individual flap transmission shafts. The FAA does not consider it practicable for U.S. operators to accomplish an inspection program that necessitates tracking the landings accumulated on individual flap transmission shaft components due to the difficulty of such tracking.

Operators should further note that, unlike the procedures described in the maintenance instructions, this proposed AD would not permit further flight if cracks are detected in the flap transmission shaft. The FAA has determined that, because of the safety implications and consequences associated with such cracking, any subject flap transmission shaft that is found to be cracked must be repaired or modified prior to further flight.

Cost Impact

The FAA estimates that 2 airplanes of U.S. registry would be affected by this proposed AD, and that it would take approximately 30 work hours per airplane to accomplish the proposed inspection and functional test, at an average labor rate of $60 per work hour. Based on these figures, the cost impact proposed by this AD on U.S. operators is estimated to be $3,600, or $1,800 per airplane, per cycle.

The cost impact figure discussed above is based on assumptions that no operator has yet accomplished any of the proposed requirements of this AD action, and that no operator would accomplish those actions in the future if this AD were not adopted.

Regulatory Impact

The regulations proposed herein would not have substantial direct effects on the States, on the relationship between the national government and the States, or on the distribution of power and responsibilities among the various levels of government. Therefore, in accordance with Executive Order 12612, it is determined that this proposal would not have sufficient federalism implications to warrant the preparation of a Federalism Assessment.

For the reasons discussed above, I certify that this proposed regulation (1) is not a 'significant regulatory action' under Executive Order 12866; (2) is not a 'significant rule' under the DOT Regulatory Policies and Procedures (44 FR 11034, February 26, 1979); and (3) if promulgated, will not have a significant economic impact, positive or negative, on a substantial number of small entities under the criteria of the Regulatory Flexibility Act. A copy of the draft regulatory evaluation prepared for this action is contained in the Rules Docket. A copy of it may be obtained by contacting the Rules Docket at the location provided under the caption **ADDRESSES**.

List of Subjects in 14 CFR Part 39

Air transportation, Aircraft, Aviation safety, Safety.

The Proposed Amendment

Accordingly, pursuant to the authority delegated to me by the Administrator, the Federal Aviation Administration proposes to amend part 39 of the Federal Aviation Regulations (14 CFR part 39) as follows:

PART 39—AIRWORTHINESS DIRECTIVES

1. The authority citation for part 39 continues to read as follows:

Authority: 49 U.S.C. 106(g), 40113, 44701.

§ 39.13 [Amended]

2. Section 39.13 is amended by adding the following new airworthiness directive:

Construcciones Aeronauticas, S.A. (CASA): Docket 98–NM–160–AD.

Applicability: All CASA Model CN–235 series airplanes, certificated in any category.

Note 1: This AD applies to each airplane identified in the preceding applicability provision, regardless of whether it has been modified, altered, or repaired in the area subject to the requirements of this AD. For airplanes that have been modified, altered, or repaired so that the performance of the requirements of this AD is affected, the owner/operator must request approval for an alternative method of compliance in accordance with paragraph (c) of this AD. The request should include an assessment of the effect of the modification, alteration, or repair on the unsafe condition addressed by this AD; and, if the unsafe condition has not been eliminated, the request should include specific proposed actions to address it.

Compliance: Required as indicated, unless accomplished previously.

To detect and correct cracking in the flap transmission shafts, and to correct a malfunctioning flap braking sub-system, which could result in the inability to move the flaps, or in an asymmetric flap condition, and consequent reduced controllability of the airplane; accomplish the following:

(a) Prior to the accumulation of 6,000 total landings, or within 30 days after the effective date of this AD, whichever occurs later, perform a high frequency eddy current (HFEC) inspection of the flap transmission shafts to detect cracking, in accordance with Annex I, dated June 16, 1997, of CASA Maintenance Instructions COM 235–113, Revision 02, dated June 16, 1997.

(1) If no cracking is detected, repeat the HFEC inspection thereafter at intervals not to exceed 2,000 landings.

(2) If any cracking is detected, prior to further flight, replace the cracked shaft with a new or serviceable shaft, in accordance with the maintenance instructions; and repeat the HFEC inspection thereafter at intervals not to exceed 2,000 landings.

(b) Prior to the accumulation of 6,000 total landings, or within 30 days after the effective date of this AD, whichever occurs later, perform a functional test (check) to verify proper operation of the flap braking sub-system, in accordance with Annex II, dated July 1, 1997, of CASA Maintenance Instructions COM 235–113, Revision 02, dated June 16, 1997.

(1) If no malfunction is detected, repeat the functional test thereafter at intervals not to exceed 300 landings.

(2) If any malfunction is detected, prior to further flight, replace any discrepant component with a new or serviceable component in accordance with the maintenance instructions; and repeat the functional test to verify proper operation of the flap braking sub-system; thereafter, repeat the functional test thereafter at intervals not to exceed 300 landings.

(c) An alternative method of compliance or adjustment of the compliance time that provides an acceptable level of safety may be used if approved by the Manager, International Branch, ANM–116, FAA, Transport Airplane Directorate. Operators shall submit their request through an appropriate FAA Principal Maintenance Inspector, who may add comments and then send it to the Manager, International Branch, ANM–116.

Note 2: Information concerning the existence of approved alternative methods of compliance with this AD, if any, may be obtained from the International Branch, ANM–116.

(d) Special flight permits may be issued in accordance with sections 21.197 and 21.199 of the Federal Aviation Regulations (14 CFR 21.197 and 21.199) to operate the airplane to a location where the requirements of this AD can be accomplished.

Note 3: The subject of this AD is addressed in Spanish airworthiness directive 11/96, Revision 1, dated June 19, 1997.

Issued in Renton, Washington, on June 2, 1998.

Darrell M. Pederson,

Acting Manager, Transport Airplane Directorate, Aircraft Certification Service.

[FR Doc. 98–15135 Filed 6–5–98; 8:45 am]

BILLING CODE 4910–13–U

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 16 and 99

[Docket No. 98N–0222]

Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to issue new regulations pertaining to the dissemination of information on unapproved uses (also referred to as ''new uses'' and ''off-label uses'') for marketed drugs, including biologics, and devices. The proposal, which would implement the dissemination provisions of the Food and Drug Administration Modernization Act of 1997 (FDAMA), would describe the new use information that a manufacturer may disseminate and describe the content of and establish procedures for a manufacturer's submissions to FDA before it may begin disseminating information on the new use. The proposal also would describe how manufacturers seeking to disseminate new use information must agree to submit a supplement for that use within a specified period of time, unless a supplemental application already has been submitted or FDA has exempted the manufacturer from the requirement to submit a supplement. The proposal also would provide for requests to extend the time period for submitting a supplement for a new use, and it would describe how a manufacturer can seek an exemption from the requirement to submit a supplement. Additionally, the proposal would discuss FDA actions in response to manufacturers' submissions, corrective actions that FDA may take, and recordkeeping and reporting requirements.

DATES: Written comments by July 23, 1998.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA–305), Food and Drug Administration, 12420 Parklawn Dr., rm. 1–23, Rockville, MD 20857. Submit written comments on the information collection requirements to the Office of Information and Regulatory Affairs, Office of Management and Budget (OMB), New Executive Office Bldg., 725 17th St. NW., Washington, DC 20503, Attn: Desk Officer for FDA.

FOR FURTHER INFORMATION CONTACT:

Regarding general questions: Margaret M. Dotzel, Office of Policy (HF–22), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–5321.

Regarding biological products and devices regulated by the Center for Biologics Evaluation and Research: Toni M. Stifano, Center for Biologics Evaluation and Research (HFM–200), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852, 301–827–3028.

Regarding human drug products: Laurie B. Burke, Center for Drug Evaluation and Research (HFD–40), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–827–2828.

Regarding medical devices: Byron L. Tart, Center for Devices and Radiological Health (HFZ–302), Food and Drug Administration, 2098 Gaither Rd., Rockville, MD 20850, 301–594–4639.

