- commissioner who is open to agency change was underlined by Jim Benson, senior vice president for product, technology, and regulatory affairs at the Health Industry Manufacturers Association, and by Jeffrey J. Kimbell, executive director of Medical Device Manufacturers Association.

MDMA is scheduled to meet with Bruce Burlington, director of FDA's Center for Devices and Radiological Health, Kimbell said, indicating one topic of discussion would center on the reforms FDA can carry out administratively and what must be done legislatively by Congress. Although there have been some improvements made during Kessler's tenure in areas the agency regulates, Kessler's attention to the tobacco issue has affected every center, Kimbell said. He also said, however, that Burlington was doing a good job and should stay on as CDRH director.

President Clinton likely will choose a commissioner who can make changes, which offers hope for FDA reform, Benson told BNA. He said he believes the Clinton administration will want to choose a candidate who is acceptable to Republicans so the confirmation process and legislation does not bog down in Congress. The worst possible scenario would be for Kessler to be kept on as a lame duck commissioner, Benson said.

Administration's Track Record

Sidney Wolfe, director of Public Citizen's Health Research Group, told BNA it might be difficult for the administration to find someone acceptable to industry and consumer groups. If the appointee fails to measure up to expectations, the White House will lose ground with consumers. However, a competent, knowledgeable individual could offend industry and Congress, he said.

George M. Burditt, Burditt & Radzius, Chicago, believes that Kessler's departure will have little effect on agency policies, however. FDA is much bigger than one individual, he said, and there are staff in place to carry through on the positive changes, including FDA's new partnership with industry effort.

Despite Kessler's outright opposition to FDA reform measures introduced in the last Congress, more FDA legislation passed in 1996 than ever before, an FDA expert said, citing the passage of bills on export reform, animal drugs, and pesticide levels in foods.

This leaves FDA reform as the only piece of legislation the new Congress will need to take up, the expert said, predicting that a reform bill will have better chances of passing under a new commissioner. In fact, since the agency wants the user fee act to be reauthorized, FDA could face a quid pro quo situation if reauthorization depends on acceptance of a reform proposal.

The expert predicted that the House Commerce Committee would take the lead on reintroducing the FDA reform debate unless, Sen. Dan Coats (R-Ind) is appointed chairman of a Labor health subcommittee, which has been rumored. In fact, a House FDA reform bill could be introduced the first day of the new Congress, the expert said.

Foreign Investment

FDA OFFICE OF WOMEN'S HEALTH ANNOUNCES
WOMEN'S HEALTH: TAKE TIME TO CARE

The FDA's Office of Women's Health is pleased to announce that it is developing a new public education effort, *Women's Health: Take Time to Care*. This program will offer FDA's expertise to urge women to take care of themselves in a number of important areas. The primary target audience will be mid-life to older women, with a special emphasis on women who are medically underserved.

The *Take Time to Care* theme reflects the phenomenon that women often do not take sufficient time to care for their own health, especially when they are busy with job, home, church, and community-related responsibilities and the care of others, such as husbands, children, and parents.

Educational messages that have appeal and resonance with women, and which fall within FDA's mission, will be carried to women across the country through brochures, posters, and public service announcements. Possible messages include:

- *Take Time to Care: Eat Smart* -- This message will encourage women to use the FDA food label in planning a healthy diet and selecting foods.

- *Take Time to Care: Get Screenings* -- This message will encourage women to talk to their doctors about mammograms, pap smears, and other tests, and to have these tests for early detection.

- *Take Time to Care: Use Medicine Wisely* -- This message will urge women to gather information about their medications, and especially about drug interactions, where some of the most serious problems can arise.

The FDA Office of Women's Health will form partnerships on *Take Time to Care* with our sister agencies within the Public Health Service and with other government entities; with national health and consumer organizations, including an emphasis on organizations that reach underserved communities around the country. These partnerships will have a multiplier effect so that the maximum number of American women can benefit from this program. Our partners will be provided with consumer education materials, which will include brochures on each one of the program's primary health messages, a poster designed to be a visual reminder, and print/radio public service announcements to deliver the *Take Time to Care* advice across the country.

The formal launch of this program is scheduled for early Fall, 1996.

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Elizabeth Drye
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FOLDER TITLE:
FDA Reform 1996 [7]

2014-0046-S
rc1405

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THE WHITE HOUSE

WASHINGTON

December 30, 1996

(b)(6) [0013]

Dear Mr. and Mrs. (b)(6)

Thank you for writing about the need to speed up the approval process of iodo–deoxydoxorubicin (I–DOX) for use in clinical trials.

In order to give your concerns the appropriate attention, I have forwarded your letter to Elizabeth Drye, chief of staff to the Domestic Policy Council, for review. You can be sure that she will give your thoughts careful consideration.

Again, thank you for writing,

Sincerely,

Christopher C. Jennings
Special Assistant to the President
for Health Policy

cc: Elizabeth Drye

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for Health Policy

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Domestic Policy Council
Elizabeth Drye
OA/Box Number: 10452

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A monthly update of developments in cancer treatment and research

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New Hope for Amyloidosis—Serendipity Strikes Again

ABSTRACT & COMMENTARY

ALTHOUGH IT IS ASSOCIATED WITH A VARIETY OF CONDITIONS, the most common type of amyloidosis is the AL-type, in which the amyloid consists largely of immunoglobulin light chain protein. Therapy consists of melphalan and prednisone and is generally of limited efficacy, being only able to slow disease progression by inhibiting production of new light chains. Other agents, such as colchicine and dimethylsulfoxide (DMSO), have been generally ineffective. Until recently, there was no way to promote resorption of established amyloid deposits.

Recently, Merlini and colleagues in Milan serendipitously observed regression of AL-type amyloidosis in a patient with multiple myeloma treated with a derivative of doxorubicin, 4'-iodo-4'-deoxydoxorubicin (I-DOX). This prompted further trials in eight additional patients (age range, 42-70 years) with advanced amyloidosis in whom previous treatment with conventional agents had been ineffective. The first few patients were given I-DOX at a dose of 80-100 mg/m^2 IV every four weeks, repeated twice. One patient was given a smaller fraction (4 doses of 30 mg/m^2/week) to avoid massive mobilization of amyloid from her liver. Later, as it became clear that these doses were unnecessarily high, patients were given 30 mg/m^2 every 7-10 days for three or four doses. No other chemotherapeutic agents were administered during this period.

After administration of I-DOX, clinically meaningful benefits were observed in five of eight patients. These benefits included improvement of speech previously impaired by macroglossia, weight gain due to improvement of diarrhea, decrease in cardiac septal thickness, decrease in previously elevated liver enzymes, and shrinkage of cutaneous amyloidomas. The onset of these salutary effects was virtually immediate in two cases, whereas in three other cases benefit was apparent after several weeks, but persisted for months. With the limited number of patients in this report, it is difficult to draw conclusions about survival. Nevertheless, in this small population of patients with advanced and imminently life-threatening disease, all but two survived at least 12 months from treatment with I-DOX, and one patient is still alive 44 months after therapy.

INSIDE

Does molecular typing decrease the toxicity of unrelated donor BMT? **page 74**

Lymph node metastases maintain prognostic value after neoadjuvan chemotherap **page 76**

We get prostat cancer from ou mother **page 7**

The authors postulated that I-DOX bound directly to amyloid fibrils, and confirmed this by demonstrating that amyloid fibrils incubated with I-DOX exhibited the characteristic anthracycline fluorescence at 610 nm. To show that I-DOX promoted resorption of established amyloid deposits, they used 1^{25I}-serum amyloid P component scintigraphy to image in vivo amyloid stores. After one and 14 months of treatment, repeat 1^{25I}-SAP scintigraphy demonstrated marked regression of amyloid deposits. (Gianni L, et al: *Blood* 1995; 86:855-861.)

■ COMMENTARY

Systemic amyloidosis is a morbid condition that is often unrecognized until the patient has advanced disease. For AL-amyloidosis, secondary to immunoglobulin light chain deposition, existing therapy consists of melphalan and prednisone, which inhibit the progression of disease by suppressing the amyloidogenic clone. Thus, further deposition of amyloid is attenuated, allowing degradative mechanisms to prevail, and sometimes leading to detectable regression of amyloid deposits.[1] This strategy depends on the responsiveness of the plasma cell clone to cytotoxic agents, and in most cases, what resorption occurs is of little or no clinical significance. The data supporting the efficacy of other agents, such as colchicine and DMSO, are conflicting and these agents are generally not recommended.[1]

I-DOX is the first agent that works directly to promote resorption of amyloid deposits. It clearly does not work through cytotoxicity, because the onset of the beneficial effects was often too rapid for such a mechanism, and only a maximum of four doses was given in this study. Unmodified doxorubicin is ineffective, and only loosely binds to amyloid fibrils. This weak amyloidolytic property may be negated by the hazard of administering an anthracycline to a patient with marginal cardiac reserve. I-DOX is currently unavailable for general use, and further studies will undoubtedly be necessary before it becomes available for routine application. Nevertheless, these promising preliminary data provide hope to afflicted patients, who at this time have limited therapeutic options.

We should probably not miss the opportunity to highlight this potentially important unexpected benefit that emerged entirely from a clinical observation. Our burgeoning understanding of molecular mechanisms involved in the regulation of cell growth has led to the hope that one can think rationally about cancer drug development. However, the journals are filled with reports of cleverly designed agents or combinations of agents with elegant scientific rationale that don't work. Even with more knowledge, empiric studies can still lead to progress.

Serendipity is the act of finding something good that you were not looking for. The word was coined by Horace Walpole, based on the story "The Three Princes of Serendip," Serendip being a former name of Sri Lanka. This story is a marvelous tale of three young brothers on a quest to find the secret formula for "Death to Dragons" because the waters surrounding their island home were so dragon-infested that travel was no longer possible for their people. The princes are very intelligent, brave, and compassionate and they have adventures with people along their quest that enrich and enlighten them. Through their tenacity, they succeed. Oncology is similarly a quest, but the goal is "Death to Cancer." Like the princes, oncologists often have experiences that enrich and enlighten them in unexpected ways, ranging from their interpersonal relationships with patients and their families to the occasional unexpected breakthrough in treatment.

This serendipitous finding of amyloidolytic effects from a chemotherapeutic agent could not have been anticipated, but systematic clinical observation made during an empiric clinical trial has led to what appears to be benefit. No matter how clever we become, we shall always be in need of serendipity. ❖

Reference

1. Merlini G. *Semin Hematol* 1995;32:60-79.

Does Molecular Typing Decrease the Toxicity of Unrelated Donor BMT?

ABSTRACT & COMMENTARY

Synopsis: *Matched unrelated donor bone marrow transplantation is associated with a high incidence of acute and chronic graft-vs.-host disease (GvHD). More precise matching of HLA class II antigens decreased the incidence of acute GvHD to what is seen with matched sibling transplants, but it did not decrease the incidence of chronic GvHD.*

Source: Nademanee A, et al: *Blood* 1995;86: 1228-1234.

