BIOTECHNOLOGY
INDUSTRY
ORGANIZATION

BOARD OF DIRECTORS

EXECUTIVE COMMITTEE

CHAIRMAN
Gordon M. Binder
Amgen

VICE CHAIRMAN
FOOD AND AGRICULTURE
Carrol D. Bolen
Pioneer Hi-Bred International, Inc.

VICE CHAIRMAN
HEALTH CARE
Mark Skaletsky
GelTex Pharmaceuticals, Inc.

SECRETARY
Vaughn M. Kailian
COR Therapeutics, Inc.

TREASURER
Mitchel Sayare
ImmunoGen, Inc.

EX-OFFICIO
Henri A. Termeer
Genzyme Corporation

MEMBERS AT LARGE

Paul Abrams
NeoRx Corporation

David W. Anstice
Merck & Co., Inc.

Richard F. Pops
Alkermes, Inc.

J. Leighton Read
Aviron

David E. Robinson
Ligand Pharmaceuticals, Inc.

EMERGING COMPANIES
SECTION

CHAIRMAN
Thomas G. Wiggans
Connetics Corporation

VICE CHAIR
H. Stewart Parker
Targeted Genetics Corporation

July 24, 1998

Mr. Christopher Jennings
Deputy Assistant to the President
for Health Policy
216 Old Executive Office Building
17th and Pennsylvania Ave., NW
Washington, DC 20502

Dear Chris:

Enclosed are BIO's comments on FDA's proposed implementation of the Mack/Frist provisions of the Food and Drug Modernization Act of 1997 (Section 401 of the legislation). We are extremely disappointed that FDA has not followed the legislative intent in its proposed rule. The Agency's approach essentially negates the provision that was carefully crafted following almost three years of discussion between Congress, FDA, and industry. It appears to us that FDA wants to continue with business as usual, restricting the controlled dissemination of peer-reviewed literature articles, rather than establishing a meaningful program designed to demonstrate the utility of providing such information to health care practitioners.

Now that the comment period has closed, we hope that FDA will reconsider its position and move towards a regulation that is consistent with Congressional intent.

Sincerely,

Alan

Alan Goldhammer, Ph.D.
Executive Director,
Technical Affairs

e-mail: agoldhammer@bio.org

1625 K STREET, N.W., SUITE 1100
WASHINGTON, D.C. 20006-1604

202-857-0244
FAX 202-857-0237
http://www.bio.org

BIO

BIOTECHNOLOGY
INDUSTRY
ORGANIZATION

BOARD OF DIRECTORS

EXECUTIVE COMMITTEE

CHAIRMAN
Gordon M. Binder
Amgen

VICE CHAIRMAN
FOOD AND AGRICULTURE
Carrol D. Boien
Pioneer Hi-Bred International, Inc.

VICE CHAIRMAN
HEALTH CARE
Mark Skaletsky
GelTex Pharmaceuticals, Inc.

SECRETARY
Vaughn M. Kailian
COR Therapeutics, Inc.

TREASURER
Mitchel Sayare
ImmunoGen, Inc.

EX-OFFICIO
Henri A. Termeer
Genzyme Corporation

MEMBERS AT LARGE

Paul Abrams
NeoRx Corporation

David W. Anstice
Merck & Co., Inc.

Richard F. Pops
Alkermes, Inc.

J. Leighton Read
Aviron

David E. Robinson
Ligand Pharmaceuticals, Inc.

EMERGING COMPANIES SECTION

CHAIRMAN
Thomas G. Wiggans
Connetics Corporation

VICE CHAIR
H. Stewart Parker
Targeted Genetics Corporation

July 23, 1998

BY HAND DELIVERY

Dockets Management Branch (HFA-305)
U.S. Food and Drug Administration
Department of Health and Human Services
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Docket No. 98N-0222, Dissemination of Information on Unapproved/New Uses for Marketed Drug, Biologics, and Devices, 63 Fed. Reg. 31143 (June 8, 1998)

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) respectfully submits these comments to the above-referenced docket. BIO appreciates the opportunity to provide input on these important new regulations implementing section 401, Dissemination of Information on New Uses, of the Food and Drug Administration Modernization Act of 1997 ("FDAMA"). 63 Fed. Reg. 31143 (June 8, 1998). As set forth in detail below, however, BIO has very serious concerns with the Food and Drug Administration's ("FDA's") proposed regulations. The goal of Congress was to allow, under balanced circumstances, the dissemination of information on new uses of approved drugs. BIO believes that, as proposed, the regulations totally thwart the clear intent of Congress and thus substantial changes, as suggested below, must

1625 K STREET, N.W., SUITE 1100
WASHINGTON, D.C. 20006-1604

202-857-0244
FAX 202-857-0237
http://www.bio.org

be made to ensure that the final regulations reflect the language and the intent of the law.

BIO represents the emerging biotechnology industry in the United States with over 790 companies and affiliated organizations as members. BIO members are involved in the research and development of health care, agricultural and environmental biotechnology products. The majority of BIO members are involved in the development and marketing of new drugs and biologics. BIO, therefore, has a significant interest in the development of regulations regarding dissemination of information on new or off-label uses of new drugs and biologics that serve the best interests of public health.

I. Executive Summary

Section 401 represents a carefully crafted approach to permit the dissemination of scientific information to physicians, insurers and other health professionals on new uses 1/ of approved medical products without reducing the incentives to file a supplemental application confirming the safety and efficacy of such new uses. As ultimately approved by Congress, the program expires in 2006. In less than three and one half years from now, the Comptroller General must submit to Congress a report on the scientific issues raised by the subchapter in order that Congress may determine whether to extend the program beyond its expiration date. Unfortunately, should the regulations be adopted as proposed, it will be impossible for the Comptroller General to prepare a meaningful report, because insufficient

---

1/ Throughout this document, we use the term "new use," a term that was adopted by Congress in the statute. It is important to note, however, that such uses may be either truly new uses or uses that have been used appropriately by health care practitioners for some time.

information will be available on which to base the study -- for the simple reason that only a very limited amount of scientific information will be disseminated under the new law. This is because the proposed regulations pervert the law and the intent of Congress by narrowing the type of scientific information eligible for dissemination and placing inappropriate limits on the ability to gain a waiver of the law's requirement to submit a supplemental application for the off-label use.

The proposal is paternalistic and cumbersome; it totally destroys the statute's balance between the desirability of dissemination and the policy favoring submission of an NDA/BLA supplement. Indeed, in many ways the proposed regulations appear to be designed for the purpose of making the program unattractive or unavailable to manufacturers. Wholesale revisions are required to conform the regulations to the intent of Congress and to make section 401 workable.

As set forth concretely below, numerous changes to the proposed regulations are necessary to recalibrate the balance Congress put into the statute. They include, among others, significant changes to FDA's definitions of "new use" and "clinical investigation"; significant changes to FDA's criteria for exemptions from the requirement for the submission of a supplemental application; and significant changes to the process FDA has proposed to ensure that the sixty-day time period for a decision by the agency regarding whether an article may be disseminated is, in fact, sixty days and not an unlimited time period subject to FDA discretion.

II. Introduction

Section 401 of FDAMA, Dissemination of Information on New Uses, was intended to allow companies to disseminate useful medical information to health care

practitioners to allow them to provide more effective treatment for their patients. It was carefully crafted to balance the need to get new use information on product labels through the submission and approval of supplemental applications with the need to permit manufacturers to provide health care providers and others with critical information about new product uses. The House Report on FDAMA succinctly describes the intent of Congress:

> The principal policy considerations that underlie this provision are the facilitation of greater access to timely and accurate information by health care providers. Coupled with this goal is a recognition that the FDA has a responsibility to protect the public health.

H.R. Rep. 105-310 at 60 (1997).

Section 401 authorizes dissemination of peer reviewed journals and reference publications (such as textbooks) that contain information on the safety or effectiveness of the new or off-label use of approved drugs and devices. In order to ensure that the desired balance was maintained in section 401, Congress drafted detailed requirements for this program. Indeed, of the approximately 75 substantive provisions of FDAMA, section 401 is the longest and most detailed provision. This level of detail was included to ensure that the intent of Congress was clear. 2/

It is critical to understand that Congress considered this program to be about dissemination of appropriate scientific information and not about promotion of unapproved uses. Therefore, Congress established a system that was intended to rely

---

2/ Section 401 requires that FDA finalize regulations implementing this provision by November 21, 1998. The provision becomes effective either on the date that final regulation takes effect, or if no regulations are finalized, on November 21, 1998.

on the independent medical experts of carefully defined peer-reviewed scientific or medical journals to determine the scientific validity of the articles eligible for dissemination under this provision. It neither considered this to be a program that would require FDA to re-review the published peer-reviewed articles in detail nor expected that FDA would set publication criteria for the nation's most prestigious scientific and medical journals. Rather, if the submitted article about a clinical investigation is fully labeled according to this provision, including the disclaimer that the use is not approved by FDA, and the manufacturer meets the requirements with regard to filing a supplemental application, then the manufacturer may disseminate the article unless FDA objects within sixty days. 3/ This time frame was considered fully adequate by Congress given the nature of the program devised by Congress, which relies heavily on the expertise of independent experts conducting peer review for select scientific or medical journals. Congress also gave FDA increased authority to require that additional information be disseminated with an article and extensive authority to promptly take corrective actions. Lastly, at the request of FDA, Congress included a seven-year sunset provision in the statute and ordered a study by the Comptroller General (General Accounting Office) to evaluate this new program.

On June 8, 1998, FDA published proposed regulations to implement section 401 of FDAMA. Instead of maintaining the careful balance established by Congress, FDA proposed rules that will only discourage the dissemination of new or off-

---

3/ The use of a disclaimer is an important factor in balancing the competing interests. Information disseminated by a company without any disclaimer that the use has not been approved by FDA could mislead. However, when it is clearly disclosed that the agency has not yet approved a use, this simple disclaimer goes a long way towards providing the necessary balance within the context of this entire program.

label use information and render meaningless any study of the program over the next seven years. These regulations would impose conditions on the dissemination program far beyond those required by the statute. As demonstrated below, they also severely limit the ability of manufacturers to disseminate to physicians and other health care providers high quality medical journals on relevant studies and pervert the law's exception to the requirement to submit a supplemental application on the off-label use if it would be economically prohibitive or unethical to do so.

III. FDA's Proposed Regulations Would Impose Conditions that Exceed the Statutory Requirements, Thereby Impeding the Flow of Important Medical Information to Health Professionals

A. Contrary to the Statute, The Proposed Regulations Contain Substantial Limitations on the Types of Clinical Investigations to Which Scientific Articles and Reference Publications May Pertain (Proposed 21 C.F.R. § 99.3)

Section 401 of FDAMA authorizes dissemination of:

> a reprint or copy of an article, peer reviewed by experts qualified by scientific training or experience to evaluate the safety or effectiveness of the drug . . . involved, which was published in a scientific or medical journal . . . which is about a clinical investigation with respect to the drug . . . and which would be considered to be scientifically sound by such experts.

21 U.S.C. § 360aaa-1(a)(1)(A).

We believe that, contrary to the clear intent of the statute, as currently proposed FDA's regulations would severely limit the types of articles that could be disseminated under this provision. As described in detail below, both the proposal's restrictions on the types of clinical trials that may be the subject of a disseminated

article and the types and amount of information about the trials that such articles must include, provide significantly less flexibility than Congress envisioned. By issuing a proposal that would enable the agency to substitute its own judgment for that of the independent scientific experts (who are the peer reviewers identified in section 401) in determining whether a study is scientifically sound, FDA has utterly failed to implement the dissemination provisions in an appropriate manner.