SUPPLEMENTARY INFORMATION:

I. Introduction/Summary of Legislation

On November 21, 1997, the President signed into law FDAMA (Pub. L. 105–115). Section 401 of FDAMA amended the Federal Food, Drug, and Cosmetic Act (the act) to permit drug, biologic, and device manufacturers to disseminate certain written information concerning the safety, effectiveness, or benefits of a use that is not described in the product's approved labeling to health care practitioners, pharmacy benefit managers, health insurance issuers, group health plans, and Federal and State government agencies, provided that:

1. The information is about a drug or device that is being legally marketed;

2. The information is not derived from another manufacturer's clinical research, unless that other manufacturer has given its permission for the dissemination;

3. Sixty days prior to the dissemination, the manufacturer submits to FDA a copy of the information to be disseminated and any other clinical trial information that the manufacturer has relating to the safety or effectiveness of the new use, any reports of clinical experience that pertain to the safety of the new use, and a summary of such information;

4. The information is not false or misleading and does not pose a significant risk to public health;

5. The information is in the form of unabridged reprints or copies of peer reviewed articles about scientifically sound clinical investigations published in scientific or medical journals or in the form of unabridged reference publications that include information about scientifically sound clinical investigations;

6. The manufacturer includes with such information a prominently displayed statement disclosing: That the use is not approved or cleared by FDA; if applicable, that the information is being disseminated at the manufacturer's expense; if applicable, the names of any authors of the information who are employees of or consultants to the manufacturer or have received compensation or have a significant financial interest in the manufacturer; if applicable, a statement that there are products or treatments that have been approved or cleared for the use that is the subject of the information; and the identification of any person that has provided funding for the study related to the new use for which such information is being disseminated;

7. The manufacturer includes the official labeling and a bibliography of other articles from scientific reference publications or journals relating to the new use;

8. If FDA determines that the information fails to provide data, analyses, or other written matter that is objective and balanced, the manufacturer includes additional objective and scientifically sound information that pertains to the safety or effectiveness of the new use and/or an objective statement prepared by FDA that bears on the safety or effectiveness of the new use; and

9. The manufacturer has: (a) Submitted a supplemental application for the new use; (b) completed the studies needed for a supplemental application for the new use and certified that such studies are completed and that a supplemental application will be submitted within 6 months of the initial dissemination; (c) provided a proposed protocol and schedule for conducting the studies needed for a supplemental application for the new use, which FDA has found to be adequate and reasonable (respectively) and certified that such application will be submitted no later than 36 months after the initial dissemination; or (d) received an exemption from the requirement to file a supplemental application on the grounds that conducting the studies needed for a supplemental application would be unethical or economically prohibitive.

Under the new law, if FDA fails to act on a request for an exemption within 60 days, the exemption is deemed approved, and a manufacturer who meets all other requirements may begin to disseminate the written information. FDA may, however, subsequently terminate the deemed approval and order a manufacturer to cease dissemination. FDA can also order the manufacturer to take corrective action if the new use would pose a significant risk to public health.

Manufacturers have an ongoing responsibility to provide FDA with additional information about the new uses that are the subject of dissemination under these provisions, and, if this information indicates that the new use may not be effective or may

present a significant risk to public health, FDA may order the cessation of the dissemination about the new use. FDA may also order cessation of dissemination if the manufacturer fails to comply with any requirement for dissemination, including the requirements relating to the completion of studies and/or the submission of a supplemental application.

Every 6 months, manufacturers that disseminate information under these provisions are required to prepare and submit to FDA lists of the titles of articles and reference publications that have been disseminated during the previous 6-month period and the categories of providers who have received the materials. In addition, manufacturers must keep records that can be used by the manufacturer or FDA to take corrective action. Such records may, at FDA's discretion, identify either the recipient of the information or the categories of such recipients. Manufacturers that have committed to doing the studies needed for submission of a supplement on a new use must also submit periodic reports to FDA that describe the status of the studies.

The dissemination of information in accordance with new section 551 of the act (21 U.S.C. 360aaa) is not construed as evidence of a new intended use of the drug or device, and it is not considered to be labeling, adulteration, or misbranding. This rule of construction applies, however, only to the dissemination of information in compliance with the statutory requirements. Moreover, disseminating information in violation of the requirements of section 551 of the act is prohibited.

Section 401(c) of FDAMA directs FDA to issue regulations to implement the new statutory provisions within 1 year of enactment (by November 21, 1998). Accordingly, the agency must solicit public comment on this proposal, consider the comments submitted, and prepare and publish a final implementing regulation by November 21, 1998. In light of this limited timeframe, the Commissioner finds good cause under 21 CFR 10.40(b)(2) for providing a shortened comment period of 45 days.

Section 401(d) of FDAMA provides that the new provisions will take effect 1 year after the date of enactment (November 21, 1998) or upon FDA's issuance of final regulations, whichever is sooner. According to section 401(e) of FDAMA, the provisions will sunset on September 30, 2006, or 7 years after the date on which the agency issues its regulations, whichever is later.

II. Description of the Proposed Rule

The proposed rule would create a new part 99 entitled ''Dissemination of Information on Unapproved/New Uses for Marketed Drugs, Biologics, and Devices.''

A. Subpart A—General Information

Proposed subpart A would consist of two provisions. Proposed § 99.1 would describe the scope of part 99. Proposed § 99.1(a)(1) would explain that the part applies to the dissemination of information on human drugs, including biologics, and devices where the information to be disseminated concerns the safety, effectiveness, or benefit of a use that is not included in the approved labeling for an approved drug or device or in the statement of intended use for a cleared device. Proposed § 99.1(a)(2) would provide that the information is to be disseminated to a health care practitioner, pharmacy benefit manager, health insurance issuer, group health plan, or Federal or State government agency. This description of the rule's scope would be consistent with section 551(a) of the act.

Proposed § 99.3 would define various terms, such as ''group health plan'' (proposed § 99.3(c)), ''health care practitioner'' (proposed § 99.3(d)), ''new use'' (proposed § 99.3(g)), and ''scientific or medical journal'' (proposed § 99.3(i)). In most cases, the definitions paraphrase or repeat the statutory definitions at section 556 of the act (21 U.S.C. 360aaa–5). However, proposed § 99.3(f) would elaborate on the statutory definition of ''manufacturer'' to include sponsors of marketed drugs or devices. FDA is proposing to elaborate in this manner so that sponsors of a drug or device who received marketing approval for the product, but do not actually manufacture the product, would be able to disseminate information under this part.

The proposed rule would track the statutory definition of ''new use'' to mean a use that is not included in the approved labeling of an approved drug or device or a use that is not included in the statement of intended use for a cleared device. A new use is one that would require approval or clearance of a supplemental application in order for it to be included in the product labeling. ''New uses'' that would require approval of a supplemental application to add the use to the labeling of an approved drug or to the labeling of an approved or cleared device and that, therefore, would be covered by this part include, but are not limited to: A completely different indication; modification of an existing indication to include a new dose, a new dosing schedule, a new route of administration, a different duration of usage, a new age group (e.g., unique safety or effectiveness in the elderly), another patient subgroup not explicitly identified in the current labeling, a different stage of the disease, a different intended outcome (e.g., long-term survival benefit, improved quality of life, disease amelioration), effectiveness for a sign or symptom of the disease not in the current labeling; and comparative claims to other agents for treatment of the same condition. This illustrative listing is consistent with the statutory intent that clearly links the new use discussed in the materials to be disseminated to the sponsor's submission of a supplemental application in order to add the use to the product labeling.

The proposed rule would also define ''clinical investigation'' and ''supplemental application,'' which are not defined in the statute. A clinical investigation would be defined as an investigation in humans that is prospectively planned to test a specific clinical hypothesis. The conduct of a clinical investigation according to a preplanned protocol generally is a fundamental aspect of hypothesis testing.