EVEN AS INVESTIGATORS STRIVE TO IMPROVE THE efficacy and safety of allogeneic bone marrow transplantation (BMT), its applicability is limited by the

RAPID COMMUNICATION

New Drug Therapy of Amyloidoses: Resorption of AL-Type Deposits With 4'-Iodo-4'-Deoxydoxorubicin

By Luca Gianni, Vittorio Bellotti, Alessandro M. Gianni, and Giampaolo Merlini

Amyloidosis caused by monoclonal Ig light chains (AL) is characterized by the tissue deposition of paraproteins as insoluble fibrils that leads to organ dysfunction and death. After serendipitous observation of its efficacy, the new anthracycline 4'-iodo-4'-deoxydoxorubicin (I-DOX) was evaluated in eight patients with biopsy-proven AL and symptomatic organ involvement who received 1 to 6 administrations of I-DOX at dosages of 15 to 100 mg/m². Five patients showed substantial clinical improvement concomitant with instrumental and physical evidence of response, and three patients presented objective evidence of amyloid resorption. The effects of I-DOX on amyloid deposits were not associated with cytotoxicity to the amyloidogenic clone. Five patients died of disease-related complications at 4 to 36 months; the remaining three are alive 29, 35, and 44 months after starting treatment. I-DOX caused short-lived granulocytopenia and minimal extra-hematologic side effects. The pharmacokinetics of I-DOX presented features exploitable for diagnosis in amyloidotic patients and documented the active metabolite in the cerebrospinal fluid. We conclude that I-DOX represents an important treatment option for subjects with AL amyloidosis and could be the prototype of a new class of drugs that interfere with and reverse the process of all types of amyloid deposition.
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AMYLOIDOSIS FORMED by monoclonal Ig light chain (AL) is a rapidly progressive disease in most patients, and is characterized by a very poor prognosis, with death usually occurring within 1 to 2 years of diagnosis.[1] The main thrust of therapy has been directed at inhibiting the production of amyloidogenic light chains through the use of alkylating agent-based chemotherapy.[2] However, this approach is beneficial in less than one fifth of patients,[3] a percentage too small to shift the median survival of the overall patient population, which remains very poor.

Anthracyclines such as doxorubicin and daunorubicin are anticancer agents of proven efficacy in a large number of hematologic and nonhematologic malignancies.[4] Although doxorubicin is an integral part of therapeutic programs for myeloma patients,[5] it has never been reported that its use specifically contributed to the amelioration of amyloidosis associated with the plasma cell malignancy. The serendipitous observation that administration of a new anthracycline anticancer drug, 4'-iodo-4'-deoxydoxorubicin (I-DOX), to a patient with AL amyloidosis associated with multiple myeloma determined a rapid and impressive clinical improvement prompted us to evaluate the effects of this drug in seven additional cases. Here we describe the clinical efficacy of this new anthracycline in the treatment of AL amyloidosis.

MATERIALS AND METHODS

After its approval by the local ethical committee as compassionate care for patients with plasma cell dyscrasias (within the context of approved ongoing I-DOX protocols for different types of neoplasias at the Istituto Nazionale Tumori), I-DOX was administered to eight patients with biopsy-proven AL amyloidosis from July 1991 to February 1993 (Table 1). All gave informed witnessed consent, had progressive disease, and none of those previously treated responded to therapy. Follow-up is updated to March 1, 1995. Evaluation included physical examination, complete blood cell count, complete blood chemistry, and urinalysis, comprising daily urinary protein excretion at study entry and weekly or twice a week thereafter during treatment with I-DOX. Bidimensional echocardiography with estimation of the left ventricular ejection fraction was performed before and after treatment with I-DOX. Patients were evaluated according to the World Health Organization (WHO) scales for grading performance status and acute and subacute toxic effects of the drug.[6] In patients 5 to 8 imaging of the amyloid deposits was performed using ^{131}I-SAP, kindly provided by Prof Mark B. Pepys (Hammersmith Hospital, London, UK), following the procedure published by his group.[7]

Treatment scheme. The first patient was treated with a single high dose of I-DOX (100 mg/m²) as part of a high-dose chemotherapy program before bone marrow transplantation (BMT). The following three patients (nos. 2, 3, and 4) were given 80 to 100 mg/m² of I-DOX, repeated two times every 4 weeks. Patient 4 first received a lower I-DOX dosage (30 mg/m²/wk four times) to avoid massive mobilization of the huge amyloid deposits in her liver, and then higher doses were administered in an attempt to maintain the transient clinical improvement that was observed. In the meantime it became clear that I-DOX activity was not caused by its cytotoxic effects on the amyloidogenic clone. Therefore, we treated the remaining patients with relatively low doses (30 mg/m²), repeated every 7 to 10 days three to four times to avoid unnecessary toxicities. This dosage was further reduced and the intervals extended in the case of severe hematologic toxicity (blood neutrophil count $<0.5 \times 10^9$/L). No other chemotherapy besides I-DOX has been administered to any patient.

Pharmacokinetic studies. The plasma pharmacokinetics of I-DOX and its major metabolite 13-dihydro-I-DOX (I-DOXOL) was studied in three patients for seven cycles. The two anthracyclines

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Table 1. Characteristics of the Patients Studied and Effects of I-DOX Treatment

Patient	Age (yrs)	Sex	Clinical Manifestation	Previous Treatment	Treatment With I-DOX	Effects of I-DOX	Survival From I-DOX (mos)	Survival From Diagnosis (present status)
1	45	M	PS: 2 Severe skin involvement, impairment of gait, macroglossia impairing speech, IVS: 13 mm	No	100 mg/m²	PS:1 Gait improved, speech improved, IVS: 11 mm, urinary excretion of light-chain fragments	10	31 (deceased)
2	49	M	Serum creatinine: 451 μmol/L, urinary protein 9.5 g/d	Alkylating agents	80 mg/m² q4wks × 2	No effect on renal function, stable clinical condition	36	76 (deceased)
3	57	M	PS: 2 Autonomic involvement causing diarrhea (8-10/d) and weight loss (15 kg/6 mos), urinary protein 7 g/d	Alkylating agents	80 mg/m² and 100 mg/m² q4wks	PS: 1 Diarrhea reduced, weight gain (5 kg), urinary protein 6 g/d	44	60 (alive)
4	42	F	Massive hepatomegaly, ascites and anasarca, terminal liver failure, serum AP: 1,225 U/L	No	30 mg/m²/wk × 4 wks; 80 mg/m² and 100 mg/m² q4wks	Serum AP: 395 U/L, stabilization of clinical condition for 4 mos	4	7 (deceased)
5	49	F	PS:2 Severe nephrotic syndrome, urinary protein 16 g/d	Alkylating agents	30 mg/m²/wk × 2 wks; 15 mg/m²/wk + 20 mg/m²/wk	PS: 1 Urinary protein 5-6 g/d for 6 mos then 10-12 g/d	35	45 (alive)
6	54	F	Congestive heart failure (NYHA class III), IVS: 11 mm	No	30 mg/m²/wk + 15 mg/m²/wk + 20 mg/m²/wk	Congestive heart failure IVS: 8 mm	12	51 (deceased)
7	48	M	Severe nephrotic syndrome, urinary protein 13 g/d	No	30 mg/m²/wk × 4 wks	Urinary protein 7.5 g/d	20	24 (deceased)
8	70	M	Sacral amyloidoma (d 10 cm) infiltrating the skin (11 × 1 cm) causing pain, ^{131}I-SAP uptake by liver, spleen, amyloidoma	Alkylating agents and ionizing radiation	30 mg/m²/wk × 2 wks + 20 mg/m²/wk × 2 wks	Shrinking of amyloidoma to 8 cm and skin infiltrate to 5 × 0.6 cm, resolution of pain, ^{131}I-SAP uptake markedly reduced	29	46 (alive)

Abbreviations: PS, performance status (WHO); IVS, heart interventricular septum thickness; AP, alkaline phosphatase; ^{131}I-SAP, labeled serum amyloid P component; q, every.

were measured by high-performance liquid chromatography (HPLC) as previously described,[8] with minor modifications.

In vitro studies. The possible effects of I-DOX on amyloid fibrils were investigated by studying urinary excretion of the amyloid precursor (light chain), using the Western blot technique as previously reported.[9] Amyloid fibrils used in the in vitro studies were extracted from an amyloidoma surgically removed from patient 1 before I-DOX therapy.

I-DOX binding to amyloid fibrils was evaluated by incubating 1 mg of fibril with 1 mL of 10^{-7} mol/L I-DOX in 0.15 mol/L NaCl. After 1 hour the fibrils were washed three times with 1 mL saline and once with distilled water. The suspension of fibrils in water was allowed to dry on a glass microscope slide, and the characteristic anthracycline fluorescence was determined with a Leitz Diaplan microscope (Leitz, Wetzlar, Germany) equipped with a fluorescence stage, using an excitation filter at 485 nm and an emission filter at 610 nm. The amyloid nature of the fibrils was proved by staining a parallel slide with alkaline Congo red (BDH Chemicals, Poole, UK) followed by analysis with a polarized light microscope. Snap-frozen cryostat sections of brain affected by Alzheimer's disease were incubated with 10^{-7} mol/L I-DOX in 80% ethanol for 20 minutes, washed, and examined by fluorescence microscopy.

RESULTS

I-DOX produced clinical benefits in five of the eight patients. All of them had a long history of symptomatic amyloidosis, with the exception of patient 4 (Table 1), who had a rapidly evolving disease with massive substitution of the liver and spleen, and of patient 7, who presented a rapidly progressing nephrotic syndrome. The therapeutic effect of I-DOX was immediate, substantial, and evident as instrumental and physical response in cases 1 and 8 (Table 1). In the other three responding patients (2, 3, and 5), the benefits appeared some weeks after treatment and persisted in subsequent months (median 6 months). The serendipitous observation of I-DOX effects in patient 1 prompted the present study

and deserves detailed description. The patient presented with skin involvement that caused widespread thickening and papulae, macroglossia that severely impaired speech, and interventricular septum thickening (13 mm). Stiffness and pain from amyloid deposition made him unable to use his hands, and bulky amyloid deposits in his thighs seriously limited his gait. I-DOX was administered as part of a program of high-dose chemotherapy to be followed by autologous BMT with in vitro and in vivo purging with murine monoclonal anti-idiotypic antibodies.[10] Within 48 hours of receiving I-DOX the patient experienced polyuria, loss of 3 kg of body weight, dramatic amelioration of the severe skin involvement, and sudden improvement in general performance. He could again flex his fingers, walk long distances (2 km), and work full time. The rapid regression of macroglossia was concomitant with such an improvement in speech that the patient resumed teaching at the university. The thickness of the interventricular septum decreased from 13 mm to 11 mm in 2 weeks. Western blot analysis of the urine collected 48 hours after the infusion of I-DOX showed light-chain fragments of the same size as those present in amyloid fibrils extracted from a small amyloidoma excised from the left thigh (Fig 1). The extracted fibrils avidly bound to I-DOX after 1-hour incubation in a 10^{-7} mol/L solution (Fig 2). Concentrations of the serum and urine monoclonal component only transiently decreased after I-DOX. The clinical improvements persisted for 6 months, then the patient's condition slowly deteriorated. He died suddenly of cardiac arrest 31 months after diagnosis and 10 months after treatment with I-DOX.