1. Definition of "New Use"
(Proposed 21 C.F.R. § 99.3(g))

Section 401 provides that "information concerning the safety, effectiveness, or benefit of a use not described in the approved labeling of a drug or device" may be disseminated "if the manufacturer meets the requirements of subsection (b)." 21 U.S.C. § 360aaa(a). While FDA incorporates this standard into its proposed definition of "new use," the preamble discussion regarding this standard indicates that the definition is so broad that it threatens to include information on approved uses. See proposed 21 C.F.R. § 99.3(g), 63 Fed. Reg. at 31145. In the preamble the agency states that, under the regulations, new uses would include, but not be limited to: completely different indications, modifications of an existing indications to include a new dose, new dosing schedules, new routes of administration, different durations of usage, new age groups, other patient subgroups, different stages of the disease, different intended outcomes (e.g., improved quality of life), effectiveness for a sign or symptom of the disease not in the current labeling, and comparative claims to other agents. 63 Fed. Reg. at 31145.

This proposed definition, as elaborated upon in the preamble, is entirely too broad. For example, certain comparative claims for approved indications may not

reflect a "new use" of the drug. Similarly, if a drug's approved labeling contains an indication that does not include a patient age limitation, statements describing the use of the drug in a certain age population should not be considered a new use unless the manufacturer makes claims for unique safety or efficacy in that group. The final regulation should narrow the scope of "new use" and, among other changes, clarify that under section 401, claims that are otherwise permitted, including certain comparative claims and those pertaining to subpopulations, will not be considered "new use" claims subject to the requirements of the statute.

2. Restrictions on the Types of Studies
(Proposed 21 C.F.R. § 99.3)

FDA's proposed regulations define a clinical investigation as "an investigation in humans that is prospectively planned to test a specific clinical hypothesis." Proposed 21 C.F.R. § 99.3(b). This definition, which restricts clinical investigations to those that are prospectively planned, is not part of the statute. Indeed, Congress provided enough detail in the statute that "clinical investigation" should not be defined at all by the agency. Congress established statutory criteria to determine whether an article about a clinical investigation is eligible for dissemination, thereby making further agency elaboration on this issue inappropriate.

Indeed, where, as here, the statute is unambiguous, FDA must effectuate Congress' intent. If a statute is clear on its face, the agency must give effect to Congress' intent. Immigration and Naturalization Service v. Cardoza-Fonseca, 480 U.S. 421, 446-48 (1987). See also National Assoc. for Better Broadcasting v. FCC, 830 F.2d 270, 275 (D.C. Cir. 1987) (agency must give effect to the clear intent of Congress and if intent is clear "that is the end of the matter"); Overseas Educ. Assoc. Inc. v.

FLRA, 876 F.2d 960, 964 (D.C. Cir. 1989) (if the meaning of the statute is clear, both the court and the agency must give effect to the "unambiguously expressed intent of Congress").

In this instance, the intent of Congress is clear. First, Congress established that, in order to be eligible for dissemination, an article must be in the form of an unabridged:

> reprint or copy of an article, peer-reviewed by experts qualified by scientific training or experience to evaluate the safety or effectiveness of the drug or device involved, which was published in a scientific or medical journal . . . which is about a clinical investigation with respect to the drug or device, and which would be considered to be scientifically sound by such experts.

21 U.S.C. § 360aaa-1(a)(1). Second, Congress defined the term "scientific or medical journal" as

> a scientific or medical publication (A) that is published by an organization (i) that has an editorial board; (ii) that utilizes experts, who have demonstrated expertise in the subject of an article under review by the organization and who are independent of the organization, to review and objectively select, reject, or provide comments about proposed articles; and (iii) that has a publicly stated policy, to which the organization adheres, of full disclosures of any conflict of interest or biases for all authors or contributors involved with the journal or organization; (B) whose articles are peer-reviewed and published in accordance with the regular peer-review procedures of the organization; (C) that is generally recognized to be of national scope and reputation; (D) that is indexed in the Index Medicus of the National Library of Medicine of the National Institutes of Health; and (E) that is not in the form of a special supplement that has been funded in whole or in part by one or more manufacturers.

21 U.S.C. § 360aaa-5(5). Accordingly, Congress has already determined the criteria an article must meet in order to be eligible for dissemination. FDA inappropriately attempts to narrow this universe of articles by restricting it to those that are prospectively designed.

Such a restriction precludes the use of retrospective studies, which may provide important information, especially in situations where a new use has evolved into standard practice. This definition also would eliminate the use of studies that report case series. FDA simply lacks any authority to establish regulations that contradict the statute in this manner. See Immigration and Naturalization Service v. Cardoza-Fonseca, 480 U.S. at 446-48.

Moreover, even if the agency had the authority to narrow the universe of articles eligible for dissemination, the agency's proposed definition of "clinical investigations" would prohibit the dissemination of many types of important medical and scientific articles. Congress never expressed an intent to limit the types of information that could be disseminated in this manner and it is wholly inappropriate for FDA to adopt such restrictions. Section 552 of the Federal Food, Drug, and Cosmetic Act ("FD&C Act") states that an article must be "about a clinical investigation" and be published in a peer reviewed medical or scientific journal meeting the standards of section 556(5). By unreasonably restricting the definition of a clinical investigation, FDA causes us to question whether the agency truly is attempting to faithfully implement the law. Accordingly, the agency's proposed definition of "clinical investigation" should be deleted from the final rule.

3. FDA's Additional Requirements Regarding the Type and Amount of Information the Article Must Include to Qualify for Dissemination Interfere With the Peer-Review Process (Proposed 21 C.F.R. § 99.101(b)(1), 63 Fed. Reg. at 31146-47)

The language of FDAMA and its statutory history express Congress' decision to rely on the peer-review publication process to determine the "scientific soundness" of clinical investigations for purposes of the dissemination provision. See 21 U.S.C. § 360aaa-1(a)(1). This process is conducted by the experts chosen by the journal that meet the criteria of section 556(5). FDA's proposed regulation would circumvent congressional intent by improperly allowing FDA to revisit such determinations:

> The determination of whether a clinical investigation is considered to be "scientifically sound" will rest on whether the design, conduct, data, and analysis of the investigation described or discussed in a reprint or copy of an article or in a reference publication reasonably support the conclusions reached by the authors.

Proposed 21 C.F.R. § 99.101(b)(1).

FDA has no authority under the statute to substitute its judgment for that of the expert peer-reviewers as it attempts to do through its proposed implementing regulations. The proposed regulations denigrate the function of peer-review. Had Congress intended for FDA to conduct the primary review of materials for purposes of the dissemination provision, Congress would have neither restricted eligible articles to those that have been "peer-reviewed and published in accordance with the regular peer review procedures of the organization" nor required that the journal be "generally

recognized to be of national scope and reputation." See 21 U.S.C. § 360aaa-5(5). Further, by limiting the information that may be disseminated to peer-reviewed articles "about a clinical investigation with respect to the drug or device, and which would be considered to be scientifically sound *by such experts,*" Congress specifically provided that the determination regarding the scientific soundness was to be made by the journal peer-reviewers. Accordingly, FDA lacks any authority to issue regulations to the contrary. Chevron U.S.A., Inc. v. Natural Resources Defense Council, Inc., 467 U.S. 837, 842-43 (1984).

In Chevron the Supreme Court developed a two-step inquiry. The first question is whether "Congress has directly spoken to the precise question at issue." Id. If intent is clear, the agency must give effect to the statute and issue regulations fully consistent with it as well. See NLRB v. United Food and Commercial Workers Union, 484 U.S. 112, 123 (1987). If the statute is silent or ambiguous, then the question is whether the regulations are based on a reasonable interpretation of the statute. See Chevron, 467 U.S. at 842. See also, Cardoza-Fonseca, 480 U.S. at 447-48; Coalition of NYS Career Schools v. Riley, 129 F.3d 276, 279 (2d Cir. 1997); NRDC v. EPA, 859 F.2d 156, 168-69 (D.C. Cir. 1988). Even then, the agency's regulations are entitled to deference only as long as the interpretation is consistent with the statute. See City of Boston v. HUD, 898 F.2d 828, 831 (1st Cir. 1990). In the case at hand, FDA's proposed interpretation of the statute is contrary to the language and intent of Congress and, therefore, must be amended.

The extent to which the agency is seeking to extend its own authority in this area is highlighted by the eight specific requirements set forth in the preamble to the proposed rule. See 63 Fed. Reg. 31143, 31146-7. The list of eight criteria

exemplifies FDA's effort at "piling on" requirements in an attempt to discourage dissemination of new use information. FDA states that it intends to use these criteria to judge whether a clinical investigation is "scientifically sound." Id. FDA's conclusion that the eight criteria cited in the preamble are necessary to "provide a basis for determining whether the conclusions [of the authors] are reasonably supported and the findings represent evidence of safety and effectiveness of the new use" demonstrate the agency's clear intent to ignore the fact that Congress already has decided that such determinations should rest in the hands of the scientific experts responsible for peer review. 63 Fed. Reg. at 31146.

FDA should not interfere with the peer-review process by imposing additional requirements on clinical trials to qualify for dissemination, some of which may not be consistent with certain current journal standards. Indeed, it appears that, through this back door route, FDA is attempting to regulate the standards and content of all journals by establishing these criteria. FDA has no place second-guessing the editorial boards and peer-reviewers of scientific and medical journals.

FDA should make clear in the final version of 21 C.F.R. § 99.101(b)(1) that the statutory criteria, and only the statutory criteria, apply. FDA should clarify that in order to be eligible for dissemination, an article must be about a clinical investigation and be published in a medical or scientific journal that meets the statutory criteria. The regulation, any preamble discussion, or future guidances should not add criteria that restrict the types of journals beyond what Congress provided. To that end, FDA should delete its proposed definition of "scientifically sound" and explicitly reject the eight criteria described in the preamble to the proposal rule.

B. FDA's Proposed Regulations Completely Undermine the Intent of Congress by Effectively Prohibiting the Distribution of Reference Publications (Proposed 21 C.F.R. §§ 99.101, 99.103)

The law requires FDA to permit the distribution of reference publications, including reference texts that meet the requirements of the statute. 21 U.S.C. § 360aaa-1(b). In order to be disseminated, reference texts must not: (1) have been written, edited, excerpted, or published for or at the request of the manufacturer, (2) have been edited or "significantly influenced" by the manufacturer, (3) be solely distributed through such a manufacturer, (4) focus on any particular drug or device of the disseminating manufacturer, or (5) be false or misleading. Id. Instead of implementing the law Congress has written, FDA deliberately attempts to undermine the intent of Congress by proposing regulations that effectively prohibit the distribution of reference texts.

FDA's discussion of the issue in the preamble implies that it is Congress' statute, not the agency's regulations, that effectively prohibits the dissemination of reference texts. This is highly misleading. The statute makes it clear that FDA must allow the dissemination of reference texts that meet the requirements of the statute. In its proposed regulations, FDA narrowly limits the content of a reference text appropriate for dissemination. Ultimately, it is FDA's narrow definition -- not the statute -- that would limit the use of reference texts. The agency's states that, "FDA recognizes that the majority of such [reference texts] would probably not meet the requirements of section 401 of FDAMA and this proposed implementing regulation." 63 Fed. Reg. at 31146. Again, many reference texts may well meet the requirements of FDAMA, it is FDA's regulations and its unnecessary hurdles that will impede the dissemination of reference texts.

The agency cannot finalize the regulations as written, thereby failing to implement the statutory provisions with regard to reference texts. An agency cannot interpret language of a statute contrary to its plain language. See American Federation of Gov't Employees v. FLRA, 750 F.2d 143, 146 (D.C. Cir. 1984) (stating that an agency's interpretation cannot be contrary to the statutory mandate); see also, Baylor Univ. Med. Center v. Heckler, 758 F.2d 1052, 1062 (5th Cir. 1985). An agency interpretation must be "rational and consistent with the statute." See City of Boston, 898 F.2d at 831. Therefore, an agency interpretation is not entitled to deference if it is contrary to the plain language of the statute.

Moreover, the "solution" the agency proposes is to issue a guidance document to address this issue. This is not an option under the statute. FDAMA requires that the agency issue regulations to implement the law or, in the absence of regulations, the law will become effective November 21, 1998. 21 U.S.C. § 360aaa-6(d). Therefore, the agency must either issue regulations, consistent with the language and intent of Congress, that permit the dissemination of reference texts or the statute, which permits the dissemination of such texts, will take effect November 21, 1998.