The proposal would define a ''supplemental application'' to mean a supplemental new drug application (NDA) for human drugs or a supplement to an approved license application for biologics. A supplement to an NDA could be a supplement to an application submitted under section 505(b)(1) of the act (21 U.S.C. 355(b)(1)) or section 505(b)(2) of the act. For devices, proposed § 99.3(j)(3) would define a ''supplemental application'' as a new 510(k) submission, if the device is the subject of a cleared 510(k) submission, or a supplement to an approved premarket approval application (PMA), if the device is the subject of an approved PMA. FDA is proposing to include new 510(k) submissions as ''supplemental applications'' because there are no ''supplements'' for a new use to a 510(k) submission, instead, a new use is the subject of a new 510(k) submission. There are instances when a new use for a 510(k) device would require the submission of a PMA, but this would not be the equivalent of a ''supplement'' and thus, has not been included in the definition. Manufacturers that would be required to submit a PMA for a new use of a device cleared under section 510(k) of the act (21 U.S.C. 360(k)) would not be eligible

to disseminate materials under the provisions of section 551 of the act.

B. Subpart B—Information to be Disseminated

Proposed subpart B would describe the types of information that manufacturers may disseminate under part 99; the information that manufacturers must disseminate if they choose to disseminate written information about the safety, effectiveness, or benefit of new uses; and the persons who may receive the information about new uses.

Proposed § 99.101 would discuss the types of information concerning the safety, effectiveness, or benefit of a new use that a manufacturer may disseminate. In brief, the proposal would require that the written information to be disseminated:

1. Concern a drug or device that has been approved, licensed, or cleared for marketing by FDA;

2. Be in the form of an unabridged copy of a peer-reviewed scientific or medical journal article or reprint, or an unabridged reference publication that pertains to a clinical investigation involving the drug or device and that is considered scientifically sound by experts who are qualified to evaluate the product's safety or effectiveness;

3. Not pose a significant risk to the public health;

4. Not be false or misleading; and

5. Not be derived from clinical research conducted by another manufacturer, unless the manufacturer disseminating the information has permission to make the dissemination.

Under the proposal, FDA could consider the information to be misleading if, among other things, the information includes only favorable publications or excludes articles, reference publications, or other information concerning risks and adverse effects that are or may be associated with the new use. This element is intended to help ensure that manufacturers disseminate balanced and objective information. FDA also could consider the information to be false or misleading if the study design, conduct, data, or analyses do not reasonably support the conclusion reached by the authors. In addition, the information would be considered misleading if the clinical study utilized a study endpoint that is not reasonably well-established as indicative of clinical benefit.

As set forth in the statute and FDA's proposal, the information that can be disseminated under part 99 must be in the form of a reprint or copy of a journal article or a reference publication. Although the requirements set forth in the statute are easily applied to journal articles, they are not as easily applied to reference publications. For example, the definition of a reference publication indicates that the publication may not focus on a particular drug or device of the manufacturer that disseminates the information under section 551 of the act and may not have a primary focus on new uses of drugs or devices that are marketed or under investigation by a manufacturer supporting the dissemination of information. This is not altogether consistent with the purpose of section 401 of FDAMA, which is to permit the dissemination of information about a clinical investigation concerning a specific new use if certain criteria are met. In addition, although journal articles typically include a detailed description and discussion of clinical investigations, reference publications often just refer generally to the results of such investigations. Because the statute requires the information being disseminated to be about a clinical investigation, it seems unlikely that many reference publications will meet the requirements for dissemination under this provision. Finally, the statute requires that a manufacturer submit (or commit to submit) a supplement for each new use discussed in the information to be disseminated. This could be construed to mean that a manufacturer that disseminates a reference publication that discusses many new uses would be required, under the statute, to submit (or commit to submit) a supplement for each of the many new uses mentioned.

Despite these issues, FDA believes that the statutory provisions can be interpreted and applied to conform with the text and spirit of the legislation. Although the statute does not allow a reference publication, as a whole, to focus on the disseminating manufacturer's products or new uses, it does not prohibit a manufacturer from citing a particular use or uses in a publication that does not have such a focus if the manufacturer complies with the requirements set forth in section 401 of FDAMA. This will, therefore, allow manufacturers to use reference publications in the same manner as they would use journal articles, i.e., to disseminate information about a specific new use. Although a manufacturer must submit (or commit to submit) a supplemental application for the new use that it has cited in the reference publication, the manufacturer would not have to submit (or commit to submit) a supplement for each new use mentioned in the publication. Nevertheless, because reference publications rarely include detailed discussions of clinical investigations, FDA recognizes that the majority of such publications would probably not meet the requirements of section 401 of FDAMA and this proposed implementing regulation. FDA, therefore, plans to develop draft guidance and solicit public comment on reference publications that do not fall within the scope of part 99.

Proposed § 99.101 would also explain that the determination of whether a clinical investigation is considered to be scientifically sound rests 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. A clinical investigation described or discussed in an article or reference publication must include a description of the study design and conduct, data presentation and analysis, summary of results, and conclusions pertaining to the new use. In order to provide a basis for determining whether the conclusions are reasonably supported and the findings represent evidence of safety and effectiveness of the new use, the article or reference publication should provide, where applicable, evidence that the investigation:

1. Was prospectively planned. Types of prospectively planned investigations include: A clinical trial in which subjects are enrolled and assigned to treatment according to a protocol; a meta-analysis of published clinical investigations in which there is a planned strategy for the inclusion of published articles and for the integrated analysis of their results; or a well-documented prospective case series that utilizes a predetermined strategy for the inclusion of cases. Ordinarily, such a case series would be considered to be a scientifically sound clinical investigation for the purposes of dissemination only in those circumstances where the disease under study had high and predictable mortality and/or morbidity and was not expected to improve spontaneously;

2. Enrolled an appropriately defined and diagnosed patient population for the specific clinical condition of interest;

3. Accounted for all patients enrolled, including all patients who discontinued therapy prematurely. An analysis that is based on only a portion of all study subjects enrolled should provide information on how this population was derived;

4. Utilized clinically meaningful endpoints or utilized surrogate endpoints that are reasonably likely to predict safety and effectiveness. These endpoints should have been assessed using well-established instruments, and using appropriate measurement frequencies;

5. Used a well-described treatment regimen with a clear description of dose, schedule, duration, and route of administration;

6. Used an appropriate control group or made reference to an appropriate historical control;

7. Collected and reported adequate information on adverse experiences, and the need for dose reductions and treatment interruptions due to toxicity; and

8. Was analyzed in a scientifically appropriate manner. In circumstances where response to therapy is expected to differ between patient subgroups, results should be reported accordingly. A clinical investigation presented in a format that does not represent a reasonably comprehensive presentation of the study design, conduct, data, analyses, and conclusions, for example, letters to the editor, review abstracts, abstracts of a publication, or other incomplete reports, would not qualify for dissemination under this provision. Such reports do not provide sufficient information to determine the adequacy of the study design and cannot be critically judged by the reader.

Proposed § 99.101 would further explain what is meant by the term ''unabridged,'' i.e., the reprint, article, or reference text must retain the same appearance, form, format, content, or configuration as the original article or publication. It cannot be accompanied by information that is promotional in nature. Because a reference text might include a discussion of many new uses and a manufacturer might want to disseminate it under part 99 for the purpose of providing information on one particular discussion in the book, proposed § 99.101(b)(2) would permit the manufacturer to cite a particular discussion about a new use in a reference publication in the information that is required to be attached to the reference publication under proposed § 99.103.

Proposed § 99.103(a) would, consistent with section 551(b) and (c) of the act, describe the information that must accompany the journal article or reference publication. Specifically it would require:

1.A prominently displayed statement that discloses that the information being disseminated is about a use that has not been approved or cleared by FDA and is being disseminated under section 551 *et seq.* of the act; if applicable, that the manufacturer is disseminating such information at its own expense, the names of authors who are employees or consultants to, or have received compensation from the manufacturer or who have a significant financial interest in the manufacturer, and a statement that there are products or treatments approved/cleared for the new use; and the identification of any person that has provided funding for the study that is the basis of the information for which such information is being disseminated;

2. The official labeling for the product;

3. A bibliography of other articles (that concern reports of clinical investigations) both supporting and not supporting the new use;

4. Any additional information required by FDA, including objective and scientifically sound information pertaining to the safety or effectiveness of the new use that FDA determines is necessary to provide objectivity and balance, including information that the manufacturer has submitted to FDA or, where appropriate, a summary of such information, and any other information that can be made publicly available; and an objective statement prepared by FDA, based on data or other scientifically sound information bearing on the safety or effectiveness of the new use of the product.