In addition to patient 1, I-DOX produced measurable reduction of amyloid deposits in two other patients. In patient 6, with overt clinical amyloid heart involvement, echocardiography showed a reduction of the thickness of the interventricular septum. Patient 8 presented an amyloidoma (diameter 10 cm) that destroyed part of the left sacrum and ilium and infiltrated the gluteus, where a palpable mass 11 × 1 cm caused piercing pain that required chronic analgesic therapy. The amyloidoma had grown in the prior 20 months despite radiotherapy with 50 Gy and chemotherapy with cyclophosphamide. I-DOX (two weekly doses of 30 mg/m², followed by two weekly doses of 20 mg/m²) caused a major reduction of the palpable mass to 5 × 0.6 cm, and of the bone amyloidoma to 8 cm in diameter as assessed by nuclear magnetic resonance. The pain completely disappeared and the patient was able to go off all analgesic drugs. Before therapy, imaging with ^{131}I-SAP showed uptake by the amyloidoma, liver, and spleen. The ^{131}I-SAP study was repeated 1 month and 14 months after treatment with I-DOX. As illustrated in Fig 3, there was a marked regression of the amyloid deposits 14 months after the last I-DOX dose even though the serum amyloidogenic precursor (IgG κ) persisted unmodified. The comparison of imaging with ^{131}I-SAP was performed in three more patients (5, 6, and 7). There was no significant change at 3 to 4 weeks after treatment with I-DOX, and a definite, although relatively modest, increase of amyloid deposits after 18 months in patient 5. In patient 2, who suffered from severe renal failure with nephrotic syndrome and initial heart involvement (interventricular septum thickness 14 mm, normal ≤10 mm), I-DOX did not affect renal function. However, after treatment with I-DOX his general condition remained satisfactory for 11 months, without progression of heart involvement, notwithstanding that his serum monoclonal component remained in the range of 9 to 12 g/L. In patient 3 I-DOX produced a significant reversal of clinical symptoms, including reduction of the diarrhea caused by autonomic nerve involvement and progressive weight gain. In patient 5, who had a severe nephrotic syndrome caused by renal amyloidosis, a single course of I-DOX was associated with a decrease in proteinuria from 16 to 6 g/d that persisted for 6 months. In none of the patients whose urinary protein excretion decreased (3, 5, and 7), was there a concomitant increase of serum creatinine.

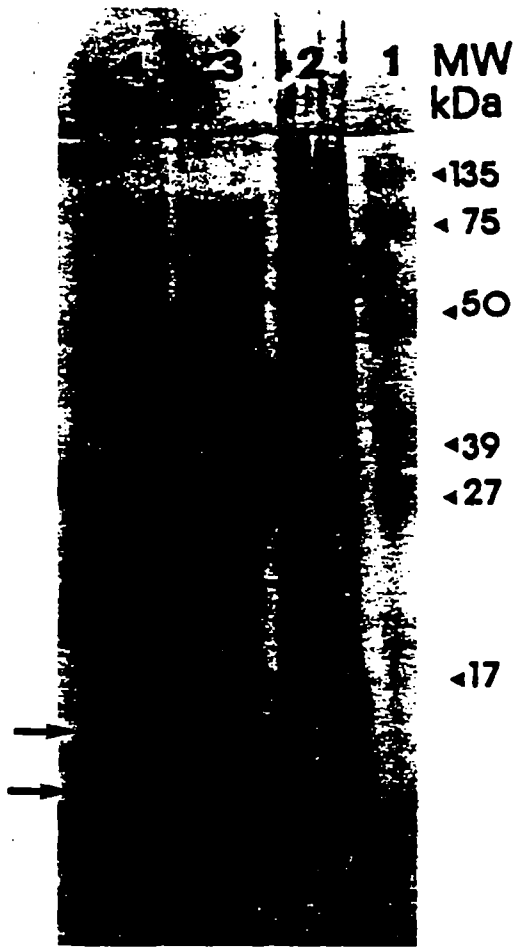

Fig 1. Western blot developed with peroxidase-labeled anti-λ antiserum of (1) molecular weight standards; (2) amyloid fibrils; (3) patient 1 urine obtained before treatment; or (4) patient 1 urine obtained 48 hours after infusion of 190 mg of I-DOX. In sample 4 new light-chain bands appeared after treatment with I-DOX; two of these bands correspond to light chain fragments present in amyloid fibrils (arrows).

In patients 4, 6, and 7 the expected natural history of the disease was not affected despite objective amyloid resorption in patient 6 and temporary reduction of urinary protein excretion in patient 7. Already irreversible organ damage caused by amyloid infiltration could explain the clinical inefficacy

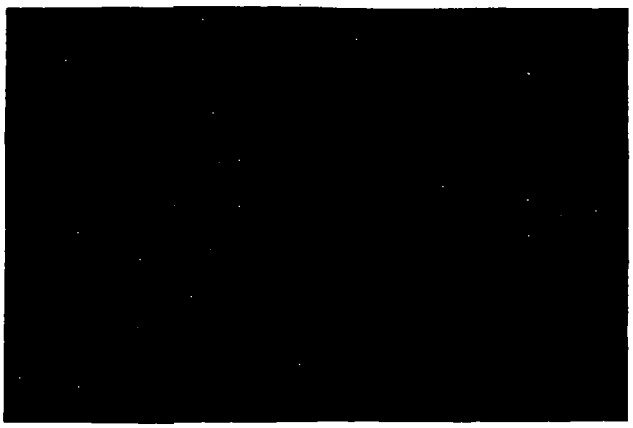

Fig 2. Binding of I-DOX to patient 1 (λ) amyloid fibrils. The characteristic anthracycline fluorescence is evident (original magnification × 50).

Fig 5. Snap-frozen cryostat section of brain affected by Alzheimer's disease. The slide was incubated with 10^{-7} mol/L I-DOX and examined by fluorescence microscopy (original magnification × 400). The amyloid deposits show characteristic anthracycline fluorescence brighter than the background.

in patients 4 and 6, whereas a single I-DOX course might have been insufficient to overcome the possibly strong amyloidogenic potential of patient 7's light chain. Overall, three patients are alive at 29, 35, and 44 months after starting treatment with I-DOX, whereas five have died of disease complications.

Toxicity. The main toxicity was reversible, clinically uneventful granulocytopenia (Table 2). The onset of neutropenia was rapid (median time from treatment to nadir 12 days, range 8 to 16) and short-lived (median time from treatment to recovery 14 days, range 9 to 22), and was not clearly dose-related as it is in cancer patients.[8] Neutropenia was never associated with infection or febrile episodes. As already reported,[6] anemia and thrombocytopenia were of minor importance. Transient nausea was reported by three patients. Because anthracyclines may have cardiotoxic effects,[5] all patients were thoroughly investigated to rule out this possibility. A comparative analysis of the left ventricular ejection fraction before and after therapy did not show any significant, consistent, or substantial modification in any of the patients. Patient 4 died in shock with acute total heart failure as the terminal event. The left ventricular ejection fraction, measured 1 day before the last dose of I-DOX, was normal (69%) and equal to that measured before the start of anthracycline therapy (66%). Postmortem examination

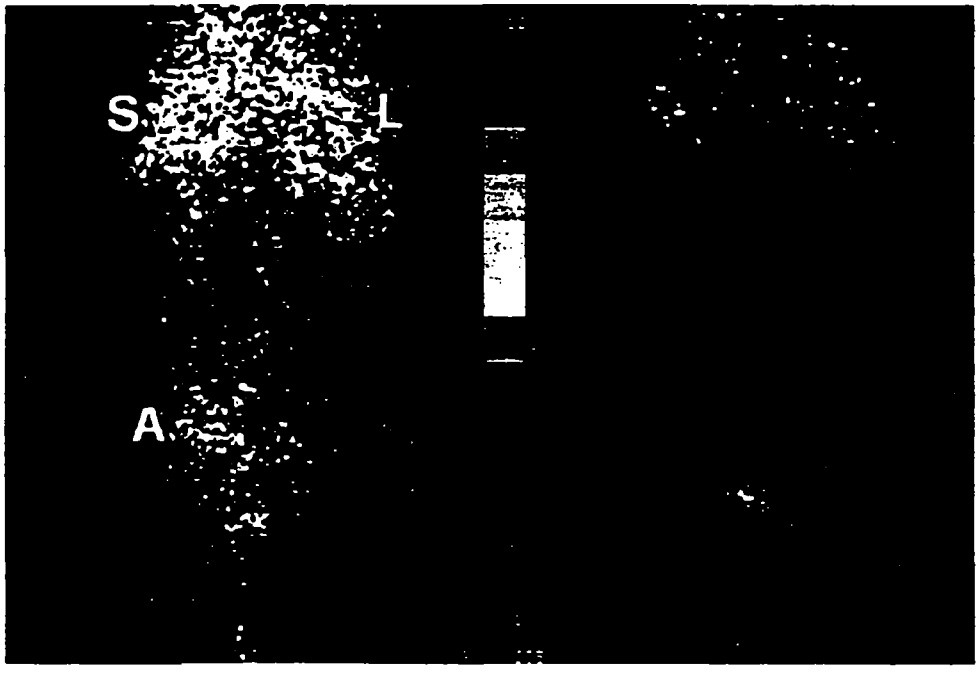

Fig 3. Imaging with ^{131}I-SAP of amyloid deposits from patient 8 (at 48 hours after injection of ^{131}I-SAP). (Left) Uptake in the spleen (S), liver (L), and at the level of the amyloidoma (A) is evident before treatment. (Right) Fourteen months after I-DOX treatment ^{131}I-SAP imaging shows marked regression of amyloid deposits.

Table 2. Hematologic Toxicity of Treatment With I-DOX

Dose (mg/m²)	Cycles (n)	Anemia (Hb g/dL)		Neutropenia (ANC/μL)		Thrombocytopenia (platelets × 10³/μL)	
		Median	Range	Median	Range	Median	Range
30	5	11.3	7.4-12.8	900	140-1,660	203	83-437
80	4	7.75	7.1-8.3	375	60-750	118.5	98-182
100	3	9.2	8.8-9.6	1,358	850-3,840	113	112-207

Abbreviations: Hb, hemoglobin; ANC, absolute neutrophil count.

showed multiple amyloid deposits that massively involved the liver, spleen, lungs, kidneys, and the adrenocortical glands, and may explain her death as the result of disease progression.

Pharmacokinetic studies. The plasma pharmacokinetics of I-DOX was studied in three patients and was significantly different from that described in subjects with solid tumors.[8,11] In patient 4, who was treated with four consecutive doses of 30 mg/m², plasma retention of I-DOX increased after each of the first three doses, as shown by a shift in total body clearance, which became progressively slower (335, 214, and 153 L/h/m² after the first, second, and third administrations, respectively). The pharmacokinetic profiles of I-DOX and I-DOXOL after administration of 80 mg/m² in patients 2 and 3 were also at odds with the plasma anthracycline disposition measured in patients with solid tumors. In these two patients I-DOX (Fig 4) and I-DOXOL (data not shown) plasma concentrations during infusion were significantly lower than and outside the 99% confidence intervals of the mean concentration in the control group (11 patients with breast cancer treated with identical doses). Patients 2 and 3 also agreed to cerebrospinal fluid (CSF) sampling for pharmacokinetic purposes. At 4 hours (patient 2) and 5 hours (patient 3) after drug administration, I-DOX was not measurable in CSF, whereas I-DOXOL concentrations corresponded to 18 and 15 nmol/L, respectively: 10 to 20 times lower than the corresponding I-DOXOL plasma concentrations.