C. The Proposed Regulations Place Unnecessary Limitations on the Waiver of the Requirement to Submit a Supplemental Application for the New Use (Proposed 21 C.F.R. § 99.205)

In order to support the dissemination of important scientific information on off-label uses while at the same time encouraging manufacturers to conduct the studies necessary to permit inclusion of such uses on product labels, Congress decided to require that a manufacturer who seeks to disseminate information about a new use must either certify that it has filed or within six months will file a supplemental

application or submit a proposed protocol and schedule for conducting the necessary studies and a certification that a supplemental application will be filed within 36 months. 21 U.S.C. § 360aaa-3. Recognizing, however, that under certain circumstances it may be appropriate to permit dissemination of information while exempting a manufacturer from filing a supplemental application, section 401 authorizes exceptions to the requirement if the cost of the studies would be economically prohibitive or if conducting the studies would be unethical. As described below, we object to FDA's proposed regulation implementing the statutory exemptions based on costs and ethical considerations because they are inconsistent with the clear language of FDAMA and the intent of Congress.

1. Exemptions Based on Economic Limitations (Proposed 21 C.F.R. §§ 99.205, 99.305)

Section 401 of FDAMA includes a provision authorizing FDA to waive the requirement that a manufacturer ultimately submit a supplemental application on the off-label use described in a journal article if it would be "economically prohibitive" to conduct the studies necessary to support the supplement. 21 U.S.C. § 360aaa-3(d). FDA's proposed regulations provide that in order to demonstrate eligibility for this exemption the manufacturer must show:

> That the estimated cost of the studies needed to support the submission of a supplemental application for the new use exceed the estimated total revenue from the drug or device less the cost of goods sold and marketing and administrative expenses attributable to the product and there are not less expensive ways to obtain the needed information.

Proposed 21 C.F.R. §§ 99.205(a)(1)(ii) and 99.305(c)(1)(ii). There are two aspects of this standard that are problematic. First, we are troubled by the requirement that manufacturers demonstrate that the costs of studies needed to support the submission of a supplemental application exceed the total revenue from *all sales* of the product (minus expenses), not just sales for the new use. Requiring that estimates of economic benefit to the manufacturer be equal to the prevalence of all diseases or conditions that the drug will be used to treat is totally at odds with the intent of the provision -- which was to authorize a waiver based on the economics of the *new* use. This intent is demonstrated by examination of the statutory provisions themselves. The two statutory considerations for determining whether studies would be economically prohibitive are (a) the lack of exclusive marketing rights *with respect to the new use* and (b) the size of the population expected to benefit *from approval of the supplemental application*. See 21 U.S.C. § 360aaa-3(d)(2)(A). Thus, we believe that the exemption envisioned by Congress requires FDA to focus solely on the sales from the new use in determining whether the costs of studies necessary to complete a supplemental application would be economically prohibitive.

We also are concerned with the notion expressed in the proposed regulations that in order to convince FDA that an exemption is appropriate, a manufacturer must virtually "open its books" to FDA in order to provide the plethora of commercial information the agency intends to require for its independent review. Proposed 21 C.F.R. § 99.205(b)(1)(ii)(A). The data FDA has proposed to request is unreasonably broad and amounts to a fishing expedition on the part of the agency for information FDA is not otherwise entitled to see, including market share information and projection and justification of pricing decisions. Not only are we concerned that FDA lacks the expertise to fairly and adequately assess information of this sort, but to the

extent commercial information is provided to the agency, no provision is made to protect the confidential nature of such information. 4/

Finally, we object to FDA's perception that "Congress made it very clear that exemptions from the requirements to submit a supplement are to be rare." See 63 Fed. Reg. at 31149. FDA lacks a statutory basis for this statement. Indeed, the only reference of this sort of which we are aware is the statement by the conferees that exemptions based solely on the size of the patient population are "intended to be the exception, rather than the rule." H.R. Rep. 105-399 at 15. As we have repeatedly acknowledged, there is no doubt that Congress intended to encourage the conduct of studies in support of supplemental applications. We do not agree, however, that Congress expected the agency to narrow the criteria for the statutory exemption provided by the economically prohibitive provision to the extent it has done so in the proposed regulation.

The statutory provisions applicable to the economically prohibitive provision require an examination of market exclusivity status and estimated population served by the new use. BIO urges that the final regulations should be revised to reflect these criteria. Such a rule will more clearly reflect Congressional intent and require minimal resources to implement.

4/ In response to the agency's request on page 31149 for input regarding use of outside auditors in lieu of submission from the company to FDA, we support providing companies with the option of using an auditor's report as opposed to a submission from the company. It is important to note that this is not the real issue here, however. Regardless of whether the information came from an auditor's report or from a company submission, FDA's regulations inappropriately seek information which is unnecessary to their decision and to which the agency is not entitled.

2. Exemptions Based on Ethical Considerations
(Proposed 21 C.F.R. §§ 99.205, 99.305)

The new law also authorizes FDA to waive the requirement that a company ultimately submit a supplemental application on the off-label use described in the journal article upon a determination that it would be unethical to conduct studies necessary to support the supplement. 21 U.S.C. § 360aaa-3(d). Proposed section 99.205(b)(2) would impose a requirement that the manufacturer demonstrate: (1) why existing data are insufficient to demonstrate safety or effectiveness and (2) why it would be unethical to conduct further studies necessary for approval of the new use. Proposed 21 C.F.R. § 99.205(b)(2). Proposed section 99.205(b)(2)(ii) would limit application of this exemption to those situations when "withholding the drug in the course of conducting a controlled clinical study would pose an unreasonable risk of harm to human subjects." 63 Fed. Reg. at 31149. The proposed regulation goes on to note that an unreasonable risk of harm ordinarily would arise only when the new use appears to affect mortality or irreversible morbidity.

This is contrary to the statute. The statute clearly provides that manufacturers should not be required to conduct trials in support of a supplemental application where patients would be denied the standard of medical care by taking part in a clinical trial. The statute states that in making determinations regarding exemptions "the Secretary shall consider (in addition to any other considerations the Secretary finds appropriate) whether the new use involved is the standard of medical care for a health condition." 21 U.S.C. § 360aaa-3(d)(2)(B). The Conference Report that accompanies

this legislation makes it clear that where a therapy represents a standard of medical care, investigations of that therapy should be considered for exemptions.

> In making the determination of whether to grant an exemption pursuant to subsection (d)(2), the Secretary may consider, among other factors, whether: the new use meets the requirements of section 186(t)(2)(B) of the Social Security Act; a medical specialty society that is represented in or recognized by the Council of Medical Specialty Societies (or is a subspecialty of such society) or is recognized by the American Osteopathic Association, has found that the new use is consistent with sound medical practice; the new use is described in a recommendation or medical practice guideline of a Federal health agency, including the National Institutes of Health, the Agency for Health Care Policy Research, and the Centers for Disease Control and Prevention of the Department of Health and Human Services; the new use is described in one of three compendia: The U.S. Pharmacopoeia-Drug Information, the American Medical Association Drug Evaluation, or the American Hospital Association Formulary Service Drug Information; the new use involves a combination of products of more than one sponsor of a new drug application, a biological license application, a device premarket notification, or a device premarket approval application; or the patent status of the product.

H.R. Rep. 105-399 at 100.

Further, this proposed regulation fails to take into account the difficulty -- or even impossibility -- of enrolling patients in a study in which some subjects will receive a placebo when a patient can go to a doctor and receive a prescription for the same drug. In BIO's view it is unethical to ask them to do so, when a therapy is known to be effective -- despite the absence of complete data to support a supplement. In fact, to require clinical trials when the treatment being investigated is the standard of care may be contrary to the Declaration of Helsinki of the World Health Organization, which provides that "[i]n any medical study, every patient -- including

those of a control group, if any -- should be assured of the best proven diagnostic and therapeutic methods." 5/ In addition, when patients already have access to a drug that is considered to be effective, patients are unlikely to agree to participate in a study where they may or may not receive the drug. In the experience of our member companies, physicians flatly refuse to participate in placebo-controlled studies of therapies they already believe to be effective. FDA must be mindful of the reality of this situation when finalizing regulations implementing this exception.

To address these concerns, FDA must make several changes to this proposed regulation. First, the agency must delete the limitation that this exemption applies only to new uses that "affect mortality or irreversible morbidity". This limitation runs counter to the language and intent of the statute. Second, FDA should include the language from the House Report, quoted above, and preamble in the regulation that describes the circumstances under which a new use is considered a standard of medical care. Finally, the regulations should clarify that where a new use constitutes a standard of medical care, it would be unethical to conduct clinical trials with that therapy and the agency will grant the manufacturer an exemption from the requirement to file a supplement.

D. FDA's Proposed Regulations Inappropriately Seek to Require Manufacturers to Distribute Additional Information not Required by the Statute (Proposed 21 C.F.R. § 99.103)

The law requires that a manufacturer distribute, along with the information to be disseminated under this section, certain information, including, if applicable, that

---

5/ Declaration of Helsinki VI, 41st World Medical Assembly, Hong Kong, September 1989, Principle II.3.

the information is being disseminated at the expense of the manufacturer, the name of any authors who are employees of, consultants to, or have received compensation from the manufacturer, and the official labeling for the drug. 21 U.S.C. § 360aaa(b)(6)(A). The law also provides that the manufacturer must distribute a bibliography of other articles or reference texts that have been previously published about the drug for the use covered by the information disseminated. Id. at § 360aaa(b)(6)(B). Finally, if FDA determines and notifies the manufacturer it has determined that the information proposed for dissemination by the manufacturer is not objective and balanced, it may require that additional objective and scientifically sound information be disseminated, including an objective statement, drafted by FDA, regarding the safety or effectiveness of the new use of the product. Id. As described below, however, several of FDA's proposed regulations designed to implement these provisions of the law are not faithful to the language of the statute but add additional requirements designed to inhibit the free flow of information.

1. "Any Additional Information Required by FDA"
(Proposed 21 C.F.R. § 99.103(a)(4))

Lacking any basis in the law, proposed section 99.103(a)(4) requires that "any additional information required by FDA" be attached to the front of the disseminated materials. Such a requirement could only be written by someone who had no intention of faithfully carrying out the statute. If additional materials, consistent with the statute, are required to be disseminated, they should be presented in a logical manner determined by the manufacturer on a case-by-case basis. The most logical presentation and the one least likely to confuse or mislead readers generally will be to attach FDA-required materials to the back of the materials prepared by the manufacturer for dissemination. A sticker could be prominently placed on the front of

the materials alerting the reader that additional information, included at the request of the agency, is attached to the article or reference text. Such an arrangement would be much more reader-friendly and consistent with the purposes of the statute. Accordingly, we recommend dropping the language "which shall be attached to the front of the disseminated information" from proposed section 99.103(a)(4).

Finally, proposed section 99.103(a)(4) fails to make it clear that the manufacturer is entitled to receive an opportunity to meet regarding this matter. The law clearly requires the agency to provide an opportunity to meet on the matter prior to FDA requiring the manufacturer to include such information. 21 U.S.C. § 360aaa(c). Proposed section 99.103(a)(4) should either reference proposed section 99.301(a)(3), which does provide manufacturers with the opportunity to meet, or incorporate the same language.

2. Prominence Requirements (Proposed 21 C.F.R. § 99.103(b))

The law requires that disclosures be "prominently displayed." 21 U.S.C. § 360aaa(b)(6). Proposed section 99.103(b) appropriately includes language contained in other FDA regulations regarding prominence and how the agency will determine whether a given statement is prominently displayed. However, proposed section 99.103(b) also includes a requirement that statements be outlined, boxed, highlighted, or otherwise graphically designed to separate that information from the other information being disseminated. This requirement lacks any foundation in the statute which requires only that mandatory disclaimers be "prominently displayed." Manufacturers should retain some discretion to determine how to meet the statutory

requirement. This portion of proposed section 99.103(b) is unnecessary and should be omitted.