Proposed § 99.103(c) would describe what is meant by a ''prominently displayed'' statement by setting forth criteria that are consistent with the agency's regulations on prescription drug advertising (21 CFR 202.1(e)(7)(viii)) and labeling (21 CFR 201.10(g)(2)). Factors to be considered in determining whether a statement is prominently displayed may include, but are not limited to, type size, font, layout, contrast, graphic design, headlines, spacing, and any other technique to achieve emphasis or notice. In addition, proposed § 99.103(c) would require such statements to be outlined, boxed, highlighted, or otherwise graphically designed and presented on the front of the disseminated information in a manner that achieves emphasis or notice and is distinct from the other information being disseminated.

For purposes of proposed § 99.103(a)(1)(iii), an author would have a significant financial interest in a manufacturer when there is a relationship that may give rise to actual or perceived conflicts of interest. The concept of relationships that may give rise to conflicts of interest has specific and well understood application to medical and scientific discourse (e.g., in the publication and peer review process). When there is a question as to whether a relationship is significant, it should be disclosed. For further guidance and direction on the disclosure of significant financial interests, manufacturers should refer to FDA's final rule on Financial Disclosure by Clinical Investigators (63 FR 5233, February 2, 1998).

The official labeling that would be required by proposed § 99.103(a)(2) would for drugs constitute the current package insert. Because devices do not always include a package insert in the same form and manner as drugs, the agency would expect device manufacturers to provide the same information that is generally found in package inserts, namely: (1) The name of the device, including its trade or proprietary name; (2) the manufacturer's name, address, and telephone number; (3) a statement of intended use, including a general description of the diseases or conditions that the device is intended to diagnose, treat, cure, or mitigate; (4) a description of the patient population for which the device is intended; (5) a description of indications that have been approved or cleared by FDA; (6) a description of any limitations or conditions that have been placed on the sale, distribution, or use of the device; and (7) all warnings, contraindications, side effects, and precautions associated with the use of the device. The agency expects that this information will be found in the information that manufacturers distribute with their legally marketed devices.

The bibliography that would be required by proposed § 99.103(a)(3) should appear in the same format used by Index Medicus and should include all authors, the full title of the article, and complete source information.

Proposed § 99.103(a)(1)(i) would require the statement that the use has not been approved or cleared by FDA and is being disseminated under section 551 *et seq.* of the act to be permanently attached to the front of each reprint or copy of an article or reference publication. Proposed § 99.103(a)(4) would require any additional information required by FDA also to be attached to the front of the disseminated information. Under proposed § 99.103(b), all other statements or information would have to be attached to the article or reference publication.

Proposed § 99.105 would identify who may receive information disseminated under this part. Possible recipients would include health care practitioners, pharmacy benefit managers, health insurance issuers,

group health plans, or Federal or State government agencies. This is consistent with section 551(a) of the act and is important because it is essential that this information be provided only to persons who have the education, training, and experience to interpret its meaning and relevance.

C. Subpart C—Manufacturer's Submissions, Requests, and Applications

Proposed subpart C would describe what must be included in the different types of submissions that manufacturers would send to FDA in order to be able to disseminate information under part 99.

Proposed § 99.201 would provide that 60 days before disseminating information on a new use, a manufacturer must submit to FDA:

1. A copy of all the information to be disseminated (i.e., including all attachments) in the form in which the manufacturer plans to disseminate it. This will enable FDA to see how the information will be presented to its intended audience and to determine whether the information is objective and balanced, and meets all of the requirements of this part;

2. All other clinical trial information that the manufacturer has relating to the safety or effectiveness of the new use, any reports of clinical experience pertinent to the safety of the new use, and a summary of such information. For purposes of this section, clinical trial information would include, but would not be limited to, published papers and abstracts, even if not intended for dissemination, and unpublished manuscripts, abstracts, and data analyses from completed or ongoing investigations. The information and reports required under this paragraph would include case studies, retrospective reviews, epidemiological studies, adverse event reports, and any other material concerning adverse effects or risks reported for or associated with the new use. If the manufacturer has no knowledge of or has no such information, it would include a statement to that effect;

3. An explanation of the search strategy for the bibliography that must be included with the disseminated information. The search strategy must include the data bases and criteria used to generate the bibliography and the time period covered by the bibliography; and

4. If a supplement for the new use has not been submitted, a certification that the manufacturer will submit a supplement or an application for an exemption from the requirement to submit a supplement. If a supplement for the new use has been submitted, the manufacturer would include a cross-reference to that supplemental application.

When the certification provides that the studies have been completed, the submission would include the protocols for the studies or would cross reference and provide the relevant information on any protocols that are already in FDA's files as part of an investigational new drug application (IND) or an investigational device exemption (IDE). The certification would state that the manufacturer will submit a supplemental application within 6 months from the date of initial dissemination of information.

When the certification is that studies will be conducted, proposed protocols and a schedule must be submitted. The proposal would require that the protocols submitted comply with all applicable requirements in 21 CFR parts 312 and 812, which relate to investigational new drug applications and investigational device exemptions. This means that the protocols must be sent to the appropriate review divisions within the Center for Drug Evaluation and Research, the Center for Biologics Evaluation and Research, or the Center for Devices and Radiological Health. The protocols will be reviewed as an original IND or IDE or an amendment to an existing IND or IDE. The schedule would include the expected dates for principal study events (e.g., initiation and completion of patient enrollment, completion of data collection, completion of data analysis, and submission of a supplemental application). The certification would state that the manufacturer will exercise due diligence to complete the clinical studies needed to submit a supplemental application for the new use and will submit such application to FDA no later than 36 months after the date of the initial dissemination of information.

Proposed § 99.201(b) would describe who should sign a submission and certification statement or application for an exemption. In general, an authorized official would sign the submission and certification statement or application for an exemption. For foreign manufacturers, proposed § 99.201(b) would require the signature, name, and address of an authorized official residing or maintaining a place of business in the United States.

Proposed § 99.201(c) would provide that manufacturers must submit three copies of the submission (including the certification statement or application for an exemption) to FDA and would provide the appropriate addresses for such submissions. The outside of the shipping container of the submission would identify the documents as ''Submission for the Dissemination of Information on an Unapproved/New Use.''

Proposed § 99.201(d) would provide that the 60-day period begins to run when FDA receives a complete submission. The submission would be considered complete if FDA determines that it is sufficiently complete to permit a substantive review.

Section 554 of the act (21 U.S.C. 360aaa–3) anticipates that there will be times when the 36-month period for filing a supplemental application for a new use based on new studies will not be enough time. It provides, therefore, that FDA may, on its own initiative at the time of initial dissemination, give the manufacturer more than 36 months, or that FDA may, upon a manufacturer's request after such studies have begun, extend the 36-month period by up to 24 months. Proposed § 99.203 would set forth the procedures that a manufacturer must follow to request an extension of time for submitting a supplemental application. In its request, the manufacturer would: (1) Identify the product and new use; (2) describe the study or studies that cannot be completed on time; (3) explain why the study or studies cannot be completed; (4) describe the current status of the incomplete study or studies; (5) summarize the work conducted, including the dates on which principal events concerning the study or studies occurred; and (6) estimate the additional time needed to complete the study or studies and submit a supplemental application. The manufacturer would submit three copies of the request to the same address identified for the initial submission.