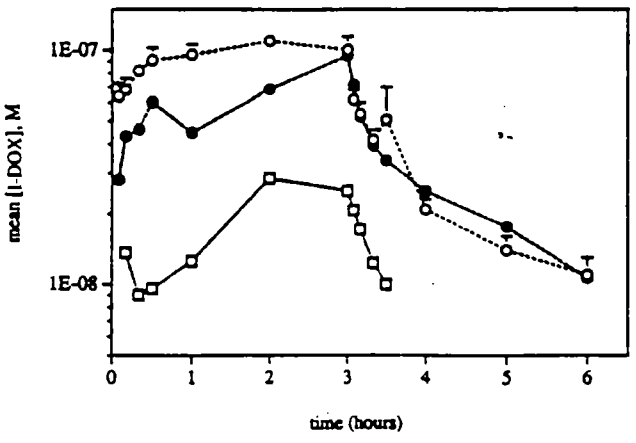

Fig 4. Plasma pharmacokinetics of I-DOX. (○) Mean (+1 SD) of concentrations measured in 11 patients with breast cancer treated with 80 mg/m² of the anthracycline. (□, ⊕) Plasma concentrations of I-DOX after administration of the same dose to patients 2 and 3, respectively.

DISCUSSION

AL-type systemic amyloidosis is a progressive disease with poor prognosis. Treatment options are mainly based on the use of anticancer agents to eradicate cells that produce the amyloid precursors or, subordinately, on the administration of colchicine or dimethyl sulfoxide (DMSO) to interfere with amyloid deposition or promote its resorption, respectively.[2] However, alkylating agents improve clinical condition and survival in only a small fraction of patients.[3] The use of more aggressive high-dose chemotherapy programs is substantially limited by poor tolerability and severe toxicity because of amyloid organ damage,[12,13] although this approach could possibly prove feasible and effective in those few AL patients without severe organ damage.[14] Colchicine was reported to improve life expectancy in a survival analysis with historical controls, but no clear-cut regression of organ involvement has been described.[15]

Finally, DMSO is substantially ineffective in AL amyloidosis and its use caused serious problems of tolerability and compliance.[16] In all these treatment modalities resorption of amyloid deposits is a rare event. Within this framework of long-standing clinical experience, the effects of I-DOX in patients with AL amyloidosis appear particularly relevant. We obtained evidence that I-DOX induced amyloid resorption in three patients, as indicated by measurable reduction of the thickness of the interventricular septum (patients 1, and 6), by massive urinary excretion of amyloid fragments (patient 1), and by the substantial reduction of a large amyloidoma and spleen and liver amyloid deposits (patient 8). The pattern of resorption was not consistently the same in all cases. The apparent urinary excretion of amyloid fragments was documented only in patient 1 (see Fig 1), despite the fact that we examined all subsequent patients with the same technique. Of note, he was also the only patient with severe skin involvement and the only one in whom the onset of the clinical improvement occurred very rapidly. A brief course of I-DOX inhibited progression of amyloidosis and improved the clinical condition of five patients (1, 2, 3, 5, and 8) for several months.

The potential impact of I-DOX treatment on patient survival cannot be assessed on the basis of the present pilot study. Ethical considerations prompted a selection of patients with progressive disease refractory to previous treatment (patients 2, 3, 5, and 8), with end-stage amyloid organ involvement (4 and 6) and/or rapidly progressing disease (4 and 7).

The median time from diagnosis of AL to treatment with I-DOX was 16.5 months (range 3 to 40 months). It is known that longer intervals from diagnosis to study entry are associated with better survival,[15,17] whereas patients seen within 1 month of diagnosis have a dramatically poorer prognosis compared with all patients seen.[18] Based on the above considerations, the patients selected for the present study could be expected to have an inherently longer and better survival independently of I-DOX treatment. A prospective controlled study of I-DOX versus chemotherapy in which patients are stratified by major prognostic factors,[19] including time from initial diagnosis to initiation of therapy, is being designed to assess the full therapeutic potential of this new anthracycline and its impact on survival.

It is important to note that the drug was well tolerated by all patients, treatment was feasible, and the period of neutropenia was short enough not to entail a risk of infection.

Besides these clinical effects, our findings also offer insights into the possible mechanism of action of I-DOX.

Pharmacokinetic analysis of plasma concentrations of I-DOX and I-DOXOL showed very peculiar features in patients with amyloidosis. As already described in patients with solid tumors,[8,11] I-DOXOL was the main anthracycline circulating in the plasma immediately after I-DOX administration. However, in the three patients with amyloidosis the pharmacokinetics were characterized by significantly lower I-DOX and I-DOXOL concentrations than those measured in patients without amyloidosis, and by a progressive increase of plasma retention of the anthracycline with each subsequent dose. This unusual drug disposition is reminiscent of the plasma kinetics of Congo red in amyloidotic patients. The dye was used in the past as a diagnostic tool because of its high affinity for amyloid. With several notable exceptions, a low serum retention (ie, fast clearance) of the dye after intravenous administration was observed in subjects with massive amyloid deposits.[20] Similarly, the faster clearance of I-DOX in amyloidotic patients is consistent with the concept that the drug avidly binds to a target easily accessible from the blood or interstitial fluid, and that this target becomes progressively less available with subsequent treatments because of saturation or removal. In vitro studies documenting the marked affinity of I-DOX for AL amyloid fibrils (Fig 2) and for several other types of amyloid deposits,[21] including Alzheimer's (Fig 5), support the hypothesis that such a target was represented by the in vivo amyloid deposits. Substitution of the C′ 4-hydroxyl group with an iodine atom is the only structural difference between doxorubicin and its derivative I-DOX.[22] Because doxorubicin only loosely binds to amyloid fibrils,[21] the presence of iodine in the anthracycline structure may well be responsible for the homing of I-DOX and I-DOXOL to the amyloid.

The binding to amyloid deposits most likely plays a key role in the mechanism of action of I-DOX. We did not observe any significant and/or persistent modification of the serum or urinary concentrations of the monoclonal protein in any of the patients described in this report. Thus, the clinical effects could not be attributed to anthracycline cytotoxicity toward the clones producing the amyloidogenic precursor. I-DOX treatment induced mobilization and resorption of amyloid deposits; however, we were unable to induce in vitro dissolution of amyloid fibrils by the addition of I-DOX or I-DOXOL. This apparent discrepancy may be reconciled by assuming that the tight binding of iodinated anthracyclines in vivo makes amyloid deposits less accessible to amyloid precursors, slowing down or even preventing their deposition and facilitating existing proteolytic mechanisms for amyloid degradation and resorption. This hypothesis would explain the relatively long duration (median 6 months) of the clinical benefits derived from a few I-DOX administrations (patients 2, 3, and 5), and the slow resorption of amyloid deposits in patient 8. The acute clinical and laboratory effects induced by a single high dose of I-DOX in patient 1 indicate that in certain patients, for reasons that still need to be investigated, the mobilization and resorption of amyloid deposits could be very rapid.

In conclusion, I-DOX represents a new, feasible, and well-tolerated treatment option for AL amyloidosis. Its effects should be investigated further, preferably in patients at an earlier stage of the disease than those described in this report. The observation that the drug appears to have high tropism for amyloid deposits on which it exerts its action over time suggests that I-DOX should be used for brief courses of low weekly doses (30 mg/m^2 for 4 consecutive weeks). In addition, its mechanism of action is independent of its cytotoxicity, produces amyloid resorption, and is most likely caused by binding to amyloid fibrils. Thus, the affinity of I-DOX for all clinically relevant types of amyloid tested (AA, AL, ATTR, Aβ, Aβ2M)[21] qualifies this new anthracycline as a prototype drug that is potentially useful for all amyloidotic diseases. With this in mind, the demonstration that I-DOXOL can be found in the CSF after systemic administration of I-DOX is surely a very attractive feature in the perspective of targeting amyloid deposits within the central nervous system, as in the case of Alzheimer's disease. Non-cytotoxic analogs of I-DOX are presently being investigated to make this novel therapeutic approach available for all forms of amyloidosis.

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THE WHITE HOUSE
OFFICE OF DOMESTIC POLICY

CAROL H. RASCO
Assistant to the President for Domestic Policy

To: _____ _____

_____ _____

Draft response for POTUS
and forward to CHR by: _____

Draft response for CHR by: _____

Please reply directly to the writer
(copy to CHR) by: _____

Please advise by: _____

Let's discuss: _____

For your information. _____

Reply using form code: _____

File: _____

Send copy to (original to CHR): _____

Schedule ? : ☐ Accept ☐ Pending ☐ Regret

Designee to attend. _____

Remarks: _____

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JUL 30 1996

CHIEF OF STAFF TO THE PRESIDENT
THE WHITE HOUSE

July 26, 1996

The Honorable Richard Katz
California State Assembly
Sacramento, California 95814

Dear Mr. Katz:

Thank you for the letter from you and your collegues. I appreciate you making me aware of your support for legislation to reform the Federal Drug Administration. I have taken the liberty of sharing your letter with other White House staff working on this legislation. You can be sure that we will keep your views and suggestions in mind.

Again, that you for writing. Please keep in touch.

Sincerely,

Leon E. Panetta
Chief of Staff

cc: The Honorable Carol Rasco
The Honorable John Hilley

LEP/bes

State Capitol
Sacramento, CA 95814

JUL 1 5 1996

Assembly
California Legislature

July 4, 1996

Leon Panetta
Chief of Staff
The White House
1600 Pennsylvania Avenue
Washington, D.C. 20500

Dear Mr. Panetta:

We are writing as representatives of the State Assembly Democratic Caucus to urge Congress to pass meaningful, bipartisan FDA reform legislation this year.

Our State's health care technology industry has grown over the past two decades to become our State's third largest industry cluster. Today more than 165,000 of our constituents are employed in biotechnology firms, medical device companies and biomedical research organizations. More than 900 companies in our State are developing new therapies and medical devices to treat unmet medical needs, including cancer, AIDS and heart disease. The ability of these enterprises to grow, create jobs and deliver these products to patients is largely dependent on FDA's ability to approve safe and effective products in a timely fashion.

In recent years, the volume of new scientific discoveries has overwhelmed the Agency. Delays in new product approval have become unreasonable, and FDA consistently fails to meet the statutory timelines for product review established by Congress. It now takes an average of 15 years to bring a new biotech drug from initial discovery to FDA approval. For new medical devices, which FDA is supposed to review in 180 days, review time averages more than two and one-half years.

The implications of slow FDA performance are serious. A recent Ernst & Young report found that California companies are increasingly establishing manufacturing facilities and clinical investigations overseas because, in a global market, they cannot afford to devote all their resources to the sluggish and uncertain FDA process. Ernst & Young estimate the cost of California at almost 18,000 jobs at an annual salary of $1 billion. Beyond economics, this "Europe-first" trend means that American patients are often the last to receive breakthrough products.

Printed on Recycled Paper

We urge you to consider legislation that focuses the FDA's mission, reduces the paperwork and inefficiencies of the current system, speeds breakthrough products to market, and makes FDA accountable to statutory timelines for review of new products. These reforms would help keep California jobs at home and improve the flow of new treatments and cures to American patients.