3. Disclosure That Use Has Not Been Approved by FDA (Proposed 21 C.F.R. § 99.103(a))

As noted above, the statute requires that the manufacturer disclose that the information concerns a use of a product not approved by FDA. 21 U.S.C. § 360aaa(b)(6). The statute does not, nor should FDA, require specific language to convey this fact. This disclosure, like the others included in section 551(b)(6) of the FD&C Act, only need be appropriately -- namely, clearly and conspicuously -- conveyed by the manufacturer. Instead, the proposed regulations contain required language for this disclosure, proposed 21 C.F.R. § 99.103(a). There is no reason to limit manufacturers' flexibility in this manner. The language proposed or similar language should be offered only as a safe harbor. In other words, the regulation should be revised to provide that if the proposed language is used, the disclosure will meet the requirements of the statute. However, manufacturers should be allowed to propose and FDA to accept alternative language that conveys the same information. The regulations should be amended to make the proposed mandatory language a safe harbor provision.

E. FDA Must Clarify the Relationship Between the Proposed Regulations and the Existing IND Regulations (Proposed 21 C.F.R. § 99.201(a))

The law provides that manufacturers wishing to disseminate information under this section that have not begun clinical trials under an IND must include in their submissions a proposed protocol and schedule for conducting the required studies. 21 U.S.C. § 360aaa-3(c). The proposed implementing regulations would require that the

manufacturer submit such protocols and that they comply with the applicable requirements in part 312 of the regulations. Proposed 21 C.F.R. § 99.201(a)(4)(ii). Further, the preamble to the proposed rule states that FDA will consider the proposed protocols an original IND or an amendment to an existing IND. 63 Fed. Reg. at 31148. Proposed section 99.301(b)(1) provides that until FDA notifies the manufacturer that the proposed protocols are adequate and the schedule is reasonable, that the manufacturer may not disseminate information.

We have several concerns regarding the proposed regulations. First, if the protocols submitted to FDA are to be treated as INDs or amendments thereto, under the existing IND regulations the manufacturer may commence such studies within thirty days unless the agency places the study on clinical hold. 21 C.F.R. § 312.40(a). Proposed sections 99.201(a)(2) and 99.301(b)(1) should be revised to be made consistent with the existing IND regulations or, at a minimum, state that nothing in the new regulation is intended to alter the requirements of section 312.40(a).

Second, if the agency does not place a clinical hold on the proposed protocol within the required thirty days, the agency should not then be allowed on day sixty, after the trial has begun, to determine that the proposed protocols are inadequate or the schedule unreasonable. Moreover, even if a protocol is put on clinical hold within thirty days, this should not be dispositive of the decision, required to be made in sixty days, regarding the dissemination of information. Finally, if FDA determines that the protocols are "adequate," the agency should be bound by this decision and proposed section 99.301(b)(1) should be amended to reflect this fact.

F. FDA's Proposed Regulations Fail to Require Prompt Review by the Agency (Proposed 21 C.F.R. §§ 99.201(d), 99.301(a))

The law requires that a person wishing to disseminate information under the new law provide the required information to the agency sixty days prior to such dissemination. 21 U.S.C. § 360aaa(b)(4). The statute also provides that FDA must approve or deny an application for an exemption from filing a supplement within sixty days of receipt of such application. Id. at § 360aaa-3(d)(3). FDA's proposed implementing regulations inappropriately seek to enlarge the congressionally-established time frames for review. Proposed section 99.201(d) provides that the sixty-day period begins "when FDA receives a complete submission. . . . For purposes of this part, a submission shall be considered to be complete if FDA determines that it is sufficiently complete to permit a substantive review." 21 C.F.R. § 99.201(d). Proposed section 99.301(a) provides that within sixty days of receiving a submission, application, or request, the agency may (1) determine that it meets the applicable requirements and the manufacturer may disseminate; (2) request additional information; or (3) determine that the information fails to meet the applicable requirements. Id. at 99.301(a).

FDA's proposed regulations enlarge the statutorily established time frames of sixty days for review. For example, FDA proposes that the sixty-day time clock will not begin until FDA determines that the submission is sufficiently complete to permit a substantive review, yet does not set a time-certain for the agency review of the submission for completeness. Accordingly, under the regulations the agency has proposed, FDA could wait for two or three months to determine whether the submission is complete, thus starting the sixty day time clock months after the submission was filed. To remedy this, FDA should provide that the agency has a certain number of days to determine whether the submission is complete enough to enable the agency to review

it. In other words, to be consistent with the statute, proposed section 99.201(d) should be revised to provide that the agency has, for example, fifteen days from the date of receipt of a submission to determine whether it is sufficiently complete to be reviewed. If it is, the agency must act on the submission within sixty days of the date the submission was received. This procedure is consistent with the way in which FDA manages its time commitments to review applications submitted under the Prescription Drug User Fee Act.

The agency should revise proposed section 99.301(a) in a similar manner to provide for review consistent with the statutory time frames. For example, the statute requires that FDA approve or deny an application for an exemption within sixty days. Currently, the proposed regulations allow the agency to approve, deny <u>or</u> <u>request</u> <u>additional</u> <u>information</u> within sixty days. As addressed above, FDA inappropriately is seeking to extend the review times established by Congress. Further, the proposed regulations do not appear to require the agency to notify the sponsor why the submission is inadequate and more information is needed. Accordingly, proposed section 99.301(a) should be revised to require that FDA make an initial determination within fifteen days after an application, submission or request is filed with FDA regarding whether more information is required. If such information is required, in this initial time frame, the sponsor should be notified why the submission is inadequate and the additional information is needed. The agency should then be required to approve or deny a submission within the sixty days provided by Congress. It is worth noting that this enlargement of the Congressionally-established time frames for review would be unnecessary if the regulations applied the statute as written instead of second-guessing

the peer-review process and allowing FDA to do its own scientific analysis of the materials intended for dissemination. 6/

G. FDA's Attempt To Preview Clinical Data is Inappropriate (Proposed 21 C.F.R. § 99.301(b)(2))

The law provides that sixty days prior to dissemination, a manufacturer supply FDA with any clinical trial information the manufacturer has relating to the safety or effectiveness of the new use. 21 U.S.C. § 360aaa(b)(4). Proposed section 99.301(b)(2) would allow FDA to "conduct a preliminary review of the completed study reports to determine whether they are potentially adequate to support the filing of a supplemental application for the new use." 21 C.F.R. § 99.301(b)(2). This requirement lacks adequate foundation in the statute.

The agency is not entitled to a "sneak peek" at preliminary clinical trial data prior to its submission to the agency in the form of a supplemental application. Such a previewing of the data may cause the agency to prejudge the supplemental application before the manufacturer even submits it to the agency. This type of inquiry simply is not authorized by the statute. Accordingly, proposed section 99.301(b)(2) should be deleted.

6/ Likewise, the regulatory program the agency has proposed is very resource-intensive. If the agency implemented the program as written, where the agency simply determined whether the article met the statutory standards and did not second-guess the peer-review process, the program would not be nearly as costly to the agency.

H. FDA's Proposed Recordkeeping and Reporting Requirements Are Ambiguous and Unnecessarily Burdensome (Proposed 21 C.F.R. § 99.501)

As described below, section 99.501 of the proposed regulations would impose burdensome recordkeeping and reporting requirements on manufacturers.

1. Recordkeeping and Reporting Requirements Tracking Individual Recipients versus Categories (Proposed 21 C.F.R. § 99.501(a))

Proposed section 99.501(a) would require that manufacturers maintain records identifying, either by name or by category, those person to whom they have disseminated information on a new use. The proposed regulations would permit FDA to require that a manufacturer maintain records by name. Proposed 21 C.F.R. § 99.501(a). In the preamble, however, the agency has stated that in most cases it does not intend to do so. While these requirements track the statute, the agency piles on additional requirements. Id. at § 99.501(a)(1)(ii)(A). These additional requirements should be deleted from the final regulations.

Our concern is that, if the agency does not require a manufacturer to maintain records identifying recipients of disseminated information by name, if corrective action later is required, manufacturers should not be subject to enforcement action for not possessing such lists. In other words, if the agency requires a manufacturer to maintain records identifying recipients of disseminated information by category -- which we believe is appropriate -- should corrective action later be required, corrective action designed to reach those categories should satisfy the manufacturer's obligation. FDA cannot expect manufacturers to generate such individually targeted lists for corrective action *ex post facto*. The current language of the preamble and

regulation are ambiguous on this point and FDA should clarify this by regulation. Manufacturers are entitled to such certainty.

2. Reporting Requirements on Ongoing Trials (Proposed 21 C.F.R. § 99.501(b))

Proposed sections 99.501(b)(3) and (b)(4) would require manufacturers to submit semi-annual reports containing, among other things, summaries of any additional clinical research or other data relating to the safety or effectiveness of the new use, including copies of any clinical research possessed by the manufacturer. Proposed 21 C.F.R. § 99.501(b)(3). In addition, manufacturers conducting studies necessary for the submission of a supplemental application are required to provide updates on such studies and, if discontinued, the reason for the discontinuance. Id. at § 99.501(b)(4).

These reporting requirements are duplicative of existing Investigational New Drug ("IND") reporting requirements. Because manufacturers already would be required to submit similar reports under the IND regulations, the proposed regulations are unnecessarily burdensome. Accordingly, FDA should either delete these proposed regulations or, at a minimum, harmonize them with existing IND requirements, including requirements relating to content and timing.

3. Reports on the Continued Need for the Exemption (Proposed 21 C.F.R. § 99.501(b)(5))

Proposed section 99.501(b)(5) requires that a manufacturer granted an exemption from the requirement to submit a supplemental application must submit to FDA, on a semi-annual basis, "any new or additional information that relates to whether the manufacturer continues to meet the requirements for such exemption." 21 C.F.R.

§ 99.501(b)(5). The regulation goes on to state that this information would include any information regarding revenues from sales of the product or new or additional information regarding the persuasiveness of the data. Id. This proposed regulation would require that manufacturers produce extensive market data. The cost of generating the required information is economically prohibitive. Given the economic burden it would impose, such a requirement is unacceptable to industry and should be deleted.

4. Corrective Actions
(Proposed 21 C.F.R. § 99.401)

As part of section 555, Corrective Actions; Cessation of Dissemination, Congress imposed obligations on manufacturers to supply additional information to FDA after dissemination of an article commences as follows:

> After a manufacturer disseminates information under section 551, the manufacturer shall submit to the Secretary a notification of any additional knowledge of the manufacturer on clinical research or other data that relate to the safety or effectiveness of the new use involved. If the manufacturer is in possession of the data, the notification shall include the data. The Secretary shall by regulation establish the scope of the responsibilities of manufacturers under this paragraph, including such limits on the responsibilities as the Secretary determines to be appropriate.

21 U.S.C. § 360aaa-4(a)(2) (emphasis added). Obviously, Congress concluded that it was important that FDA set forth, by regulation, the "limits on the responsibilities" of manufacturers "as the Secretary determines to be appropriate." FDA has not issued any proposed regulations on this issue and it must do so.

IV. Conclusion

Clearly, FDA's proposed regulations were drafted by persons who do not respect the Congressional position that dissemination of balanced information on off-label use is appropriate. It denigrates the function of peer review and substitutes FDA's judgment for that of scientific experts in determining whether a study is scientifically sound. It inappropriately limits the types of studies that may be described in journals eligible for dissemination, and imposes requirements for a journal's description of studies that are not met by peer-reviewed scientific journals today. And it makes a mockery of the "economically prohibitive" exception to the requirement to submit a supplement. In many other ways, it piles on new requirements designed to discourage dissemination of peer-reviewed journals and reference texts. The proposed regulations thus totally upset the balance crafted by Congress between the desirability of dissemination of information and the incentives to file a supplemental application.

Sincerely,

Carl B. Feldbaum
President

Counsel:
Hogan & Hartson, LLP
555 Thirteenth Street, N.W.
Washington, D.C. 20004

FDA MedGuide File CCJ

Status of MedGuide Initiatives Regarding Written Prescription Information

FDA recently indicated that it would be finalizing a part of the MedGuide regulation which the agency initially proposed in August, 1995. The FDA believes that the language in the FY 97 Agriculture Appropriations bill prohibits them from implementing the "voluntary" part of the regulation, but they can go ahead with the part of the regulation relating to drugs which could result in "serious and significant" public health concerns if unaccompanied by useful, written information. The recent FDA unified agenda (published in the April 27 *Federal Register*) indicates that final action will be taken on this part of the proposed regulation in July, 1998.