When Congress passed these provisions of the act, it recognized that there may be rare circumstances in which it would be appropriate to exempt a manufacturer that seeks to disseminate information about a new use from the requirement to submit a supplement for that new use. The act sets forth two very narrow exemptions: (1) When, for reasons defined by the agency, it would be economically prohibitive to incur the costs necessary for the submission of a supplement, and (2) when, for reasons defined by the agency, it would be unethical to conduct the studies necessary for the supplemental application.

In making a determination that it would be economically prohibitive to conduct the needed studies, section 554 of the act directs FDA to consider (in

addition to any other considerations the agency finds appropriate): (1) The lack of the availability under law of any period during which the manufacturer would have exclusive marketing rights with respect to the new use, and (2) the size of the population expected to benefit from approval of the supplemental application. In making a determination that it would be unethical to conduct the needed studies, the act directs FDA to consider (in addition to any other considerations the agency finds appropriate) whether the new use involved is the standard of medical care for a health condition.

Proposed § 99.205 would set forth what a manufacturer must submit when seeking an exemption from the requirement to file a supplemental application relating to a new use. It would require the manufacturer to include an explanation as to why an exemption is sought and include materials demonstrating that it would be economically prohibitive or unethical to conduct the studies needed to submit a supplemental application.

To obtain either exemption, a manufacturer must first explain why existing data, including data from the scientifically sound study described in the information to be disseminated, are not adequate to support approval of the new use. This is a critical element of the request because submitting the existing data in a supplement, which may require some attempt to retrieve old records, is almost never unethical and would almost never be economically prohibitive. The manufacturer should make every effort, therefore, to determine whether existing data would be adequate, and should include reference to discussions with the agency concerning the adequacy of existing data.

If the manufacturer is seeking an exemption on the grounds that it would be economically prohibitive to conduct the study or studies needed for approval of the use, it must also show, at a minimum, that the estimated cost of the necessary studies would exceed the estimated total revenue from the product minus the cost of goods sold and marketing and administrative expenses attributable to the product, and that there are not less expensive ways to obtain the needed information.

Proposed § 99.205(b)(1) would set forth the type of evidence that the manufacturer must include to meet the requirements for an economically prohibitive exemption. These would include:

1. A description of the current and projected U.S. patient population for the product and an estimate of the current and projected economic benefit to the manufacturer from the use of the drug or device in this population. The estimate would assume that the total potential market for the drug or device is equal to the prevalence of all of the diseases or conditions that the drug or device will be used to treat and involve the following considerations:

(a) The estimated market share for the drug or device during any exclusive market period, a summary of the exclusive market period for the product, and an explanation of the basis for the estimate;

(b) a projection of and justification for the price at which the drug or device will be sold; and

(c) comparisons with sales of similarly situated drugs or devices, where available.

2. A description of the additional studies that the manufacturer believes are necessary to support the submission of a supplemental application for the new use and an estimate of the projected costs for such studies; and

3. An attestation by a responsible individual of the manufacturer verifying that the estimates included with the submission are accurate and were prepared in accordance with generally accepted accounting procedures. The data underlying and supporting the estimates shall be made available to FDA upon request.

FDA considered requiring a report of an independent certified public accountant made in accordance with the Statement on Standards for Attestation established by the American Institute of Certified Public Accountants with respect to the estimates submitted under this section. FDA is soliciting comment on whether such a report should be required in lieu of or as an alternative to the attestation that would be required by the proposal.

Although Congress made it very clear that exemptions from the requirement to submit a supplement are to be rare, it left it up to the agency to determine when it would grant these exemptions. This was a particularly difficult task for the ''economically prohibitive'' exemption because it is difficult to assess cost and income projections. The agency is proposing to compare the cost of the studies needed for a supplement with the total revenue of the product minus the cost of goods sold, and marketing and administrative expenses attributable to the product. FDA is not focusing only on sales from the new use because the agency does not believe that it would be ''prohibitive'' if the sales from the new use did not cover the cost of the studies. In such a situation, it might not be economically wise to conduct the studies, but it would not rise to the level of being prohibitive. The agency considered whether it should also require that the cost of conducting the studies needed for the supplement substantially exceed revenues and be unusually great compared to the typical costs of developing products for similar uses. Given the uncertainty about cost and revenue streams, it is possible that these measures would better define what is economically prohibitive. Although FDA decided not to include these requirements in the proposal, they are still under consideration and, therefore, the agency invites comment on whether they are useful in the determination of what is economically prohibitive. FDA also is seeking comment on other possible ways to define economically prohibitive.

If the manufacturer is seeking an exemption on the grounds that it would be unethical to conduct a needed study or studies, proposed § 99.205(b)(2) would require the manufacturer also to show that, notwithstanding the insufficiency of existing data to support the submission of a supplemental application for the new use, the data are persuasive to the extent that withholding the drug in the course of conducting a controlled study would pose an unreasonable risk of harm to human subjects. For purposes of determining what is unethical under this part, an unreasonable risk of harm would ordinarily arise only in situations in which the intended use of the drug or device appears to affect mortality or irreversible morbidity. Evidence suggesting that the drug or device is the standard of care for the intended use can add weight to an argument that conduct of a needed study or studies would be unethical. To support its conclusion that the conduct of a needed study or studies would be unethical, the manufacturer would need to provide evidence that it had explored various alternative study designs (e.g., active control studies, studies in different populations, studies where the product is added to existing treatment), discussed these alternatives with the agency, and determined that there were no options that were both ethical and capable of generating data adequate to support approval. Specifically, the proposal would require the manufacturer to provide:

1. An explanation of why, notwithstanding the insufficiency of available data to support the submission of a supplemental application for the new use, the data are persuasive to the extent that withholding the drug or device in a controlled study (e.g., by

providing no therapy, a placebo, an alternative therapy, or an alternative dose) would pose an unreasonable risk of harm to human subjects. For purposes of determining what is unethical under this part, an unreasonable risk of harm would ordinarily arise only when the new use appears to affect mortality or irreversible morbidity; and

2. A discussion of the possibility of conducting studies in different populations or of modified design (e.g., adding the new therapy to existing treatments or using an alternative dose if monotherapy studies could not be conducted).

In assessing the appropriateness of conducting studies to support the new use, the manufacturer may provide evidence that the new use represents standard medical treatment or therapy. Evidence that the new use represents standard medical therapy can be one element of an argument that studies cannot ethically be conducted, but the persuasiveness of available data is equally important. Evidence that the new use represents standard medical therapy might be obtained from a number of different sources. Some possible considerations might include:

(1) Whether the new use meets the requirements of section 1861(t)(2)(B) of the Social Security Act, which defines ''medically accepted indications'' with respect to the use of a drug;

(2) whether 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;

(3) whether 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 and Research, and the Centers for Disease Control and Prevention of the Department of Health and Human Services; and

(4) whether the new use is described in a current compendia such as the United States Pharmacopoeia Dispensing Information, the American Medical Association Drug Evaluations, or the American Hospital Formulary Service.

While these sources would not be definitive evidence of standard medical treatment or therapy, they may provide evidence of it in certain circumstances.

FDA has struggled to develop an approach to these exemptions that strikes the proper balance. It should be emphasized that Congressional intent was clear in expecting exemptions to be rare. Congress emphasized the importance of having safe and effective uses of drugs and devices reflected in labeling. The agency believes that it has struck the proper balance, but it invites comment on the exemption criteria it has developed.

D. Subpart D—FDA Action on Submissions, Requests, and Applications

Proposed subpart D would describe FDA's actions in response to a submission, a request for an extension of the time period to conduct studies, and an application for an exemption from the requirement to conduct clinical studies and to submit a supplemental application.

Proposed § 99.301(a) would provide that within 60 days of receiving a submission, FDA may:

1. Determine that the manufacturer does not comply with the requirements under this part (e.g., the new use poses a significant risk to public health or the clinical investigation described in the publication is not scientifically sound) and thus, cannot disseminate information about the new use;

2. Request additional information or documents to assist in determining whether the information to be disseminated complies with the requirements under this part;

3. Determine that the information fails to provide data, analyses, or other written matter that is objective and balanced. In this case, FDA would provide the manufacturer notice and an opportunity for a meeting, may require the manufacturer to disseminate additional information that is objective and scientifically sound, pertains to the safety or effectiveness of the new use, and is necessary to provide objectivity and balance, and may require the manufacturer to disseminate an objective statement prepared by FDA that is based on data or other scientifically sound information available to the agency; and

4. Require a manufacturer to maintain records that will identify individual recipients of the information that is to be disseminated.