Sincerely,

Kevin Murray
47th Assembly District

Richard Katz
39th Assembly District

Martin Gallegos
57th Assembly District

Diane Martinez
49th Assembly District

Willard Murray
52nd Assembly District

Carole Migden
13th Assembly District

Marguerite Archie-Hudson
48th Assembly District

Sheila Kuehl
41st Assembly District

Curtis R. Tucker, Jr.
51st Assembly District

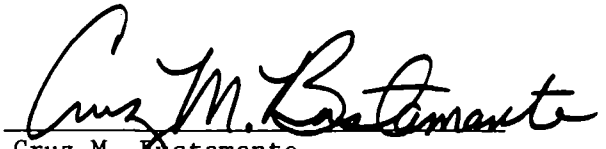
Sal Cannella
26nd Assembly District

Tom Hannigan
8th Assembly District

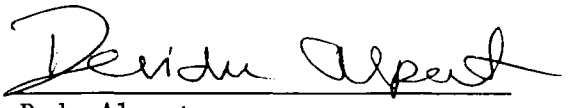
Barbara Lee
16th Assembly District

John Burton
12th Assembly District

John Vasconcellos
22nd Assembly District



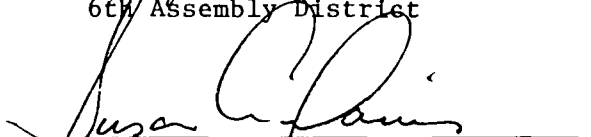
Cruz M. Bustamante
31st Assembly District



Dede Alpert
48th Assembly District

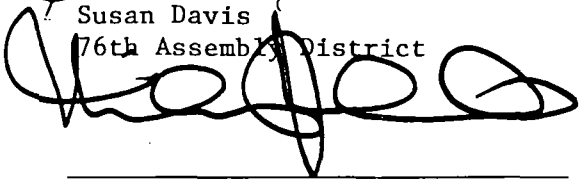
Kerry Mazzoni
6th Assembly District

Jackie Speier
19th Assembly District

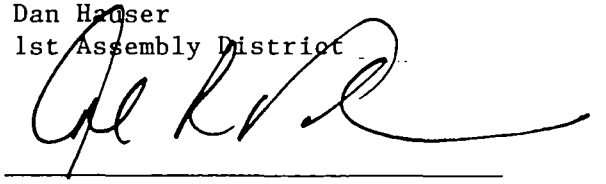


Susan Davis
76th Assembly District

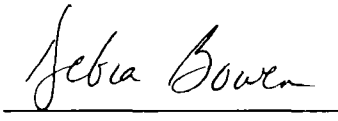
Dan Hauser
1st Assembly District



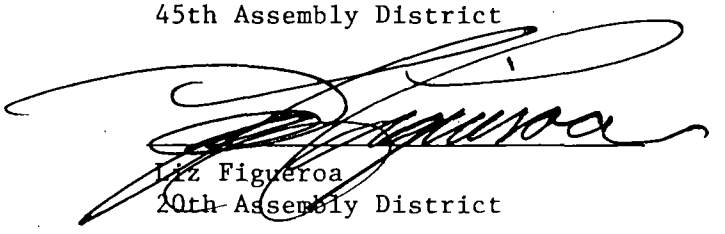
Mike Machado
17th Assembly District



Antonio R. Villaraigosa
45th Assembly District

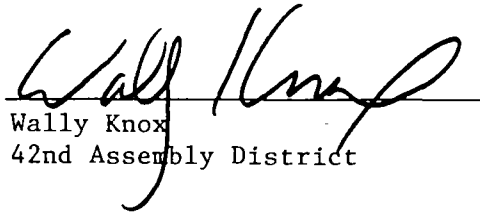


Debra Bowen
53rd Assembly District

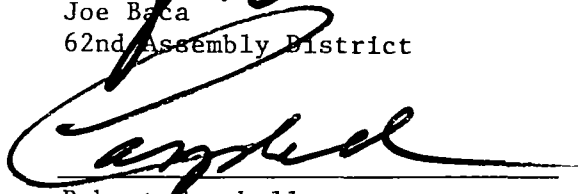


Liz Figueroa
20th Assembly District

Joe Baca
62nd Assembly District



Wally Knox
42nd Assembly District



Robert Campbell
11th Assembly District

THE WHITE HOUSE

WASHINGTON

July 15, 1996

MEMORANDUM FOR MARY ELLEN GLYNN

FROM: Elizabeth Drye

SUBJECT: FDA Product Review Times

The press is focusing increasingly -- both in stories on tobacco and on pending FDA reform legislation -- on the timeliness of FDA's drug and device approvals (the Washington Post published three pieces in the last three days on the issue). Opponents of FDA's tobacco proposal argue that FDA isn't reviewing drugs and devices fast enough and should not divert resources to tobacco control. Opponents of the tobacco rule, and proponents of FDA reform bills, argue that slow FDA reviews are hurting patients. The President may be asked about FDA's performance.

As indicated in the attached Q&A's, the facts tell a positive story and refute FDA's critics.

Q: Some critics say FDA can't handle the proposed tobacco regulations because they can't even do their current job of approving drugs and medical devices in a timely fashion. What do you say to that?

A: They should start with the facts. FDA is already a world leader in the speed of its drug approvals. The General Accounting Office found that the U.S. approved drugs faster than the United Kingdom. An industry-funded group found U.S. drug approvals as fast as those in the United Kingdom, and faster than those in France, Spain, Germany, Australia, Japan, Italy and Canada.

And we want to do even better. That is why I announced in March FDA's reinvention effort to speed up the approval of cancer drugs and to increase access to promising cancer drugs even before final approval. We did that as part of the Vice President's National Performance Review. There's a right way and a wrong way to improve drug reviews, and we are doing it the right way.

We already have the amazing success stories with AIDS drugs. The newest drugs -- the three protease inhibitors -- were approved in days: 97 days, 72 days and 42 days.

Q: What about medical devices, though?

A: The FDA has said it needs to improve its performance there, and is working hard in that area as well. The overwhelming majority of medical devices are being reviewed faster than they were a couple of years ago: an average of 138 days in fiscal 1995 compared to 182 days in fiscal year 1994.

But again, the Vice President's National Performance Review has been hard at work and the FDA has announced a number of new initiatives in the area of medical devices.

The key thing is that we want to maintain the high standards of safety and effectiveness that protect American consumers while improving performance. We are not prepared to give up consumer safety, and we don't have to.

August 20, 1996

The Honorable Evan Bayh
Governor of Indiana
Indianapolis, Indiana 46204

Dear Evan:

Thank you for writing to me regarding the Food and Drug Administration. I appreciate your support for the FDA's work to improve its regulatory processes, and I share your belief that more must be done, particularly in the FDA's medical device program.

The United States has the most reliable device approval system in the world. My Administration is working with Congress, patient groups, industry, the FDA, and other interested parties to develop solid, bipartisan legislation that improves the FDA's effectiveness and speed without compromising its safety and efficiency standards.

The FDA recognizes that more can be done to reduce delays, and it is moving forward with its own internal reforms. It already has established an expedited review system for devices that represent true medical breakthroughs, and exempted nearly 300 low-risk devices from premarket review requirements, allowing them to enter the market sooner. As a result, backlogs of routine device applications have been virtually eliminated.

As my Administration continues these efforts, I welcome your interest and involvement, and I am grateful for your advice. Thank you for taking the time to write.

Sincerely, BILL CLINTON

BC/SEM/RSM/JAD/RLM/ckb-jfc (Corres. #3041818)
(8.bayh.evan)
cc: Elizabeth Drye, 222 OEOB/Sally Katzen, 350 OEOB/
Nancy-Ann Min, 262 OEOB/Greg Simon, 288 OEOB/
John Emerson, 106 OEOB

Xeroxed copy of personally signed original to NH through Todd Stern

CLEAR THRU TODD STERN

PRESIDENT TO SIGN

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

TO: Elizabeth Arke

FROM: JIM O'HARA

Number of pages (includes cover) _____

Message: Please call w/ any comments

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

FDA BACKGROUNDER

U.S. FOOD & DRUG ADMINISTRATION

FDA: A Record Of Accomplishment

Faster Drug Approvals

- 82 new drugs approved in **16.5 months** (median) in Calendar Year (CY)1995, compared with 62 new drugs approved in **19 months** in 1994
- 28 of the 1995 approvals were new molecular entities (NMEs)—brand new drugs as opposed to new formulations —and were approved in **15.9 months** (median), compared with 22 NMEs approved in **17.5 months** in 1994
- 15 of the 1995 approvals were "priority" drugs —having important therapeutic value—and were approved in **6 months** (median), compared with 17 "priority" drugs approved in **15 months** in 1994
- 13 of the 1995 "priority" approvals were user fee drugs approved in **5.9 months** (median), compared with 12 "priority" user fee drugs approved in **10.4 months** in 1994

Improved Device Reviews

- 5,594 510(k)s (which account for about 98% of medical devices) reviewed by FDA in **138 days** (mean) in Fiscal Year (FY) 1995, compared with 5,498 in **182 days** in FY 1994
- 27 PMAs (premarket applications for certain Class III devices) reviewed by FDA in **20.2 months** (mean) in FY 1995, compared with 26 PMAs in **21.6 months** in FY 1994

The Record on Reinvention

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

The International Record

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

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

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

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

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

#

THE WASHINGTON POST

MONDAY, JULY 15, 1996 A17

FDA Often Blamed for Problems That Aren't Agency's Fault

By John Schwartz
Washington Post Staff Writer

Kay Holcombe recalled the meeting as very —and very troubling.

More than a dozen people came to her office one day last spring to ask her to urge boss, Rep. John D. Dingell (D-Mich.), to support efforts to reform the Food and Drug Administration. The visitors or their relatives were afflicted with dire diseases, and they wanted laws passed that would speed promising new therapies to market.

What Holcombe, the House Commerce Committee's top Democratic staff member on FDA issues, did not learn until well into the meeting was that her guests' trip to Washington had been paid for by the leading trade organization for the pharmaceutical industry, the Pharmaceutical Research and Manufacturers of America (Pharma).

They were among approximately 140 victims or family members who were flown in to visit lawmakers during recent months as part of a lobbying effort by the industry in support of bills that would scale back the power of the FDA.

The industry contends that changing the way the FDA operates would get new medicines to market faster. The bills would set tight deadlines for drug approvals, reduce the number of clinical trials required to test new drugs and shift some of the responsibility for evaluating such products to FDA-accredited private companies.

Yet, Holcombe said, the visitors to her office failed to make a persuasive case that their problems in obtaining treatment were really the fault of the FDA. She said that, although they blamed the agency, most often they were caught up in struggles with insurance companies over reimbursement or were simply frustrated by the lack of a cure anywhere in the world for what ailed them.

For example, a woman complained that the FDA was not releasing therapies for Parkinson's disease, a disorder of the nervous system for which no cure exists. Another visitor was distraught over state budget cuts that would mean a lower quality of nursing home care for his Alzheimer's-afflicted wife. The FDA does not regulate nursing homes.

Only one visitor had a problem that Holcombe could lay at the feet of the FDA: a woman who described repeated disputes with a local FDA official over paperwork required for her to import dietary supplements to treat her son.