While the agency has the authority to require (and has required) the dispensing of written information with these types of drugs (such as Accutance, oral contraceptives, certain estrogens), finalizing this part of the original MedGuide rule would formalize their authority in this area. The agency would have new authority to require the dispensing of written information with select drugs or categories of drugs without going through a formal rulemaking process each time.

The current procedure requires the agency to publish a regulation for each drug (or class) for which it wants to require a written information leaflet. This procedure serves as a "check" on the agency's enthusiasm for such requirements by forcing them to go through a rulemaking procedure for each drug. The agency would not have to go through this process each and every time if they finalize this part of the MedGuide rule. A significant "check" on the agency would thus be lost.

Moreover, if part of the MedGuide rule is finalized, the written information distributed would have to conform to FDA-specific criteria for style and substance. This would likely result in all written information leaflets – both mandatory and voluntary – looking the same. Database companies are unlikely to have one style of information for mandatory leaflets and another for voluntary leaflets. Moreover, simply for liability reasons, database companies and pharmacies are likely to conform to FDA's specifications for what the agency considers useful information for all drugs, not just a limited class of drugs. Thus, it is possible that the effect of finalizing this part of the MedGuide regulation could achieve the uniformity that FDA wants, without finalizing the entire rule.

Conflicting Evidence About Agency's Authority on Finalizing Part of the Rule

There are conflicting points of view as to whether the agency really has this authority under the MedGuide language in the FY 97 Appropriations bill to finalize part of the rule. For example, there are two conflicting colloquies from the August 1, 1996 floor debate about MedGuide regarding the agency's ability to finalize part of the MedGuide regulation. In the colloquy between Senators Cochran and Coats (both of whom opposed the MedGuide regulation), the discussion focused on assuring FDA that it continued to retain its existing authority in the area relating to drugs with potential serious and significant side effects, not giving them the authority to finalize part of the regulation to give them new authority.

In his part of the discussion, Coats says that the language in the bill prohibiting the finalizing of the MedGuide rule does not *"preclude the FDA from using its existing authority to require, on a drug by drug basis, the provision of written information prepared by the manufacturer to consumers about prescription drugs that pose a serious health risk."* Coats goes on to say that *"we have been informed by the FDA that it will only be required to use its existing authority to require patient information for a very limited number of products."* There is no discussion about new authority, or finalization of part of the MedGuide rule. This language was just inserted to reassure FDA that it was not losing its existing authority.

In contrast, the colloquy between Senators Bumpers and Kennedy, (both of whom supported the Medguide regulation), suggests that the prohibition does not preclude giving FDA new authority in this area. Kennedy says that the prohibition in the language pertains *to "voluntary information provided by pharmacists. However, there was another part of the pending FDA regulation that was not intended to be affected by this provision. That was FDA's intention to require FDA-approved patient leaflets for drugs that pose a serious and significant public health risk."*

To support the case, Kennedy cites report language from the House report language to H.R. 3603 (FY 97 House Ag Appropriations bill), which stated that the MedGuide provision was "not to be construed as prohibiting the FDA from using its existing authority or regulatory authority to require as part of the manufacturers' approved product labeling the dispensing of written information..."

This language was meant to suggest that the agency could continue to use its existing authority to, on a case-by-case basis, issue a regulation that would require a certain drug or class of drugs to be dispensed with written, consumer-oriented information. It was not meant to suggest that the FDA would be given new regulatory authority on the issue of "serious and significant drugs."

Clearly, there are two interpretations of the impact of the Medguide prohibition. One interpretation is that only part of the proposed rule was stopped, giving FDA the ability to finalize the other part and gain new, consolidated authority in this area. The other interpretation is that the entire rule was stopped, but in doing so, FDA's existing authority remains in tact. The agency is taking the more expansive view of the legislative language.

CRS Analysis Supports Prohibition on Entire Regulation

Shortly after the 1996 law was enacted, Congressional Research Service (CRS) did an analysis of the agency's ability to finalize part of the regulation. The analysis supports the view that FDA cannot implement part of the MedGuide regulation. It says that "the statutory provisions prohibit the Secretary from implementing the entire proposed rule and all components thereof (or a similar MedGuide program) as published in the Federal Register on August 24, 1995."

The analysis goes on to say that the language *"prohibits the agency to act as to the various components of the proposed rule except in accordance with the appropriations measure...but the agency could continue to exercise its statutory and regulatory authority to develop and implement rules mandating PPIs for certain prescription drugs...the amendment appears to preclude a repackaging of the MedGuide proposal or a reproposal of the same or similar plan geared toward implementation in a manner divorced from the appropriations provisions."*

The agency appears to be moving ahead with finalizing part of a regulation for which they do not have statutory authority.

8/98

TITLE VI

RELATED AGENCIES AND FOOD AND DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

GENERAL PROVISIONS

SEC. 601. EFFECTIVE MEDICATION GUIDES.— 21 USC 353 note.

(a) IN GENERAL.—Not later than 30 days after the date of enactment of this Act, the Secretary of the Department of Health and Human Services shall request that national organizations representing health care professionals, consumer organizations, voluntary health agencies, the pharmaceutical industry, drug wholesalers, patient drug information database companies, and other relevant parties collaborate to develop a long-range comprehensive action plan to achieve goals consistent with the goals of the proposed rule of the Food and Drug Administration on "Prescription Drug Product Labeling: Medication Guide Requirements" (60 Fed. Reg. 44182; relating to the provision of oral and written prescription information to consumers).

(b) GOALS.—Goals consistent with the proposed rule described in subsection (a) are the distribution of useful written information to 75 percent of individuals receiving new precriptions by the year 2000 and to 95 percent by the year 2006.

(c) PLAN.—The plan described in subsection (a) shall—

(1) identify the plan goals;

(2) assess the effectiveness of the current private-sector approaches used to provide oral and written prescription information to consumers;

Guidelines.

(3) develop guidelines for providing effective oral and written prescription information consistent with the findings of any such assessment;

(4) contain elements necessary to ensure the transmittal of useful information to the consuming public, including being scientifically accurate, non-promotional in tone and content, sufficiently specific and comprehensive as to adequately inform consumers about the use of the product, and in an understandable, legible format that is readily comprehensible and not confusing to consumers expected to use the product.

(5) develop a mechanism to assess periodically the quality of the oral and written prescription information and the frequency with which the information is provided to consumers; and

(6) provide for compliance with relevant State board regulations.

(d) LIMITATION ON THE AUTHORITY OF THE SECRETARY.—The Secretary of the Department of Health and Human Services shall have no authority to implement the proposed rule described in subsection (a), or to develop any similar regulation, policy statement, or other guideline specifying a uniform content or format for written information voluntarily provided to consumers about prescription drugs if, (1) not later than 120 days after the date of enactment of this Act, the national organizations described in subsection (a) develop and submit to the Secretary for Health and Human Services a comprehensive, long-range action plan (as described in subsection (a)) which shall be acceptable to the Secretary of Health and Human Services; (2) the aforementioned plan is submitted to the Secretary of Health and Human Services for review and acceptance: *Provided,* That the Secretary shall give due consideration to the submitted plan and that any such acceptance shall not be arbitrarily withheld; and (3) the implementation of (a) a plan accepted by the Secretary commences within 30 days of the Secretary's acceptance of such plan, or (b) the plan submitted to the Secretary commences within 60 days of the submission of such plan if the Secretary fails to take any action on the plan within 30 days of the submission of the plan. The Secretary shall accept, reject or suggest modifications to the plan submitted within 30 days of its submission. The Secretary may confer with and assist private parties in the development of the plan described in subsections (a) and (b).

(e) SECRETARY REVIEW.—Not later than January 1, 2001, the Secretary of the Department of Health and Human Services shall review the status of private-sector initiatives designed to achieve the goals of the plan described in subsection (a), and if such goals are not achieved, the limitation in subsection (d) shall not apply, and the Secretary shall seek public comment on other initiatives that may be carried out to meet such goals.

Timetable:

Action	Date	FR Cite
NPRM	03/14/94	59 FR 11842
NPRM Comment Period End	08/01/94	
Final Action	07/00/98	

Small Entities Affected: Businesses, Organizations

Government Levels Affected: State, Federal

Additional Information: Previously reported under RIN 0905-AD44.

Agency Contact: Lee D. Korb, Regulatory Counsel, Regulatory Policy Staff, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (HFD-7), 1451 Rockville Pike, Suite 3047, Rockville, MD 20852
Phone: 301 594-2041
Fax: 301 827-5562

RIN: 0910–AA08

982. BIOLOGICAL PRODUCTS: REPORTING OF ERRORS AND ACCIDENTS IN MANUFACTURING

Priority: Substantive, Nonsignificant

Legal Authority: 21 USC 321; 21 USC 331; 21 USC 351 to 353; 21 USC 355; 21 USC 360; 21 USC 360i; 21 USC 360j; 21 USC 371; 21 USC 374; 42 USC 216; 42 USC 262 to 264; 42 USC 300aa-25

CFR Citation: 21 CFR 600; 21 CFR 606

Legal Deadline: None

Abstract: FDA is amending the regulations that require licensed manufacturers of biological products to report errors and accidents in manufacturing that may affect the safety, purity, or potency of a product. FDA defines terms used; establishes a reporting period for all licensed biological products; and amends the current good manufacturing practice (CGMP) regulations for blood and blood components to require error and accident reporting by unlicensed registered blood establishments and transfusion services currently reporting on a voluntary basis. The reporting requirements will expedite reporting of errors and accidents in manufacturing of biological products; provides FDA with a more accurate surveillance of the Nation's blood supply, enabling FDA to monitor actions taken in response to the errors and accidents detected for all establishments involved in the manufacture of blood and blood components; and facilitate a rapid response where public health may be at risk. The cost to licensed establishments would be minimal, since they already are required to report. Unlicensed establishments would only have to make some changes in standard operating procedures. Unlicensed establishments are already required to keep records and conduct investigations. Under the final rule they would have to establish reporting procedures and report to FDA. The transfusion services would have to assure that their recordkeeping and investigation procedures are sufficient, and establish reporting procedures.

Timetable:

Action	Date	FR Cite
NPRM	09/23/97	62 FR 49642
NPRM Comment Period End	12/22/97	
Final Action	12/00/98	

Small Entities Affected: Businesses, Organizations

Government Levels Affected: None

Additional Information: Previously reported under RIN 0905-AD67.

Agency Contact: Valerie A. Butler, Consumer Safety Officer, Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research (HFM-17), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448
Phone: 301 827-6210

RIN: 0910–AA12

983. TAMPER-EVIDENT PACKAGING REQUIREMENTS FOR OVER-THE-COUNTER HUMAN DRUG PRODUCTS

Priority: Substantive, Nonsignificant

Legal Authority: 21 USC 321; 21 USC 351; 21 USC 352; 21 USC 355; 21 USC 371

CFR Citation: 21 CFR 211

Legal Deadline: None

Abstract: FDA has required tamper-resistant packaging features for OTC drug products since 1982. The tamper-resistant packaging regulations were revised in 1989 in response to continuing tampering incidents. Despite the regulatory protection provided by the regulations, two-piece, hard gelatin capsules remain vulnerable to malicious tampering and were implicated in tampering incidents in 1991. This action is in response to the 1991 tampering incidents and requires use of the term "tamper-evident" instead of "tamper-resistant", and that all OTC human drug products marketed in two-piece, hard gelatin capsules be sealed.

Timetable:

Action	Date	FR Cite
NPRM	01/18/94	59 FR 2542
NPRM Comment Period End	03/21/94	
Final Action	06/00/98	
Final Action Effective	06/00/99	

Small Entities Affected: Businesses

Government Levels Affected: Federal

Additional Information: Previously reported under RIN 0905-AE27.