This last provision is tied to the statutory requirement that manufacturers keep records of the recipients of the disseminated materials so that the manufacturer or FDA can take appropriate corrective action, e.g., so that the manufacturer or FDA can notify recipients if it is later determined that the new use that is the subject of the dissemination may not be effective or may present a significant risk to public health. Section 553 of the act (21 U.S.C. 360aaa–2) provides that such records, at the agency's discretion, may identify recipients of the information or the categories of such recipients. Although keeping records that identify the individual recipients of the information might best ensure that the people who have seen and relied on the information will learn of problems or risks associated with the use, FDA recognizes that it may not be necessary to keep such specific records if the manufacturer is willing to take steps to ensure that the individual recipients will see any materials that might correct any misperceptions. Under proposed § 99.501, FDA would generally permit the manufacturer to decide whether to keep individual records or to keep more general records and take more conspicuous corrective action. However, there may be instances when it would be in the best interest of public health if the manufacturer kept the names of the individual recipients. In these cases, proposed § 99.301(a)(4) would provide that FDA will generally notify the manufacturer in advance, i.e., within the 60-day period for review of the submission, that such records must be kept.

Proposed § 99.301(b) would set forth FDA actions in response to a manufacturer's submission when the manufacturer is committing to submit a supplement for completed studies or is agreeing to conduct the necessary studies and then submit a supplement. If the manufacturer has planned studies and submits proposed protocols (either as a new IND or IDE or as an amendment to an existing IND or IDE) and a schedule for completing such studies, FDA will, within 60 days, review the manufacturer's proposed protocol and schedule for completing such studies to determine whether the protocols are adequate and the schedule for completing the studies is reasonable for purposes of disseminating the new use information. The manufacturer cannot disseminate the new use information until FDA determines that the proposed protocol is adequate and the proposed schedule is reasonable. If the manufacturer has completed studies that it believes would be an adequate basis for the submission of a supplemental application for the new use, FDA will, under the proposal, conduct a preliminary review of the study reports to determine whether the studies are potentially adequate to support the filing of a supplemental application for the new use. If FDA determines that they are inadequate to support the filing of a supplemental application for the new use or are not

complete, FDA will notify the manufacturer and the manufacturer shall not disseminate the new use information under this subpart.

Proposed § 99.303 would describe FDA's ability to allow a manufacturer more than 36 months to submit a supplemental application on its own initiative, based on the review of the protocols(s) and planned schedule, or to grant a manufacturer's request to extend the 36-month period (for up to 24 months). Proposed § 99.303(a) would describe FDA's ability to determine, on its own initiative, that a manufacturer needs more than 36 months to complete the studies needed for submission of a supplemental application and to submit such application. Proposed § 99.303(b) and (c) would describe FDA's ability, after such studies have begun, to grant an extension of the time to submit a supplement by up to 24 months. FDA can grant such an extension if the manufacturer makes a request for an extension in writing and FDA determines that the manufacturer has acted with due diligence to conduct the studies needed for the submission of a supplemental application for a new use and to submit such a supplemental application, but still needs more time. In this context, ''due diligence'' refers to a manufacturer's good faith effort to develop the data necessary to support a supplemental application for the new use and to pursue approval of an application based on those data in a timely manner. In its consideration of a request to extend the time for completing studies, the agency will look at all relevant factors and will focus on the manufacturer's efforts to meet the milestones identified in the schedule submitted with the manufacturer's certification to complete required studies (i.e., completion of patient enrollment in clinical studies, completion of data collection, completion of data analysis, and submission of a supplemental application). If a manufacturer has failed to meet identified milestones despite reasonable efforts to do so and, in the agency's judgment, an extension of time to complete the studies will enable a manufacturer to complete development of the necessary data and submit a supplemental application, the agency may grant an extension of the time to complete studies and submit the supplemental application.

If FDA extends the time period for completing the studies and submitting a supplemental application or grants a manufacturer's request for an extension, the manufacturer shall submit a new certification under § 99.201(a)(4)(ii)(B) that sets forth the timeframe within which clinical studies will be completed and a supplemental application will be submitted to FDA.

Proposed § 99.305 would describe FDA action on an application for an exemption from the requirement to submit a supplemental application. FDA may grant an application for an exemption if it determines that it would be economically prohibitive for the manufacturer to conduct the studies needed for a supplemental application or it would be unethical to conduct clinical studies needed to approve the new use.

FDA may find that it would be economically prohibitive if, at a minimum, existing data characterizing the product's safety and effectiveness, including data from the study described in the information to be disseminated, are not adequate to support the submission of a supplemental application for the new use and the estimated cost of the studies needed to support the submission of a supplemental application for the new use would exceed the estimated total revenue from the product minus the cost of goods sold and the marketing and administrative expenses attributable to the product and that there are not less expensive ways to obtain the needed information. FDA may find that it would be unethical to conduct the clinical studies needed to support the submission of a supplemental application for the new use when existing data characterizing the product's safety and effectiveness, including data from the study described in the information to be disseminated, are not adequate to support the submission of a supplemental application for the new use and there is sufficiently persuasive evidence that withholding the drug or device in a controlled study would pose an unreasonable risk of harm to human subjects and no studies in different populations or of modified design can be utilized. In determining whether it would be unethical to conduct clinical studies, the agency will consider, in addition to the persuasiveness of available evidence, whether the new use of the drug or device is broadly accepted as current standard medical treatment or therapy.

The evidence and factors that FDA will consider in granting an exemption were discussed previously. The agency reiterates, however, that these exemptions cannot and will not be liberally granted. Congress was trying to balance the need to get potentially important information on new uses to physicians with the need to get these new uses studied, approved, and in the labeling. If FDA were to liberally grant exemptions from the requirement to submit a supplemental application, the exemptions would undermine Congress's intent to ensure, through the review and approval of supplemental applications, that the drug or device is safe and effective for the new use.

Proposed § 99.305(a)(1) would acknowledge that FDA must act on an application for an exemption within 60 days of receipt or it will be deemed approved. However, under proposed § 99.305(a)(2), FDA may, at any time, terminate such deemed approval if it determines that the requirements for granting an exemption have not been met.

E. Subpart E—Corrective Actions and Cessation of Dissemination

Proposed subpart E would discuss various actions FDA could take or require a manufacturer to take after a manufacturer has begun disseminating information on a new use.

Proposed § 99.401 would pertain to corrective actions and orders to cease dissemination of information. These corrective actions and orders to cease dissemination of information could apply under three different situations, which are set forth in paragraphs (a), (b), and (c). Under proposed § 99.401(a), if FDA receives data after a manufacturer has begun disseminating information on a new use and the agency determines that the new use may not be effective or may present a significant risk to public health, FDA would consult the manufacturer and, after such consultation, take appropriate action to protect the public health. These actions might include ordering the manufacturer to cease disseminating information on the new use and to take appropriate corrective action. Appropriate corrective action might include, among other things, issuing ''Dear Doctor'' letters, publishing corrective advertising, including warning labels on the product, or including warnings or otherwise revising the product labeling.

Proposed § 99.401(b) would address FDA actions in response to information disseminated by a manufacturer. If the agency determined that the disseminated information did not comply with the regulations, proposed § 99.401(b) would give FDA two options: (1) If the manufacturer's noncompliance constituted a minor violation, provide the manufacturer an opportunity to bring itself into compliance; or (2) if the manufacturer's noncompliance does not constitute a minor violation, order the manufacturer to cease dissemination and to take

corrective action, such as issuing ''Dear Doctor'' letters, publishing corrective advertising, including warning labels on the product, or including warnings or otherwise revising the product labeling. These orders would be issued only after FDA provided notice of its intent to issue an order to cease dissemination and provided an opportunity for a meeting to the manufacturer. However, an opportunity for a meeting would not be required if the manufacturer's noncompliance was failure to submit a supplemental application within 6 months as certified in the initial submission.