"They truly believed that all of their problems will be solved by FDA reform," Holcombe said, "and I truly believe that they won't." She said she ended the meeting feeling that the patient lobbyists were "a little bit victimized" by the industry that had paid their way.

Patrick Korten, until last month Pharma's chief spokesman, acknowledged that many of the patients' problems were not the fault of the FDA, but said, "We brought them to Washington because they're really people. If we wanted lobbyists, we would have brought them from here."

Pharma provided The Washington Post with the names of some of the people it had brought to Washington to meet with lawmakers. All of those contacted by a reporter told of problems in obtaining treatment for themselves or family members, but it appeared that none of those problems would be addressed by FDA reform proposals.

Julie Full-Lopez teaches English at Southern Illinois University in Edwardsville, Ill. A single mother with a 13-year-old, she suffers from multiple sclerosis, a degenerative disease of the nervous system that slowly robs its victims of the use of their muscles. Her heroic fight for better MS treatments earned her a singular honor this year: On May 28, she carried the Olympic torch in St. Louis as one of the "community heroes" selected to show the American spirit.

In the weeks before that run, Lopez came to Washington to lobby lawmakers on behalf of FDA reform proposals. Along with other people suffering from chronic diseases, Lopez said, she was asked to tell her story and to encourage the lawmakers to make the FDA work faster by passing the bills.

But the drug Lopez credits with saving her life, Betaseron, was approved in the United States before it became available in any other country. When asked about this, she explained, "I was sort of the poster child of how a drug can be successful if it's approved in time."

Stephanie Hudson, of St. Louis, whose child suffers from sickle cell anemia, is upset that the FDA has not officially approved the drug hydroxyurea for the disease. Hydroxyurea has been approved for other uses since the 1960s, and doctors are free to prescribe it as they see fit. Hudson complains, however, that many insurance companies don't reimburse patients for such "off-label" prescriptions.

But Hudson's problems are not with the FDA. The agency has little influence over insurers' policies, and Bristol-Myers Squibb Co., which holds the patent on the drug, has never applied for the new use to be approved, although a company spokesman said that "there are conversations going on with the FDA."

Janet McDermott, of Marshfield, Mass., also came to Washington to lobby legislators for FDA reform and was the subject of a profile in the Boston Globe. Her daughter has epilepsy so severe that she can suffer 100 seizures in a single day and is using four medications—and taking 21 pills each day—to bring the seizures down to a few per week. "It's been a roller coaster for the past six years," she says.

McDermott wants her daughter to be able to take Sabril, a promising anti-seizure drug available in Europe and Canada but not yet approved in this country. She obtained an initial supply of the drug on a recent trip to Canada but says her family can ill afford the expense of such a trip on her husband's wages as an ironworker, and cannot depend on being able to obtain a reliable source of the medicine.

McDermott is worried about some provisions of the FDA reform bills. But she believes that "they could cut out a lot of red tape."

Sabril is manufactured by Hoechst Marion Roussel. Company spokesman Charles F. Rouse III said the drug has only been available in Canada for about a year, and added that, although his company believes some drug approvals are slowed by FDA policies, the company bears responsibility for the current Sabril delay because it is gathering data requested by the FDA. "The ball is in our court, now, so to speak," he said.

His company denied McDermott's request for special access to the drug under FDA's "compassionate use" procedures because, Rouse said, it would divert resources from the ongoing large clinical trials and "that would delay the ability to get the drug approved for the population at large that could benefit from it."

Lopez, Hudson and McDermott's names were supplied by Pharma as people whose stories best illustrated the need for FDA reform. When asked why Pharma chose those examples, Korten said, "I was counting on the fact that our folks upstairs would have vetted the list pretty well" for the people whose problems were most on point. He added, "It's possible that what they gave me instead were the people who were the most articulate."

BY TOM GANNAM—ASSOCIATED PRESS

Julie Full-Lopez, who has multiple sclerosis, carries Olympic torch through Crestwood, Mo. She credits a new drug with saving her life.

THE WASHINGTON POST
EDITORIALS/COLUMNISTS C1
SUNDAY, JULY 14, 1996

The Cure That Could Kill You

FDA Reforms Are Bad Medicine

By Morton Mintz

HERE'S A true story you won't hear from House sponsors of three complementary bills to "reform" the Food and Drug Administration, or from free-marketeer think tanks, or from the regulated industries that contribute generously to the lawmakers and think-tankers:

In 1960, a then-new sedative was being widely sold abroad. The William S. Merrell Co. sought FDA approval to the drug here, claiming its safety for the morning sickness of early pregnancy was "firmly established." FDA medical officer Frances Kelsey, seriously doubting the drug's safety, stalled. Two studies vindicated her. The first found that some adult users suffered nerve damage that impaired their ability to walk, with ominous implications for fetal development. The second—coming after the infuriated manufacturer had waited 14 months for approval—revealed that West German women who had taken the sedative in early pregnancy had given birth to armless, legless or limbless infants.

The drug was thalidomide. In the 20 countries where government officials didn't demand substantial evidence of safety (including Germany, England, Canada, Australia, Japan and Brazil) an estimated 7,000 to 11,000 thalidomide babies were born. Had the FDA approved thalidomide, thousands more of these limbless babies would have been born in the United States.

Why didn't the FDA approve the drug? Helen Taussig, a Johns Hopkins pediatrician who investigated the catastrophe in Germany, said at the time that the explanation was "a lucky combination of circumstances" and Kelsey's alertness.

What if the three bills—one for drugs, one for food, and one for medical devices—now being considered by Congress had been law in the 1960s? Pediatric cardiologist John Nestor, a FDA colleague of Kelsey who had reinforced her skepticism about thalidomide, reviewed the drug bill at my request. "It is my opinion that thalidomide would have been approved . . .and that a catastrophe would have occurred," said Nestor, now retired. "If the bill becomes law we can expect more drug catastrophes."

The FDA reformers, emboldened by the Republican takeover of Congress, want nothing less than to transform the way food and drugs have been regulated in the United States since the 1930s. They hope to speed the process of approving regulated products, proposing that the reviews now conducted by the FDA be replaced by reviews paid for by industry. FDA bureaucrats, says Rep. James Greenwood (R-Pa.), the floor manager for the bills, must be stopped from "nitpicking" new-drug applications by "saying 'not yet, not yet, not yet' for years and years and years."

The reformers' pitch sounds appealing. Victims of terrible diseases want relief for their suffering quickly and companies want their drugs and devices to get to market without undue delay. But, in their desperation, victims and their families may, for very human and understandable reasons, put their faith in a nostrum or unproved drug or device. Drug companies and politicians are exploiting these hopes in their campaign to remake the FDA. The bills could all but dismantle the agency as the guarantor of the safety and effectiveness of medicines and medical devices and of the safety of foods.

For starters, the FDA's clear-cut mission—"protect the public health and safety"—would be eroded by a "yes, but" directive. The new proposed mission statement asserts that clinical research should be reviewed "promptly and efficiently" and "take appropriate action on the marketing of regulated products" so as not to "unduly impede innovation or . . . availability." Last week, with action by the House Commerce Committee apparently imminent, the drug and medical-device bills were shorn of some extreme provisions.

Even so, key FDA functions would be transferred to private contractors. Unapproved drug uses could be promoted to physicians with unreliable information on safety and effectiveness, but the agency is forbidden from requiring that patients receive brochures containing FDA-approved information with their drugs. Supplemental uses of a drug could be approved without clinical testing for safety and effectiveness. A requirement that hospitals inform the FDA of deaths and serious injuries associated with medical devices would be weakened. New regulatory mechanisms could threaten food safety and sanitation.

The proposed privatization of reviews for scientific trials for safety and effectiveness would create new risks for public health and safety. Makers of medical devices, food additives and colorings, and, when the FDA is willing, drugs, could retain nominally independent third parties to review their new products. On paper, the third parties would be accountable to the public. In reality, they would face pressures to please well-paying clients free to take their patronage elsewhere. The FDA would have a perilously brief period to examine their recommendations.

For 34 years, 26 of them as a Washington Post reporter and then as an author, I've written about FDA-related issues and drug and medical-device disasters, starting with thalidomide in 1962. Two questions about the pending bills strike me as basic: Whom do you trust? Who benefits?

■ *The manufacturers.* The FDA has found that the nation's top pharmaceutical houses—the ones that provide life-preserving medicines—sometimes engage in life-threatening practices that violate the FDA law. These manufacturers need more scrutiny, not Consider just one key FDA requirement: to report alarming drug reactions within 15 days. Violators include G.D. Searle, Hoffmann-LaRoche and Johnson & Jo n. In 1994-95, Pfizer was 44 to 514 days late in reporting alarming reactions from no fewer than eight drugs. Criminal violations were admitted by SmithKline Beecham in 1984, Eli Lilly in 1985, Hoechst AG in 1991 and Warner-Lambert in 1995. Recently, the FDA admitted it "should have" referred Upjohn's reporting and nonreporting of problems with its Halcion sleeping pill to the Justice Department for criminal investigation four s ago.

■ *The sponsors.* In the three years ending Dec. 31, according to the Center for R nsive Politics, the political action committees of FDA-regulated companies invested $881,635 in 33 Republican and 10 Democratic s s of the reform bills. The tobacco industry, striving to block FDA regulation of advertising of tobacco products to children, i d an additional $428,449. Of the combined total of $1,310,084, the three lead sponsors—GOP Reps. Richard Burr (N.C.), Joe ton (Tex.), (devices), and Scott Klug (Wis.), (food)—got $121,500.

■ *The guru.* In 1994, Newt Gingrich asked the Progress and Freedom Foundation to design a replacement for the FDA. Gingrich is close to foundation president Jeffrey Eisenach, who acknowledged to the Wall Street Journal that drug companies help finance the foundation. In 1995, the foundation revealed initial proposals—mirrored in the bills—for privatizing review and approval of FDA-regulated products and stripping the FDA of all but limited power to block unsafe or ineffective products. Gingrich has called the FDA "the leading job-killer in America."

■ *The opponents.* Impressively, foes of the pending legislation include fierce critics of the FDA. Over the last 25 years, the nonprofit Public Citizen's Health Research Group, filed more than 50 petitions with the FDA to force warning labels onto dangerous drugs or devices or to take other strong actions. Yet Sidney Wolfe, the group's founder and director, says the reform bills "would cripple [the FDA's] ability to adequately protect Americans."

At the heart of the reformers' argument is the assumption that new drugs waiting to get on the market are better drugs. In fact, most

new drug applications are not for therapeutic breakthroughs, but for "copy-cats" offering little or no gain for public health. And new can sometimes be worse. Thalidomide was new in 1961. The Dalkon Shield was new in 1971, but those FDA nitpickers had no opportunity to say "not yet" to the disastrously defective IUD. Why? Congress declined numerous presidential appeals to require a pre-marketing showing of safety and efficacy for devices until 1976—after the device had sterilized of tens of thousands of women.