Agency Contact: Thomas Kuchenberg, Regulatory Counsel, Regulatory Policy Staff, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (HFD-7), 1451 Rockville Pike, Suite 3047, Rockville, MD 20852
Phone: 301 594-2041
Fax: 301 827-5562

RIN: 0910–AA26

984. PRESCRIPTION DRUG PRODUCT LABELING; MEDICATION GUIDE

Priority: Other Significant

Legal Authority: 21 USC 321; 21 USC 352; 21 USC 371; 21 USC 355; 42 USC 262

CFR Citation: 21 CFR 201; 21 CFR 208; 21 CFR 314; 21 CFR 600

Legal Deadline: None

Abstract: In August, 1995 the Food and Drug Administration (FDA) published a proposed rule that specified standards for the distribution and quality of useful prescription medication information, designed for patients, that voluntary, private-sector efforts should supply to patients receiving new prescriptions. On August 6, 1996, section 601 of the Agriculture Rural Development, Food and Drug Administration, and Related Agencies Appropriations Act, 1997 was enacted which places the proposed rule as it relates to a voluntary program in abeyance. The legislation did not address the provisions that would have required mandatory Medication Guides in relatively rare instances (approximately 5 products annually)

where a product poses a serious and significant public health concern requiring immediate distribution of FDA-approved patient information. FDA is in the process of finalizing the requirement for mandatory Medication Guides for these rare products.

Timetable:

Action	Date	FR Cite
NPRM	08/24/95	60 FR 44182
Final Action	07/00/98	

Small Entities Affected: Businesses

Government Levels Affected: State, Federal

Additional Information: Previously reported under RIN 0905-AE43.

Agency Contact: Nancy M. Ostrove, Division of Drug Marketing, Advertising, and Communications, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (HFD-240), 5600 Fishers Lane, Rockville, MD 20857
Phone: 301 594-6828

RIN: 0910–AA37

985. CURRENT GOOD MANUFACTURING PRACTICE; AMENDMENT OF CERTAIN REQUIREMENTS FOR FINISHED PHARMACEUTICALS

Priority: Other Significant

Legal Authority: 21 USC 321; 21 USC 351 to 352; 21 USC 355 to 357; 21 USC 360b; 21 USC 371; 21 USC 374

CFR Citation: 21 CFR 210.3; 21 CFR 211.22; 21 CFR 211.68; 21 CFR 211.82; 21 CFR 211.84; 21 CFR 211.101; 21 CFR 211.103; 21 CFR 211.110; 21 CFR 211.111; 21 CFR 211.113; 21 CFR 211.115; 21 CFR 211.160; 21 CFR 211.166; 21 CFR 211.192; 21 CFR 211.220; ...

Legal Deadline: None

Abstract: FDA is finalizing revisions to the current good manufacturing practice (CGMP) regulations at 21 CFR parts 210 and 211 regarding finished pharmaceuticals. The new regulations codify current agency policies or current industry practices. Among other things, the rule will create or clarify requirements for process and methods validation, appropriate laboratory testing procedures, and protection against contamination. The rule is designed to update the CGMP regulations in response to technological changes and the agency's experience with the regulations.

Timetable:

Action	Date	FR Cite
NPRM	05/03/96	61 FR 20104
NPRM Comment Period End	09/30/96	
Final Action	12/00/98	
Final Action Effective	03/00/99	

Small Entities Affected: Businesses

Government Levels Affected: Federal

Additional Information: Previously reported under RIN 0905-AE63.

Agency Contact: Thomas Kuchenberg, Regulatory Counsel, Regulatory Policy Staff, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (HFD-7), 1451 Rockville Pike, Suite 3047, Rockville, MD 20852
Phone: 301 594-2041
Fax: 301 827-5562

RIN: 0910–AA45

986. PARENTERAL DRUG PRODUCTS CONTAINING ALUMINUM AS AN INGREDIENT OR CONTAMINANT; LABELING REQUIREMENTS; WARNING STATEMENT

Priority: Other Significant. Major status under 5 USC 801 is undetermined.

Unfunded Mandates: Undetermined

Legal Authority: 21 USC 321; 21 USC 331; 21 USC 351 to 353; 21 USC 355 to 358; 21 USC 360; 21 USC 371; 21 USC 374; 21 USC 379; 42 USC 216; 42 USC 241; 42 USC 262; 21 USC 264

CFR Citation: 21 CFR 201

Legal Deadline: None

Abstract: The rule will establish a maximum level of aluminum permitted in large volume parenterals used in total parenteral nutrition therapy; require that the maximum aluminum content present at the time of release be stated on the immediate container label of certain small volume parenterals and pharmacy bulk packages; require that the package insert of all parenterals include a warning statement on the effects of aluminum toxicity in patients with impaired kidneys receiving total parenteral nutrition therapy; and require manufacturers to develop validated assay methods for determining the aluminum content.

Timetable:

Action	Date	FR Cite
NPRM	01/05/98	63 FR 176
NPRM Comment Period End	04/06/98	
Final Action	11/00/98	

Small Entities Affected: Undetermined

Government Levels Affected: Undetermined

Agency Contact: Leanne Cusumano, Regulatory Counsel, Regulatory Policy Staff, Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (HFD-7), 1451 Rockville Pike, Suite 3047, Rockville, MD 20852
Phone: 301 594-2041
Fax: 301 827-5562

RIN: 0910–AA74

987. NEW DRUG APPLICATIONS; DRUG MASTER FILE

Priority: Substantive, Nonsignificant

Reinventing Government: This rulemaking is part of the Reinventing Government effort. It will revise text in the CFR to reduce burden or duplication, or streamline requirements.

Legal Authority: 21 USC 321; 21 USC 331; 21 USC 351 to 353; 21 USC 355 to 357; 21 USC 371; 21 USC 374; 21 USC 379

CFR Citation: 21 CFR 314

Legal Deadline: None

Abstract: The final rule eliminates Type I Drug Master Files, which contain information about manufacturing sites, facilities, operating procedures, and personnel, because these files contain outdated information, duplicate information contained in marketing applications, and are not used by application review divisions or field inspectors.

Timetable:

Action	Date	FR Cite
NPRM	07/03/95	60 FR 34486
NPRM Comment Period End	10/02/95	
Final Action	06/00/98	
Final Action Effective	12/00/98	

Small Entities Affected: None

Government Levels Affected: None

Agency Contact: Thomas Kuchenburg, Regulatory Counsel, Department of

Congressional Research Service • The Library of Congress • Washington, D.C. 20540-7000

October 11, 1996

TO:

FROM: American Law Division

SUBJECT: Analysis of Proposed FDA Rule on Medication Guides (MedGuide) and a Recent Appropriations Provision which Affects Implementation of the MedGuide Rule

This responds to your request for an analysis of several questions concerning the FDA's proposed MedGuide rule published on August 24, 1995 and the effect of a recent appropriations provision on the proposed rule. The following (a) summarizes the proposed rule and appropriations amendment as enacted; (b) provides an overview of relevant statutory provisions and case law as it relates to the FDA's authority to require the inclusion of patient labeling information with certain prescription drugs; and (c) in sequential order, discusses your questions.

Background: Proposed Rule and Appropriations Amendment

On August 24, 1995, the FDA issued a proposed rule[1] aimed at improving the quality and distribution of patient information relating to prescription drugs and biological products. Under the rule, useful information would be provided to most outpatient prescription drug users at the time the drug was dispensed. If finalized, the rule would require a Medication Guide (MedGuide) for most prescription drug products and would require manufacturers to prepare and distribute, or provide the means for distributing, a MedGuide that would accompany prescription drug products to the patient. In addition, the proposed rule includes performance standards which, if met, would help to ensure that patients receive understandable and useful information concerning the drug they are using. For example, the rule proposes that private sector initiatives meet the goal of distributing useful patient information to 75 percent of people receiving new prescriptions by the year 2000 and 95 percent by the year 2006. The agency proposes two alternative approaches to ensure that the performance

[1] 60 Fed. Reg. 44182 (August 24, 1995).

standards are achieved for most outpatient drugs and biological products. Under Alternative A, the proposed comprehensive MedGuide program and requirements would be *deferred* for most prescription drugs in order to give voluntary efforts a chance to meet specific goals of distribution of patient information within certain timeframes. The agency would conduct periodic evaluations to measure success. If standards are not met in the timeframes, the proposed rule would be finalized.

Under Alternative B, the agency would also give voluntary efforts a chance to meet the goals of distribution of useful patient information. However, if the standards are not met, the agency would not finalize immediately the proposed provisions. Rather, it would seek public comment on whether a comprehensive MedGuide program, as described in the proposal, should be finalized or whether other steps should be taken to meet patient information goals.[2] The proposed rule provides that regardless of which alternative is chosen, the agency is also proposing regulations that would require FDA-approved MedGuides for products that pose a "serious and significant public health concern" requiring immediate distribution of FDA-approved patient information. The agency anticipates that about 10 products or product classes would be involved. For these products, the regulations would become effective 30 days following publication of the final rule (under Alternatives A or B).[3] In sum, the proposed regulatory plan proposes to defer implementation of a mandated federal MedGuide program, except for those drugs posing serious and significant public health concerns, in order to give voluntary efforts a chance and until the agency determines that certain performance standards have not been met.[4]

In various sections throughout the proposed rule, the agency stated its objectives with respect to improving patient information:

> The primary objective ... is to enhance the nation's public health by allowing patients to make better use of their medications. FDA believes that the distribution of written prescription drug information to patients, when combined with licensed practitioner and/or pharmacist counseling, would accomplish this goal in two ways. First, it would reduce the incidence of therapeutic failures due to poor compliance with drug regimens. Second, it would decrease the number of preventable adverse drug reactions and preventable drug-drug and drug-food reactions. FDA believes that both outcomes are at least partly attainable with adequate patient knowledge.[5]

---

[2] 60 Fed. Reg. 44203 (1995).

[3] 60 Fed. Reg. 44198, 44203-4 (1995).

[4] 60 Fed. Reg. 44204 (1995).

[5] 60 Fed. Reg. 44204 (1995).

The proposal states further:

> FDA also believes that improved patient education will improve adherence with prescribed regimens, decreasing unnecessary hospitalizations, and will give patients the information they need to make truly informed decisions about the drugs they take .... It is FDA's hope and belief that a renewed partnership to encourage voluntary distribution of prescription drug information, coupled with feedback and accountability, is the best mechanism for achieving the goal of improved patient information.[6]

With respect to the proposed MedGuide for drugs that pose serious or significant public health concerns, the proposed rule indicates that the agency in the past has found it necessary, on some occasions, to require that patient labeling be prepared by the manufacturer and distributed with the prescription drug product. This information was intended to make patients better informed about the product's risks and benefits and to better assure safety and effectiveness in the best interests of the public health. In these cases, e.g., oral contraceptives, certain estrogen drug products, etc., the risks associated with using the product "should be carefully assessed in light of the product's potential benefits for the patient."[7] The patient labeling information proposed in the August 1995 rule is intended to assure that the patient understands the risks and consequences of using the drug, including the significance of proper adherence to the directions. The proposed rule contains the agency's criteria for determining which products or classes should be considered for a required MedGuide or required patient labeling information as products that pose a serious and significant public health concern. The agency seeks comment on the criteria.[8] But as noted above, the proposed rule indicates that regardless of how Alternative A or B unfolds, the agency intends to finalize and implement patient labeling information requirements for drugs that pose serious or significant public health concerns.

Recent legislative developments have affected the status and implementation process for the proposed MedGuide rule. The 1997 Department of Agriculture (USDA) and related agencies appropriations act[9] directs the Secretary of Health and Human Services (HHS) to request that national organizations representing health care professionals, consumer organizations, and other named entities, collaborate to develop a long-range comprehensive action plan to achieve goals consistent with the goals of the proposed rule on prescription drug product

---

[6] 60 Fed. Reg. 44183 (1995).

[7] 60 Fed. Reg. 44198 (1995).

[8] For example, the proposed criteria include: products for which patient labeling could help prevent serious adverse effects; products that have significant risks; products that pose risks in particular populations, etc.