Proposed § 99.401(c) would describe when FDA may order a manufacturer to cease disseminating information and/or take corrective action based on the manufacturer's supplemental application for the new use. These orders would be issued when: (1) FDA determines that a supplemental application for a new use does not contain adequate information for approval of the new use; (2) the manufacturer has certified that it will submit a supplemental application within 6 months or within 36 months and has not done so; (3) the manufacturer has certified that it will submit a supplemental application within 36 months and FDA, after an informal hearing, determines that the manufacturer is not acting with due diligence to initiate or complete the studies needed to support the submission of the supplemental application; or (4) the manufacturer has certified that it will submit a supplemental application within 36 months and it has discontinued or terminated the studies needed to support such supplemental application. The latter provision is intended to deter a manufacturer from certifying that it will complete the studies needed to submit a supplement so that it can begin disseminating information even though it has no intention of completing such studies and submitting a supplement.

The agency's determination of what corrective action would be appropriate will be based on a number of factors, including the seriousness of any violation of this part, whether there is evidence of abuse of this part, and the potential risk to the public health. For example, consistent with past agency practice, FDA generally would require warnings on the product or in the approved product labeling only when there are serious public health concerns.

Proposed § 99.401(e) provides that a manufacturer must immediately (on its own) cease disseminating information under this part if it falls out of compliance with the requirements set forth in this part.

As set forth in proposed § 99.305, if FDA fails to act within 60 days on an application for an exemption from the requirement to file a supplemental application, such request shall be deemed approved. Proposed § 99.403 would provide, however, that FDA may, at any time, terminate the deemed approval of an application for an exemption if FDA determines that the manufacturer has failed to meet the requirements for granting an exemption, i.e., the manufacturer has failed to show that it would be economically prohibitive or unethical to conduct the studies needed to submit a supplemental application. If FDA terminates such approval, it may order the manufacturer, within 60 days, to cease disseminating the information about the new use and, if the new use would pose a significant risk to public health, FDA could order the manufacturer to take corrective action. FDA must notify a manufacturer if it terminates a deemed approval of an application for an exemption.

Under proposed § 99.403(d), FDA may, at any time, terminate the approval of an application for an exemption from the requirement to file a supplemental application for a new use if, after consulting with the manufacturer that was granted such exemption, FDA determines that the manufacturer no longer meets the requirements for an exemption on the basis that it is economically prohibitive or unethical to conduct the studies needed to submit a supplemental application for the new use. If FDA terminates an approval of an application for an exemption under § 99.403(d), proposed § 99.403(e) would require such manufacturer within 60 days of being notified by FDA that its exemption approval has been terminated, to file a supplemental application for the new use that is the subject of the information being disseminated under the exemption, certify, under § 99.201(a)(4)(i) or (a)(4)(ii) that it will file a supplemental application for the new use, or cease disseminating information on the new use. FDA may require a manufacturer that ceases the dissemination of information on the new use to undertake corrective action.

Proposed § 99.405 would provide that the dissemination of information about a new use could constitute labeling, evidence of a new intended use, adulteration or misbranding of the product if such dissemination fails to comply with the requirements in section 551 of the act and the requirements of this part. A manufacturer who fails to act with due diligence to submit a supplement or to begin or complete the clinical studies needed to submit a supplement would be deemed to be not in compliance with the requirements of this part.

F. Subpart F—Recordkeeping and Reports

Subpart F would describe the recordkeeping and reporting requirements of a manufacturer that disseminates information under this part.

Proposed § 99.501(a) would require a manufacturer that disseminates information under this part to maintain records sufficient to allow it to take corrective action that is required by FDA. Under the proposal, such records must either identify, by name, those persons receiving the disseminated information or identify, by category, the recipients of the disseminated information. However, manufacturers who choose to identify the recipient by category must be willing to ensure that any corrective action FDA requires will be sufficiently conspicuous so as to reach the individuals who have received the information about the new use. Moreover, if FDA determines that, because of the nature of the information being disseminated or the seriousness of the new use, it is essential to keep records that identify the name of the persons receiving the disseminated information, it can require a manufacturer to keep such records.

Proposed § 99.501(a) would also require manufacturers that disseminate information under this part to maintain an identical copy of any information disseminated under this part and, upon submission of a supplemental application to FDA, to notify the appropriate office, identified in proposed § 99.201, which is responsible for overseeing the implementation of this part.

Proposed § 99.501(b) would require manufacturers that disseminate information under this part to, on a semiannual basis, provide FDA:

1. A list of articles and reference publications disseminated under this part during the 6-month period preceding the date on which the list is provided;

2. A list identifying the categories of health care practitioners, pharmacy benefit managers, health insurance issuers, group health plans, or Federal of State government agencies that received the articles and reference publications in the 6-month period described above; such list must identify which category received a particular article or reference publication;

3. A notice and summary of any additional clinical research or other data relating to the safety or effectiveness of the new use, and if the manufacturer possesses such clinical research or data, a copy of the research or data. Such other data may include, but is not limited to, new articles, reference publications, and summaries of adverse events that are or may be associated with the new use; and

4. If the manufacturer is conducting studies needed for submission of a supplemental application, reports that describe the studies' current status (i.e., progress on patient enrollment, any significant problems that could affect the manufacturer's ability to complete the studies, and expected completion dates). If the manufacturer discontinues or terminates a study before completing it, it would, as part of this semiannual report, notify FDA of the discontinuation or termination of the study and state the reasons for such discontinuation or termination.

Proposed § 99.501(c) would require manufacturers to maintain a copy of all information, lists, records, and reports required or disseminated under this part for a period of 3 years after it has ceased dissemination of the new use information that triggered such requirements and make such documents available to FDA for inspection and copying.

G. Conforming Amendments

The proposal would make a conforming amendment to part 16. Part 16 describes the procedures for regulatory hearings before FDA. Section 16.1 lists the statutory and regulatory actions that may be the subject of a part 16 hearing. The proposal would amend § 16.1(a)(2) to add the due diligence determinations under proposed § 99.401(c) to the list of regulatory actions that may be the subject of a part 16 hearing.

III. Analysis of Impacts

FDA has examined the impacts of the proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U.S.C. 601–612). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages). Under the Regulatory Flexibility Act, unless an agency certifies that a rule will not have a significant impact on small entities, the agency must analyze regulatory options that would minimize the impact of the rule on small entities. Title II of the Unfunded Mandates Reform Act (Pub. L. 104–114) (in section 202) requires that agencies prepare an assessment of anticipated costs and benefits before proposing any rule that may result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million or more (adjusted annually for inflation).

The agency has reviewed this proposed rule and has determined that it is consistent with the regulatory philosophy and principles identified in Executive Order 12866, and these two statutes. Although this proposal is not an economically significant regulatory action, it is still a significant regulatory action as defined by the Executive Order due to the novel policy issues it raises. With respect to the Regulatory Flexibility Act, the agency certifies that the rule will not have a significant effect on a substantial number of small entities. Because the proposed rule does not impose any mandates on State, local, or tribal governments, or the private sector that will result in a 1-year expenditure of $100 million or more, FDA is not required to perform a cost-benefit analysis under the Unfunded Mandates Reform Act.

The proposed rule implements section 401 of FDAMA by describing the new use information that a manufacturer may disseminate and setting forth the procedures that manufacturers must follow before disseminating information on the new use. FDA has long recognized that in certain circumstances, new (off-label) uses of approved products are appropriate, rational, and accepted medical practice. There are important off-label uses of approved products. The benefits of the rule will derive from the public health gains associated with the earlier dissemination of objective, balanced, accurate information about such important new uses. In addition, the proposed rule may actually stimulate new studies or the collection of evidence about these new uses.