In the late 1980s, without FDA approval, physicians hoping to prevent sudden death in high-risk heart patients began prescribing a certain group of drugs to suppress mild irregular heartbeat. Then a National Institutes of Health study demonstrated that instead of preventing cardiac arrest, two of the medicines, 3M's Tambacor and Bristol-Myers' Enkaid, sometimes caused it. Under the current drug bill, this off-label use for this group of medicines could have been heavily promoted. "At least 50,000" deaths in the United States attributable to these drugs have already occurred, according to Thomas Moore, a senior fellow at George Washington University's Center for Health Policy Research. Under the proposed legislation, "thousands more unnecessary deaths would have occurred," David Kessler, commissioner of the FDA, told Congress in May.

The reformers complain that foreigners get new drugs faster than we do. Is this necessarily bad? Between 1970 and 1992, 56 new drugs marketed in the United States, United Kingdom, Germany and France were withdrawn for safety reasons in at least one of those countries. There were 31 withdrawals in France, 30 in Germany, 23 in the United Kingdom, and 9 in the United States. Sidney Wolfe, who assembled the data, testified that FDA regulation weakened by the drug bill to Europe's level would have led to "thousands of serious injuries or deaths" from these drugs here.

In any case, the General Accounting Office says, the FDA has been sharply shortening approval times for new-drug applications. The 1987 average was 33 months; 1992's was 19 months. In 1995, the FDA approved 82 applications in an average of 16.5 months. More importantly, the approval time for the 15 drugs given priority because they were deemed major therapeutic advances was only six months. "We already have achieved one of the major 1997 performance goals," Kessler testified. "We achieved it in 1994." These improvements flowed significantly from a benign reform, a 1992 law giving the FDA more resources financed by drug company "user" fees.

It's possible that "not yets" have undesirably delayed marketing of certain promising products. But consider this: Every day, diabetics prick a finger to draw a drop of blood to test in one of many available blood-sugar meters. Unpleasant, certainly for small children. But they almost always get accurate measurements of their blood sugar to use in adjusting their dosage of insulin. This is literally vital: Inaccuracy can lead to coma, dehydration, even death.

A device that measures blood sugar by looking through the skin would be a blessing. It exists—the Diasensor. Is the FDA blocking it, as some critics claim? No. To expedite the marketing application, the FDA summoned a panel of outside experts. At the manufacturer's request, they delayed meeting for five months, until last February. Even then, however, complete test information was available on only eight patients. The advisers judged eight patients too few to justify mass-marketing. Effectively, they said, "not yet." So did the company: It is testing a new model.

It took a 25-year crusade by Harvey Wiley to win passage of the Pure Food and Drug Act of 1906. He became the first head of what is now the world's most admired regulatory agency. Wiley sounded this warning in 1930: "There is a distinct tendency to put regulations and rules for the enforcement of the law into the hands of the industries engaged in food and drug activities. I consider this one of the most pernicious threats to pure food and drugs."

The current legislation poses just such a threat. It is as if numerous drug and device catastrophes had never occurred, or had taught nothing. Or are the GOP sponsors out to prove Wiley right about the Republican Party? He had given it "unswerving loyalty," his biographer wrote, but finally became convinced that it "had become the shield of the cheat and the adulterator."

THE WASHINGTON POST

A4 SATURDAY, JULY 13, 1996

FDA Reformers Race the Calendar

Sponsors of New Plan Expect Legislation to Reach House Floor Before August Recess

By John Schwartz and Ruth Marcus
Washington Post Staff Writers

After months of inertia, proponents of reforming the Food and Drug Administration—the government's chief consumer protection agency for food and medical products—are trying to build eleventh-hour momentum in Congress.

The latest version of a House plan to revamp the FDA was unveiled Wednesday at a briefing for reporters. The package's sponsors said they expect to move it through the Commerce Committee over the next two weeks and send it to the H floor before the August recess. A similar reform plan is pending in the Senate.

To drug companies, medical device makers, biotechnology firms and food producers, FDA reform is a critical issue and they have been pouring money into an all-out lobbying effort. The agency's vast bailiwick includes the regulation not just of food, drugs and medical devices, but also of blood, veterinary feeds and other products that, taken together, comprise 25 cents of each consumer dollar spent.

Supporters of legislative change at the FDA argue that for decades overregulation has stifled medical innovation and delayed new therapies. "Patients are waiting needlessly—patients are dying needlessly—while they wait for the wheels in the FDA to turn," Rep. James C. Greenwood (R-Pa.), who is managing the House package, said Wednesday.

"The purpose of FDA reform is to try to modernize the agency to assure that they can keep up with the pace of technological innovation, which in turn assures that products will get to patients in a timely fashion," said Alan H. Magazine, head of the Health Industry Manufacturers Association, whose members make medical devices.

Studies on drug approval by the General Accounting Office and others suggest that the FDA generally approves new medicines about as quickly as its counterparts in other developed countries. But it remains slow to act on some medical devices. Although the FDA has made strides in reducing the backlog of applications for most kinds of medical devices, it still takes more than 700 days, on average, to gain approval for new devices, far more than the statutory deadline of 180 days.

The bills under consideration—one in the Senate and three in the House—would force the FDA to hand over much of its work in evaluating drugs, devices and new food additives to agency-accredited private companies. In some cases, companies would be selected and paid by the makers of the products seeking agency approval. The four bills would set tighter deadlines for all drug device approvals.

The bills also would relax the requirements for testing drugs and devices for safety and effectiveness by requiring fewer clinical trials and by reducing the amount of data companies would have to supply the FDA. The House bills also would loosen restrictions on the ways companies may promote unapproved uses for drugs and devices that are already on the market.

Congressional sources last week expressed pessimism about the passage of such complex legislation so late in the session. Rep. Fred Upton (R-Mich.), who pressed for reforms of FDA export rules as part of the continuing resolution in April, said, "There's not a lot of sand in the hourglass. . . . Though people said, 'It's on the respirator' a couple of weeks ago, they do have a chance to get out of the hospital door."

The Congressional Budget Office estimates that implementing the Senate bill would cost the government an additional $555 million over six years. No estimate on the cost of implementing the House bills is available.

Food and Drug Commissioner David A. Kessler maintains that his agency already has taken steps to streamline its activities. He warned that the congressional proposals, particularly those in the House, would cut holes in America's public health safety net and "end up rolling back 50 years of public protection."

Sen. Edward M. Kennedy (D-Mass.), the leading opponent of the Senate's FDA reform bill, said the proposals are "driven by powerful and well-funded interests to gut the regulatory agency that stands between them and increased profits."

Lobbying over the issue has been fierce. Companies pushing for FDA reform have provided hefty donations to key congressional supporters of reform, a review of Federal Election Commission records shows. The interested companies have dramatically increased the amount of their corporate donations this year to the GOP, whose leaders on Capitol Hill back the initiative.

Pharmaceutical and tobacco companies have donated to conservative think tanks that produce studies and advertisements advocating FDA reform, papers that are used by industry in its effort to bolster the case for FDA overhaul. The Pharmaceutical Research and Manufacturers of America (Pharma) has flown in 140 patients with dire diseases, or their relatives, to urge lawmakers to reform the agency.

Many patient groups that have testified in favor of reforming the FDA receive funding from industry. Six of the nine largest funders of the National Coalition for Cancer Survivorship, which has testified in favor of FDA reform, are pharmaceutical manufacturers and their law firm.

Coalition executive director Ellen Stovall that less than 30 percent of her organization's money comes from corporate sources. She said it does not influence her organization's positions and points as proof to the coalition's opposition to the current version of the FDA reform proposals. "We are calling for very moderate reforms," Stovall said. "We are not in favor of privatization of the FDA."

Michael Langan, director of public policy for the National Organization for Rare Disorders (NORD), a federation of 140 voluntary health agencies for people with rare diseases, recalled that pharmaceutical companies and Washington think tanks invited NORD and other groups to attend conferences on FDA reform, beginning year.

"What we quickly realized is that they already had their agenda set out straight in advance," Langan said, "and wanted to push it on us and have us stand side by side." Langan said his group refused, but added that many other of the patients' organizations could scarcely afford to do so.

The pharmaceutical industry has greatly increased donations this year to the Republican Party, whose lawmakers are sponsoring the FDA reform plans.

Eli Lilly & Co., which gave $188,000 in "soft" money (unlimited corporate donations not contributed to specific candidates) to the two major political parties last year, about 70 percent to Republicans, has been far more generous to the GOP in 1996. In the first four months of the year, according to FEC reports, Lilly gave $305,000 to the Republican National Committee. In the first three months of 1996, the only period for which full reports from Democratic committees are available, it gave $32,250 to the Democratic National Committee and its congressional arms.

Likewise, Bristol Myers-Squibb, which gave just under $70,000 in soft money contributions last year, almost all of it to Republicans, dc ed $275,000 to the RNC in the first four months of 1996. The company gave $15,000 to the Democrats.

Key members of the committees handling the FDA reform legislation have received substantial donations from political action committees sponsored by companies with an interest in the subject.

An analysis by the Center for Responsive Politics of political action committee contributions by pharmaceutical, medical device and biotechnology companies found substantial contributions to members of the House Commerce and Senate Labor and Human Resources committees in 1995; a review of 1996 contributions shows even more in the first quarter of this year.

Rep. Joe Barton (R-Tex.), who sponsored the House bill to reform regulation of medical devices, received $41,000 from the interested industry PACs in 1995 and 1996. Rep. Christopher Cox (R-Calif.), who sparred with Kessler and his aides in a number of recent hearings, received $41,700.

Barton's press secretary, Craig Murphy, said Barton had worked on the issue for years and said the PAC contributions represent "a sigh of relief from people who wanted reform at the FDA."

On the Senate labor committee, Bill Frist (R-Tenn.), who has pushed a provision that would allow drug companies to distribute information about unapproved uses of their products, was the leading recipient of interested industry funds, collecting $58,500 in 1995 and 1996.

Frist's press secretary said that as a physician he had a long-standing interest in the topic and that the PAC funds were unrelated to his involvement with the issue.

Rep. Greenwood said the industry lobbying push has not been as important in building support for the legislation as informal calls to lawmakers from executives of medical companies in their congressional districts and discussions with concerned constituents.

"There is a lot more grass-roots interest in this issue than you might guess," Greenwood said. The idea that "industry is in the driver's seat," he added, "really doesn't hold up."

Staff researchers Nathan Abse, Alice Crites and Barbara J. Saffir contributed to this report.

FOR MORE INFORMATION

For a list of all the drugs and devices approved by the FDA this year, visit The Post's site on the World Wide Web at http://www.washingtonpost.com

BY DENNIS COOK—ASSOCIATED PRESS

Food and Drug Commissioner David A. Kessler and associate commissioner Diane Thompson confer in April during Senate labor committee hearings on legislation to overhaul the FDA.

Los Angeles Times
July 8, 1996

COLUMN LEFT/
ROBERT KUTTNER

GOP Fights to Weaken the FDA

■ Bills would privatize oversight of drug manufacturing and limit alerts about problem products.

Americans oppose government regulation in the abstract. But whenever a preventable disaster strikes, there are indignant cries of "where were the regulators?" Yet the Republican crusade to deregulate continues.

The latest assault is a measure to hamstring the Food and Drug Administration. Both the House and Senate are due to consider FDA legislation this month.

The House Commerce Committee is likely to bundle three separate bills into one that would weaken FDA regulation of drugs, medical devices and food additives. Among other things, the measure would allow pharmaceutical companies and makers of medical devices to promote products for uses that have not been proved safe and effective.