[9] Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriation Act, 1997, Pub. L. No. 104-180, Title VI, § 601, 110 Stat. 1569, 1593 (1996).

labeling, i.e., distribution to inform 75 percent of people receiving new prescriptions by the year 2000 and 95 percent by the year 2006. The Act provides expressly that the Secretary shall have no authority to implement the proposed rule or develop a similar rule or other agency guideline if (1) not later than 120 days after enactment, the national organizations develop and submit an action plan which is acceptable to the Secretary; (2) the plan is submitted to the Secretary for review and acceptance; and (3) the implementation of a plan accepted by the Secretary commences within 30 days of acceptance or the plan submitted commences within 60 days of the submission if the Secretary fails to take any action on the plan within 30 days of submission. The Act states that the Secretary, after due consideration and good faith, is authorized to accept, reject or suggest modifications to the plan and is authorized to confer with and assist private parties in development of the plan. Not later than January 1, 2001, the Secretary must review the status of private sector initiatives designed to achieve these patient information goals and, if the goals have not been achieved, the prohibition on secretarial action shall not apply. At that point, the Secretary is directed to seek public comment on other initiatives that could meet the goals.

In response to the requirements in the appropriations act, the Secretary issued a notice on August 29, 1996 requesting that national organizations having an interest in providing prescription drug information to patients collaborate to develop a long range plan for distributing useful information to consumers. Written requests to participate in this process were due by September 3, 1996.

Overview of FDA's statutory and regulatory authority

FDA is the agency responsible for the proper labeling of prescription drugs and biological products. Under the Federal Food, Drug, and Cosmetic Act (FFDCA) and implementing regulations, a drug must bear certain warning labels to communicate its dangers, benefits, risks and other information to the user.[10] However, prescription drug containers are exempt from warning requirements contained in 21 U.S.C. § 352, but they still must carry proper identifying labeling.[11] The Act presumes that expert intermediaries, e.g., practitioners, will communicate appropriate warnings to the user and/or take into account appropriate factors when ordering the administration of the drug.[12] Notwithstanding this exemption, the FDA allows, and in some cases has required, communications or information be dispensed with a prescription drug. The information may relate to adverse reactions, warnings, precautions, contraindications, and other information. For instance, to better ensure safety and effectiveness, the FDA requires that each dispenser of an oral contraceptive

---

[10] 21 U.S.C. §352. Regulations governing general labeling requirements for human prescription drugs are set forth at 21 C.F.R. Part 201. See also, 31 C.F.R. 310.

[11] 21 U.S.C. § 353(b)(2).

[12] Food and Drug Administration, James O'Reilly, 2d Ed., p. 14-33.

provide a patient package insert (PPI) so that the patient is fully informed of the benefits and risks involved. An oral contraceptive drug product that does not comply with the requirements of 21 C.F.R. §501 is misbranded under section 502 of the FFDCA and subject to the enforcement provisions of the Act. The manufacturer and distributor must provide a PPI in or with each package of the drug. The regulations indicate what information must be contained in the PPI. Moreover, the FDA has developed informational guidance texts to assist those who must meet these requirements.

In 1989, after notice and comment procedures, the FDA revised the requirements for the PPI for oral contraceptives to allow the inclusion of general categories of information, e.g., side effects, risks associated with smoking, etc., rather than mandate a specific warning. The agency again relied upon its asserted statutory authority to ensure that certain labels inform consumers and understandably communicate the risks and benefits of the drug.

The agency has required patient labeling information for certain drug products which include estrogens. The FDA has concluded that the safe and effective use of drug products containing estrogens requires that patients be fully informed of the benefits and risks of these drugs. Accordingly, each estrogen drug product restricted to prescription distribution must contain a PPI containing benefits/risks information.[13] Again, the manufacturer and distributor must include a PPI in the package and the contents of the PPI is set forth in the regulation. Guidance language has been developed and is available from the agency. Similar PPI labeling requirements have been issued for progestational drug products. FDA regulations provide that the safe and effective use of progestational drugs requires that patients be informed that there is an increased risk of birth defects in children whose mothers have taken the specific drug during the first four months of pregnancy.[14]

In the August 1995 MedGuide proposed rule, the FDA listed instances where it has required that labeling be distributed to patients when a prescription drug is dispensed. These instances include: isoproterenol inhalation drug products; oral contraceptive drug products; estrogenic drug products and progestational drug products. The proposed rule also indicates that FDA has approved voluntary patient labeling for certain individual products: Roferon, Introna, Nicoderm, Nicorette, Rogaine, Halcion, Norplant System, Proscar, Accutane, and others.[15] In another Federal Register publication, the FDA has indicated that it has required drug marketers to add special pediatric use instructions to prescription drug products.[16]

---

[13] 21 C.F.R. §310.515.

[14] 21 C.F.R. §310.516.

[15] 60 Fed. Reg. 44184 (1995).

[16] FDA Final Rule, Drug Labeling, 59 Fed. Reg. 64240 (Dec. 13, 1994).

The FDA has relied upon certain provisions of the FFDCA to establish its statutory authority to develop, implement and enforce patient labeling inserts which accompany certain human prescription drugs.[17] Section 505 of the Act[18] governing new drugs provides that a new drug application (NDA) may only be approved as a new drug if shown to be both safe and effective under the conditions of use set out in its labeling. Section 201(p) of the Act[19], which sets forth the definition of a new drug, provides an exemption from the requirement of a new drug application only if the drug is generally recognized as safe and effective under the conditions of use set out in its labeling. And, sections 502(a)[20], which sets forth the misbranding provisions of the Act, and 505(d) of the Act[21], prohibit prescription drug labeling that is false or misleading in any particular. Moreover, section 201(n)[22] of the Act provides that if an article is determined to be misbranded because the labeling is misleading, then in determining whether the label is misleading there shall be taken into account not only representations made or suggested by statement, word, etc., but also the extent to which the labeling fails to reveal material facts. Thus, the agency has concluded that the Act requires the Commissioner to make a determination that the information contained in the labeling for a prescription drug is sufficient to assure the safe and effective use of that drug by consumers. "The Commissioner concludes that such determination may well require specific information to be provided to consumers about the drug, as has already been required for the oral contraceptives in ... 21 C.F.R. 310.501."[23]

The agency recently affirmed its position that it is vested with the statutory authority to revise and create new requirements for prescription drug labeling.[24] In 1994, the FDA amended its content and format prescription drug labeling regulations in Part 201 of the CFR by revising the "pediatric use" section. The change provided for the inclusion of more complete information about the use of a drug, including biological drug products, in the pediatric

---

[17] 42 Fed. Reg. 37636 (July 22, 1977); Final rule mandating patient package insert for estrogen drug products; statement of statutory authority for requiring labeling. The sections relating the agency's legal authority for requiring PPI is an affirmation of an earlier stated position which accompanied the FDA's proposed new format for prescription drug labeling. See, 40 Fed. Reg. 15392.

[18] 21 U.S.C. §355.

[19] 21 U.S.C. §321(p).

[20] 21 U.S.C. §352.

[21] 21 U.S.C. §355 [Grounds for refusing application, etc.].

[22] 21 U.S.C. §321(n).

[23] 42 Fed. Reg. 37636 (1977); estrogen regulation.

[24] 59 Fed. Reg. 64240 (December 13, 1994), Final rule, "Specific Requirements of Content and Formal Labeling for Human Prescription Drugs; Revision of Pediatric Use Subsection in the Labeling."

population. The FDA restated its position that the FFDCA and relevant provisions of the Public Health Service Act provide the statutory jurisdiction for regulating in this manner.

The agency's position has been upheld in federal court. In *Pharmaceutical Mfrs. Ass'n v. FDA*,[25] the appeals court held the FDA had the statutory jurisdiction to promulgate regulations requiring the patient package insert be provided to every patient receiving certain estrogen drugs. The court expressly affirmed the lower court's reasoning and concluded that the FDA issued the rule to effectuate the objectives of the FFDCA, specifically 21 U.S.C. §352(a) which authorizes the agency to act if it finds a drug's labeling to be false or misleading, as those terms are defined in the Act. The court supported the agency's determination that it had found that without the PPI, the estrogen labeling was "'misleading'" because it failed to reveal facts "'with respect to consequences which may result from the use of the article ... under the condition of use prescribed in the labeling ... or under such conditions of use as are customary or usual.'"[26] The court specifically rejected the Association's argument that the legislative history of the Act requires a contrary decision.[27] The court cited the Senate report:

> [This section] provides that a drug dispensed on prescription shall be exempt from the provision of the act relating to misbranding ... except those [provisions] which specify that a drug shall be deemed to be misbranded if its labeling is false or misleading in any particular ... These provisions continue to apply to any drug subject to the act, whether sold over-the-counter or on prescription.[28]

The court held that the FDA has broad statutory authority to protect the public health by making such rules and regulations as may be necessary to carry out the provisions of the FFDCA, however, the agency must exercise that power pursuant to a congressional objective expressed in the Act.[29]

And recently, in 1996, a federal court upheld the FDA's decision to decline to modify the oral contraceptive PPI in order to include warnings proposed by the petitioner that estrogen has been shown to cause breast cancer and other

---

[25] 634 F.2d 106 (3d Cir. 1980).

[26] 634 F.2d, at p. 108.

[27] 21 U.S.C. §353(b) exempts prescription drugs from certain warning requirements.

[28] 634 F.2d, at p. 108, citing, Sen. Rep. No. 946, 82d Cong. 1st Sess. 9-10 (1951).

[29] The lower court's opinion is more detailed in its assessment of the FDA's arguments and asserted statutory and regulatory jurisdiction. The trial court expressly upheld the agency's position that pertinent sections of the FFDCA, as well as relevant portions of the legislative history, supported its asserted legal authority to require PPI in certain estrogen drug products.

types of cancer in animals and may do so in humans. In *Henley v. FDA*[30], the petitioner challenged the FDA's decision to not modify the PPI and argued, *inter alia*, that the decision was arbitrary and capricious. The petitioner also argued that the agency's labeling information was misleading because its content did not disclose certain animal studies. The lower court and the appeals court granted the agency's motion for summary judgment and dismissed the petitioner's complaint. In its opinion, the appeals court held that the agency's decision not to modify the PPI was not irrational, unsupported by relevant factors, an abuse of discretion, or otherwise not in accordance with the law. In addressing the argument that the label is misleading due to its omissions, the court in effect upheld the agency's authority over PPI labeling particularly under the misbranding provisions of the Act. The court expressly held that the label as developed by the agency was not contrary to the law.[31]

Questions summarized and discussion

Question 1. Under what authority does the FDA currently require that manufacturers provide labeling information with prescription drugs, e.g., oral contraceptives?

The foregoing discussion identifies the statutory provisions upon which the FDA relies when promulgating regulations which require a PPI to accompany certain prescription drugs when dispensed to the patient. The agency has asserted consistently over the years that it is exercising its grant of broad substantive rulemaking authority in order to fulfill its duty to protect the public health under the Act. As seen in *Pharmaceutical Mfrs.*, this position has been upheld in federal court.

Question 2. Does the appropriations amendment prohibit the agency from going forward with any part of the proposed regulation?

As enacted, the appropriations provision expressly prohibits the Secretary (or agency) from implementing the proposed Medguide rule as issued in 60 Fed. Reg. 44182 (1995). Moreover, the Act expressly forbids the Secretary to develop a similar rule, policy statement or other guideline which would specify a uniform content or format for written information voluntarily provided to consumers. It appears that this statutory provision prohibits the Secretary from implementing the entire proposed rule and all components thereof (or a similar MedGuide program) as published in the Federal Register on August 24, 1995.

Question 3. Is it a correct interpretation that the amendment does not preclude the agency from using its existing authority to require patient labeling information for certain prescription drugs, but that the provision precludes the FDA from having new authority in this area, at least under the proposed MedGuide rule?

---

[30] 77 F.3d 616 (2d Cir. 1996).

[31] 77 F.3d, at p. 620.