In the past, when drugs certified for one use were marketed for other purposes, tragedies have resulted. When, for example, some doctors prescribed the hormone DES to prevent miscarriages, the result was an epidemic of cancers in the offspring.

The House bill would also allow drug companies to "privatize" many FDA responsibilities. It would repeal many reporting requirements that alert the FDA (and doctors) to problems with drugs and medical devices that the manufacturer would just as soon camouflage.

The FDA carefully regulates the testing of new drugs involving human subjects. Under the House bill, the manufacturer would merely notify the FDA that testing was beginning.

Actual supervision of drug testing would become mainly the responsibility of industry-sponsored and -controlled review boards. The FDA would get less clinical data and would have sharply reduced authority to insist on changes if it found evidence of testing abuse.

According to the Public Citizen Health Research Group, between 1980 and 1995 the FDA intervened in 84 cases of new drug studies because of serious lapses by drug companies. These included fabrication of data, failure to obtain informed consent of subjects, submission of false test results and failure to report adverse reactions, including a subject's death.

The House bill would also hobble the FDA in its job of consumer protection by providing that companies submit only research summaries rather than the raw data on which the summaries are based. In the past, drug makers have often glossed over negative effects, which FDA researchers have ferreted out only by examining the raw experimental data.

'Having lost most efforts at regulatory rollback this year, Republicans are eager for one major win.'

The FDA monitors drug manufacturing. The House bills would allow manufacturers to rely instead on private contractors for this vital function. This of course is a gross conflict of interest. It is hard to imagine a private inspector hired by the drug company being as vigilant as one responsible to a public agency.

The Senate bill is not quite as extreme as the House counterpart, but would include many of the privatization measures, as well as tighter deadlines for FDA approvals of new drugs and devices. In some cases, if the FDA missed a deadline, the product could be approved by default.

In fact, FDA drug-review time has been cut roughly in half since 1987 because of congressional and industry prodding and internal FDA reforms. In 1994, 96% of all applications for new drugs were approved within 12 to 15 months.

The combination of reduced data reporting and shorter deadlines means that more dangerous or ineffective products would slip through the regulatory net. And, as if anticipating that result, a "national uniformity" provision of the bill that preempts state laws could make it harder for consumers to collect damages if injured by defective or contaminated products.

The campaign to weaken the FDA reflects a deadly combination of ideological hostility to regulation coupled with a self-interested push by the drug, medical device and biotech industries. Having lost most efforts at regulatory rollback this year, Republicans are eager for one major win.

President Clinton has vetoed other anti-regulatory measures, but this time the administration is sending mixed signals on what final compromise might be acceptable. Some of Clinton's political advisors would like to claim credit for "pro-business" regulatory relief.

Special-interest bills are a constant temptation, especially for Democrats. Biotech is hot. So is privatization. So is the idea that even liberals need to be "pro-business." This is also an election year and the drug and biotech companies are generous campaign spenders.

The FDA is a national resource. Let's remember why we had to regulate food and drugs in the first place, and let's remind wavering politicians that the public interest transcends special interests.

Robert Kuttner writes a syndicated column on economic policy.

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.

ST. LOUIS POST-DISPATCH SUNDAY MAY 19, 1996

EDITORIALS

Close The Food Supplement Loophole

Congress has been holding hearings on bills to privatize, or at least limit the Food and Drug Administration's current role in policing the safety of prescription drugs and other medical devices. It's not a good idea. What's largely unknown, though, is that in respect to food supplements, the deed has already been done. It was a great mistake.

In 1994, Congress passed the Dietary Supplement Health and Education Act, which freed supplement makers from having to demonstrate that their wares were safe or effective before marketing them. Instead, the burden has been shifted to the FDA to show they are unsafe. Given the public's mistaken belief that virtually anything natural must be safe and its assumption that the FDA regulates almost everything anyway, the law is dangerous.

The New York Times recently reported that some 15 people have died in the United States from taking herbal products containing ephedrine. Products combining koka nut (which resembles caffeine) with ephedrine (which resembles speed) have caused strokes, heart attacks and death. Yet ephedrine is marketed across the country under names like Herbal Ecstasy, Xphoria and Cloud 9 (not the same as the health-food candy bar). The FDA is powerless to do anything about it.

While many natural medications are safe even if, in a number of instances, worthless, mixing them can be dangerous. One so-called natural doctor gave a patient an herb from Romania to combat depression while she was already on Prozac. When the patient's regular doctor found out he warned the natural doctor the combination could kill her. The natural doctor was reported as glad to know.

Fixing this gigantic loophole in drug safety won't be easy. The FDA's long accepted role as primary policeman of pharmaceuticals is under attack by Republicans, who would privatize almost everything in sight. As the FDA fights efforts to dismantle it, the agency should cite the dangers in the food supplement industry resulting from the lack of regulatio the GOP wants.

Bill would weaken FDA's monitoring of products

Some anniversaries or birthdays have such national importance, we all should celebrate them.

The birth of our independence is one. Martin Luther King's birthday is another.

The list goes on. One recently celebrated event, the 25th anniversary of the Center for Science in the Public Interest, went unnoticed by most. That's a shame. This national, non-profit group has played a significant role as a watchdog for the food and nutrition industry.

Several months ago, Food and Drug Administration Commissioner David Kessler awarded Michael Jacobson, CSPI founder, with the Commissioner's Special Citation for his work.

The People Helper

"The vision you have had over the last 25 years has been clear and compelling," Kessler said.

"You have led us, you have led the government, you have led industry, and you have led the public in understanding the connection between diet and health."

The CSPI not only educates us — providing the latest information about nutrition, vitamins and food advertising — it also alerts us to issues that affect the quality or safety of our foods. The organization was founded by three former Nader's Raiders to advocate health and nutrition policies that are in the public's best interest.

Recently the center issued an alert, urging consumers to oppose Senate Bill 1477.

"If you like the new unsafe fat substitute olestra and contaminated seafood, you'll love Sen. Nancy Kassebaum's industry-backed bill to 'reform' (translation: weaken) the Food and Drug Administration," CSPI says.

The center says Senate Bill 1477 would allow the FDA to authorize manufacturers to hire private inspectors to carry out its food inspections.

The conflict seems clear to the CSPI. To me. And perhaps to you.

The bill, if passed, also would "effectively transfer from the FDA to private contractors — which might have industry ties — much of the responsibility for reviewing the safety of food additives, drugs, and medical devices like heart valves," the CSPI warns, adding: "And it would weaken the FDA's control over labels that deceptively claim that foods can reduce the risk of cancer, heart disease, etc."

As regular readers of this column know, it's silly to think businesses always will put consumer safety first.

Take, for example, the U.S. Consumer Product Safety Commission's recent announcement that Taito of America would pay a $50,000 civil penalty to settle charges that it failed to report a potentially dangerous product.

The penalty will settle the commission's allegations that Taito failed to file a report, required by the Consumer Product Safety Act, regarding problems with its Supersonic Blastman video arcade games.

The commission alleges that between 1991 and 1994, the company failed to report about 70 cases in which young players fractured or injured wrists and arms as a result of hitting the Blastman's punching pad.

The center is urging consumers to call (1-202-224-3121) or write to their senators (U.S. Senate, Washington, D.C. 20510) to register strong opposition to Senate Bill 1477.

Think of it as a late anniversary present to Jacobson.

■

If you have a question or problem, write to The People Helper at The Times-Picayune, 3800 Howard Ave., New Orleans, La. 70140, or call 821-1727. Consumer complaints about mail-order companies or local businesses must be in writing and should include copies, not originals, of the necessary documentation. Every question received will be considered but only the most interesting and helpful ones will be published. Requests not answered in the column cannot be answered or otherwise acknowledged.

Our perspective

Risky reform

Go slow in making FDA changes

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

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

The legislation goes way too far, way too fast.

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

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

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

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

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

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

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

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

EDITORIALS

Sniping at the FDA

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

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

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

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

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

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

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

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Tuesday, *May 7, 1996*

HOW WE SEE IT

Keep watchdogs on job

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

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

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

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

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

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

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

THE WASHINGTON POST

The House and the FDA

A CERTAIN disconnect persists between the goals expressed by proponents of Food and Drug Administration reform legislation—currently beginning its trek through the House after hearings last week—and the more sweeping, problematic and sometimes downright dangerous measures that are actually being proposed. Much of the testimony at the hearings consisted of wrangles over whether the House-sponsored measures on drugs and device review would, as FDA analysts testified, irresponsibly preempt a wide range of safety regulations at the state level. More general and urgent is the concern over whether the Republican-backed strategy of farming out significant chunks of the safety review process for even the riskiest medical devices and drugs—what some would call "privatizing" the main FDA functions—would effectively remove any government ability to enforce a standard on which consumers could rely.

Unhappily, the answers to both these questions appear to be yes, though the proponents of the bills keep reiterating that their only aim is to streamline the FDA's functions, ease the burdens on U.S. drug and device manufacturers and help the agency do its job better. But if the FDA for many years loomed over the medical approval process like some sort of terrible bureaucratic demon, with small companies telling horror stories about rooms full of documents and endless, unexplained delays, that isn't the ground over which the current legislative battle is being fought. You rarely hear in these criticisms any account taken of the several-years push to speed up those processes under FDA Administrator David Kessler—with the result that the United States now approves most new drugs as quickly as the British and European approval systems. The Senate finished a similar process two weeks ago, bringing out of the Labor and Human Resources Committee a bill that had gone in with elaborate safeguards for the few pilot programs that would allow contracting out—but that emerged from the committee with those pilot programs suddenly and inadvisably expanded to full-fledged changes of approach and philosophy.

Would it be easier and better for drug and device companies to bring out new products if, as many device manufacturers want, the FDA were simply to rule that a drug cleared in Europe could be marketed here without further testing? Would yet more simplification of the safety testing and outright removal of the standard for "efficacy"—a drug or device must actually do something, not just avoid harm—increase the flow of possibly therapeutic new medical products? Maybe—in a world where all devices and drugs *could* be assumed to be safe and no peddler of an experimental treatment had ever been known to cut a safety corner or miss a possible danger. That's not the world as it is, though. Streamlining beyond a reasonable point carries costs—costs that are being too little acknowledged by the proponents of these reforms.

The Buffalo News/Friday, May 3, 1996

Make sure new drugs are safe

Don't sacrifice FDA safeguards for speed and profit

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

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

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

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

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

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

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

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

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

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

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

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

The Boston Globe

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The FDA and Shannon McDermott

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

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

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

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

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

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

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

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

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

WEDNESDAY, APRIL 10, 1996 THE WASHINGTON POST

The FDA Legislation

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

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

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

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

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

New York Times, Saturday, April 6, 1996

Streamlining the F.D.A., Safely

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

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

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

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

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

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

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

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

Houston Chronicle March 23, 1996

Don't let Congress cripple the FDA

By JOE GRAEDON
and TERESA GRAEDON

People's Pharmacy

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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The New Haven Register

March 21, 1996

EDITORIAL

Keep hands off drug safety checks

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

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

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

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

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

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

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

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

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

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

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

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

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

The Des Moines Register

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THE REGISTER'S EDITORIALS

Rushing drugs to market

If the FDA speeds approval,
mistakes are more likely.

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

It also saves lives. But that gets little attention.

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

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

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

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

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