The amendment prohibits the agency to act as to the various components of the proposed rule except in accordance with the appropriations measure, at it relates to the comprehensive MedGuide rule. The amendment appears to relate specifically to the elements of the MedGuide proposal. However, in accordance with the above-cited statutory provisions and past agency practice, it appears that the agency could continue to exercise its statutory and regulatory authority to develop and implement rules mandating PPIs for certain prescription drugs, similar to those issued for oral contraceptives, progestational drugs, or estrogen containing drugs. Ostensibly, these actions would comport with the agency's duties under the Act to protect the public health and to prevent misleading labeling so as to better assure the safety and effectiveness of prescription drugs.

Question 4. Given the amendment, what would the FDA have to do to attain the authority for serious and significant drugs that it sought in the rule? Can it re-propose sections of the proposed rule governing serious and significant drugs? What options are available to the FDA in light of the amendment?

To a certain extent, the agency's authority to mandate PPI information under the Act is separate and apart from the MedGuide proposed rule and the mechanics of its implementation. The FFDCA charges the agency with the statutory obligation to protect the public health and to enforce the misbranding provisions the Act. As discussed above, special patient labeling information requirements for estrogen drugs and other drugs come within the agency's authority vis-a-vis the Act's misbranding, new drug, definitional, and other relevant provisions. Thus, it could be argued that the agency could continue to require patient labeling information for drugs which pose serious and significant risks (or benefits) in order to better assure safety and effectiveness. In light of its weighty statutory duties, it is reasonable to conclude that the FDA may do this on a case-by-case basis, as it has in the past. However, the amendment appears to preclude a "repackaging" of the MedGuide proposal or a re-proposing of the same or similar plan geared toward implementation in a manner divorced from the appropriations provisions.

Diane T. Duffy
Legislative Attorney
American Law Division

File FDA Reform

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

October 7, 1997
(House)

STATEMENT OF ADMINISTRATION POLICY

(THIS STATEMENT HAS BEEN COORDINATED BY OMB WITH THE CONCERNED AGENCIES.)

H.R. 1411 - FDA Regulatory Modernization Act of 1997
(Rep. Burr (R) NC and 16 cosponsors)

The Administration applauds the House for its efforts to produce a bipartisan FDA reform bill, and appreciates the responsiveness to concerns that have been raised. Because of the importance of obtaining a five-year extension of the Prescription Drug User Fee Act (PDUFA), the Administration has no objection to House passage of H.R. 1411 at this time.

This legislation represents a significant step toward accomplishing the mutual goal of assuring the Food and Drug Administration's (FDA) optimum performance while protecting the health of the American public. The Administration, however, continues to have major concerns with the bill and will work to ensure that these concerns are addressed. For example:

-- The PDUFA funding mechanism undercuts the bipartisan budget agreement (BBA) by requiring budget increases for FDA not envisioned by the BBA, and would interfere with HHS' ability to allocate resources appropriately throughout the Department.

-- The third-party review for medical devices provision is too broad. It makes almost all Class II devices eligible for third-party review and requires FDA to include all eligible devices in the third-party review pilot. By contrast, the Senate bill would establish a pilot that would include only 60 percent of eligible devices and gives FDA authority to exempt any device that is of substantial importance in preventing the impairment of human health.

In order to be able to support a final bill, the Administration will continue to work in conference to resolve these and other issues, including (1) the lack of user fees for food contact substances, (2) the effective restriction on public comment on regulations issued under the Nutrition Labeling and Education Reform Act, and (3) the imbalance between the regulatory and resource requirements in H.R. 1411 and in S. 830, the Senate companion bill.

Pay-As-You-Go Scoring

According to CBO estimates, H.R. 1411 would be subject to the pay-as-you-go requirement of the Omnibus Budget Reconciliation Act of 1990 because the bill's provision extending market exclusivity for certain drugs would increase direct spending. CBO estimates that H.R. 1411 would increase direct spending by $65 million during FYs 1999-2002. OMB's preliminary scoring of H.R. 1411 is under development.

* * * * * * * * * *

FDA Reform File

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

SEP 5 1997

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

Dear Mr. Chairman:

I am writing to reiterate the Administration's commitment to continue working with you to accomplish the timely reauthorization of the Prescription Drug User Fee Act (PDUFA) of 1992 and the passage of constructive bipartisan Food and Drug Administration (FDA) reforms. I very much appreciate your leadership and hard work on the important issues that are raised by the FDA legislation and the spirit of cooperation and accommodation that resulted in agreement on so many of the provisions in the Food and Drug Administration Accountability Act of 1997, S. 830. However, we are concerned that a timely reauthorization of PDUFA is in jeopardy.

Mr. Chairman, since S. 830 was reported out of Committee in June, we have come a long way and have reached agreement on what appeared to be the most difficult issues in the bill, including the dissemination of information by drug and device manufacturers, the effectiveness standard for drugs and biologics, the regulation of health economic claims, and the regulation of drugs made through pharmacy compounding. Unfortunately, we continue to have serious concerns about a number of issues that remain unresolved. We think that most of these issues can be worked out, but there are four issues that have the potential for jeopardizing our mutual goal of timely reauthorization of PDUFA and passage of constructive, bipartisan FDA reform.

The first of these issues is preemption of the state regulation of over-the-counter drugs and cosmetics. The Administration has serious concerns about far-reaching preemption -- particularly in the absence of a strong federal program. The second issue relates to what FDA may consider in making substantial equivalence determinations for newly marketed devices. For example, the bill requires the Agency to review the intended use of a new device based on the manufacturer's proposed labeling -- even if the device's technology clearly indicates that the device will be used for a use not included in the labeling. Third, the bill seriously undermines what was sought to be accomplished by the National Environmental Policy Act by virtually eliminating the requirement that FDA disclose the environmental impact of new products that it approves. The Administration recently took significant steps to decrease the burdens that were associated with conducting environmental assessments for FDA-approved products. We can think of no reason to jeopardize the environment by eliminating a review that is not costly to industry. Fourth, the PDUFA trigger as currently proposed in the bill

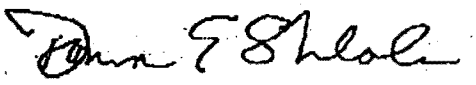
SEP-05-1997 09:43 FROM HHS-OFFICE OF THE SECRET TO 93959184 P.02

would undercut the bipartisan budget agreement by denying FDA access to user fees at expenditure levels consistent with the Balanced Budget Agreement and would interfere with my ability to allocate resources appropriately throughout the Department. Finally, with respect to the pediatric labeling issue, we want to work with the Congress to assure that any provisions in the final bill complement the recent FDA actions and reach our mutual goal of effectively protecting our nation's children and providing needed information to health professionals who treat them.

Mr. Chairman, we in the Administration all agree that reauthorization of PDUFA is in the best interest of the American public. We believe that we are close to reaching consensus on a bipartisan bill that includes this essential reauthorization. However, if the bill were maintained in its present form, and the outstanding issues were not addressed, I would be forced to recommend to the President that he veto this legislation.

The Office of Management and Budget advises that there is no objection to the presentation of this report, and that enactment of S. 830 would not be in accord with the President's program.

Sincerely,



Donna E. Shalala

The Honorable Judd Gregg
United States Senate
Washington, D.C. 20510

Dear Senator Gregg:

I am writing to express my gratitude for your willingness to work with me and Administration staff in crafting compromise language on the issue of preemption of state over-the-counter drug and cosmetic laws. The language that we have agreed to support in the Senate bill will provide for broad preemption for OTC drugs (once their OTC monograph is completed) in exchange for records inspection and ingredient labeling. If the Federal government has specifically acted with respect to labeling and packaging of a cosmetic or class of cosmetics, the bill would preempt states from enacting laws in that area. Where the Federal government has not required specific labeling, the states would be free to enact their own laws and regulations. In addition, the language makes it clear that California's Proposition 65 would not be affected vis a vis OTC drugs or cosmetics.

Again, I greatly appreciate your willingness to work with us in resolving this and other critical issues related to FDA reform legislation. You and your staff have been very helpful in resolving our differences to this point, and we look forward to continuing to work with you and your colleagues to resolve the remaining outstanding issues.

Sincerely,

Donna E. Shalala

FDA - off-Label Dissemination File

Changes Necessary to Conform Proposed Regulations on Dissemination of Information on Off-Label Use to Congressional Intent

1. Definition of "Clinical Investigation" and "Scientifically Sound" Determination. The law authorizes distribution of scientific articles, peer reviewed by experts, "about a clinical investigation . . . which would be considered to be scientifically sound *by such experts*". Instead of relying on peer review as the basis for insuring quality and accuracy, the proposed regulations would significantly restrict scientific articles and reference publications eligible for dissemination in two ways. First, the proposal crafts a narrow definition of "clinical investigation", which restricts "clinical investigations" to those that are prospectively planned. Second, the proposed regulation would authorize *FDA* to determine whether the clinical investigations described in articles are "scientifically sound". Congress intended that a scientific journal's peer reviewers, and not FDA, be the judge of scientific soundness.

The definition of "clinical investigation" should be deleted from the proposal. In addition, the entire concept of FDA review of whether a clinical investigation is scientifically sound must be deleted.

2. "Economically Prohibitive" Exception. The law requires that a manufacturer who seeks to disseminate information about a new use either certify that it has filed (or within 6 months will file) a supplemental NDA/BLA for the new use, or will submit a proposed protocol and schedule for conducting studies

necessary to do so. The law authorizes an exception to these requirements if the Secretary determines that it would be economically prohibitive to incur the costs necessary for the submission of a supplemental application. The law *requires* FDA to consider (in addition to other considerations it may find appropriate) the lack of availability of exclusive marketing rights for the drug and the size of the patient population expected to benefit from the approval of the supplement.

The proposed regulation ignores the mandate to consider the two factors specified in the statute and instead makes the "economically prohibitive" exception available only in the case in which the estimated cost of studies of the *new use* exceeds the estimated *total revenue* from the drug (less expenses). Enormously detailed information about pricing and market share would be required to be submitted. The final regulations should dispense with the entire concept of requiring that estimates of economic benefit to the manufacturer from all sales of the drug be less than the costs of studies of the new use. In its place, FDA should establish a simple, bright line test, based on the two statutory criteria, specifying that (1) no market exclusivity resulting from patents, orphan drug exclusivity or Waxman-Hatch statutory exclusivity provisions are available for the medical product that is the subject of the scientific publication or (2) the patient population likely to be served by the new indication will not exceed an established number, such as 100,000.

3. "Ethical" Exception. The law likewise authorizes an exemption from the supplement/protocol requirements on the basis that it would be unethical

to conduct the studies necessary for the supplemental application. The law *requires* the FDA, in determining whether such studies would be unethical, to consider whether the new use involved is the standard of care. Detailed language in the conference report spells out circumstances that may be used by FDA in making its determination as to whether the new use represents the standard of care; examples include inclusion in specified compendia or practice guidelines. The law also suggests consideration of whether the new use involves a combination of products involving more than one sponsor. But the proposed regulations would limit application of the exemption to situations in which withholding the drug in the course of a clinical trial would present an unreasonable risk of harm to patients. Again, in the interests of creating only a very narrow exemption, FDA has ignored Congressional intent.

The final regulations should establish a bright line to be applied by FDA in determining whether to grant an exemption on ethical grounds. The bright line test should be (1) that the new use represents the standard of care, as represented by inclusion in specified compendia or practice guidelines; or (2) the new use involves a combination of products of more than one sponsor. FDA should grant exceptions on other grounds on a case-by-case basis.

4. <u>60 Day Review Period</u>. Despite the fact that the law requires that FDA make a determination on an application to disseminate within 60 days, the proposed regulations contemplate that during the 60 day period FDA could determine that FDA requires more information. In such case, the proposed

regulations impose on FDA no time frames for obtaining additional information and approving/disapproving the application. The final regulations should honor the 60 day requirement by requiring that any judgment as to completeness, as well as the decision to allow or disallow dissemination, be made within the 60 day statutory period.

5. Definition of "New Use". The law applies to dissemination of scientific information on a "new use" of an approved drug, defined as "a use not included in the labeling" of the product. The definition of "new use" in the proposed regulations and its preamble should be narrowed to delete comparative claims for approved indications and claims for subpopulations.