The costs of the rule are modest. Firms typically conduct clinical studies in support of supplemental applications for new uses only where the firm believes that the added revenues associated with the new use would exceed the cost of the supporting studies. Because this rule will accelerate the receipt of these revenues, it is possible that some new use supplemental applications that would not have been economically justified in the absence of this rule will now be submitted. FDA cannot estimate the number or cost of the additional clinical studies that would accompany these applications, but emphasizes that they would be undertaken voluntarily by the affected firms in the expectation that they would raise company profitability.

Manufacturers that choose not to disseminate new use information will incur no costs. Firms choosing to disseminate new use information will experience added paperwork costs for each submission to the agency, but gain sales revenues from the information dissemination. FDA cannot make a precise estimate of the number of submissions that will be filed each year, but as explained in section IV of this document, the agency preliminarily forecasts that it will receive approximately 300 submissions from manufacturers for disseminating new use information. FDA also estimates that the paperwork associated with these submissions might total over 33,000 hours, at an average labor cost of $35 per hour. Thus, the total cost of the added paperwork is estimated to cost industry approximately $1.2 million per year.

The proposed rule, however, will not have an adverse impact on any manufacturer. Firms will compare the expected sales revenue from the new dissemination activity to the associated paperwork cost and disseminate the new information only if it increases their profitability. As noted previously, firms choosing not to disseminate the new use information will face no increased costs due to this rule. Firms choosing to disseminate the new use information will do so only if the expected increased sales revenues exceed the associated regulatory costs. Because no firm will experience a reduced net income, the proposed rule will not have a significant adverse effect on a substantial number of small entities and no further analysis is required under the Regulatory Flexibility Act.

IV. Paperwork Reduction Act of 1995

This proposed rule contains information collection requirements that are subject to public comment and review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501–3520). A description of these provisions is given below in this section of the document with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

FDA invites comments on: (1) Whether the proposed collection of

information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Title: Dissemination of Treatment Information on Unapproved Uses for Marketed Drugs, Biologics, and Devices.

Description: The proposed rule implements sections 551 through 557 of the act (21 U.S.C. 360aaa-360aaa-6) as amended by FDAMA, which requires a manufacturer that intends to disseminate certain treatment information on unapproved uses for a marketed drug, biologic, or device to submit that information to FDA. The proposed rule sets forth the criteria and procedures for making such submissions. Under the proposed rule, a submission would include a certification that the manufacturer has completed clinical studies necessary to submit a supplemental application to FDA for the new use and will submit the supplemental application within 6 months after its initial dissemination of information. If the manufacturer has planned, but not completed, such studies, the submission would include proposed protocols and a schedule for conducting the studies, as well as a certification that the manufacturer will complete the clinical studies and submit a supplemental application no later than 36 months after its initial dissemination of information. The proposal would also permit manufacturers to request extensions of the time period for completing a study and submitting a supplemental application and to request an exemption from the requirement to submit a supplemental application. The proposal would prescribe the timeframe within which the manufacturer shall maintain records that would enable it to take corrective action. The proposal would require the manufacturer to submit lists pertaining to the disseminated articles and reference publications and the categories of persons (or individuals) receiving the information and to submit a notice and summary of any additional research or data (and a copy of the data) relating to the product's safety or effectiveness for the new use. The proposal would require the manufacturer to maintain a copy of the information, lists, records, and reports for 3 years after it has ceased dissemination of the information and to make the documents available to FDA for inspection and copying.

Description of Respondents: All manufacturers (persons and businesses, including small businesses) of drugs, biologics, and device products.

The estimated burden associated with the information collection requirements for this proposed rule is 2,907 hours.

FDA estimates the burden of this collection of information as follows:

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	Number of Responses per Respondent	Total Annual Responses	Hours per Response	Total Hours
99.201(a)93)	172	1.7	297	1	297
99.201(a)(4)(i)(A)	57	1.7	98	1	98
99.201(a)(4)(ii)(a)	57	1.7	98	10	980
99.201(a)(5)	57	1.7	98	1	98
99.20(c)	172	1.7	297	0.5	148.5
99.203(b)	1	1.7	1	10	10
99.203(c)	1	1.7	1	0.5	0.5
99.205(b)	2	1.7	3	125	375
99.301(a)(2)	2	1.7	3	1	3
99.501(b)(2)	172	3.4	594	1	594
99.501(b)(4)	2	1.7	3	2	6
Total					2,610

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

TABLE 2.—ESTIMATED ANNUAL RECORDKEEPING BURDEN[1]

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
99.501(a)(2)	172	1.7	297	1	297

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.

The above estimates reflect the reporting or recordkeeping burden that would be attributable solely to the rule. FDA derived these estimates from existing data on submissions made under supplemental applications and other submissions to the agency, as well as information from industry sources regarding similar or related reporting and recordkeeping burdens.

The agency has submitted the information collection requirements of this proposed rule to OMB for review. Interested persons are requested to send comments regarding information collection by July 8, 1998, to the Office of Information and Regulatory Affairs, OMB (address above).

V. Environmental Impact

The agency has determined, under 21 CFR 25.30(h) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VI. Request for Comments

Interested persons may, on or before July 23, 1998, submit to the Dockets Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects

21 CFR Part 16

Administrative practice and procedure.

21 CFR Part 99

Administrative practice and procedure, Biologics, Devices, Drugs, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR chapter I be amended to read as follows:

PART 16—REGULATORY HEARING BEFORE THE FOOD AND DRUG ADMINISTRATION

1. The authority citation for 21 CFR part 16 is revised to read as follows:

Authority: 21 U.S.C. 141–149, 321–394, 467f, 679, 821, 1034; 42 U.S.C. 201–262, 263b, 364; 15 U.S.C. 1451–1461; 28 U.S.C. 2112.

2. Section 16.1 is amended in paragraph (b)(2) by numerically adding an entry for § 99.401(c) to read as follows:

§ 16.1 Scope.

* * * * *

(b) * * *

(2) Regulatory provisions:

* * * * *

§ 99.401(c), relating to a due diligence determination concerning the conduct of studies necessary for a supplemental application for a new use of a drug or device.

* * * * *

3. Part 99 is added to read as follows:

PART 99—DISSEMINATION OF INFORMATION ON UNAPPROVED/NEW USES FOR MARKETED DRUGS, BIOLOGICS, AND DEVICES

Subpart A—General Information

Sec.

Subpart B—Information To Be Disseminated

Subpart C—Manufacturer's Submissions, Requests, and Applications

Subpart D—FDA Action on Submissions, Requests, and Applications

Subpart E—Corrective Actions and Cessation of Dissemination

Subpart F—Recordkeeping and Reports

Authority: 21 U.S.C. 321, 331, 351, 352, 355, 360, 360c, 360e, 360aa–360aaa-6, 371, and 374; 42 U.S.C. 262.

Subpart A—General Information

§ 99.1 Scope.

(a) This part applies to the dissemination of information on human drugs, including biologics, and devices where the information to be disseminated:

(1) Concerns the safety, effectiveness, or benefit of a use that is not included in the approved labeling for a drug or device approved by the Food and Drug Administration for marketing or in the statement of intended use for a device cleared by the Food and Drug Administration for marketing; and

(2) Will be disseminated to a health care practitioner, pharmacy benefit manager, health insurance issuer, group health plan, or Federal or State government agency.

(b) This part does not apply to a manufacturer's dissemination of information that responds to a health care practitioner's unsolicited request.

§ 99.3 Definitions.

(a) *Agency* or *FDA* means the Food and Drug Administration.

(b) For purposes of this part, a *clinical investigation* is an investigation in humans that is prospectively planned to test a specific clinical hypothesis.

(c) *Group health plan* means an employee welfare benefit plan (as defined in section 3(1) of the Employee Retirement Income Security Act of 1974 (29 U.S.C. 1002(1))) to the extent that the plan provides medical care (as defined in paragraphs (c)(1) through (c)(3) of this section and including items and services paid for as medical care) to employees or their dependents (as defined under the terms of the plan) directly or through insurance, reimbursement, or otherwise. For purposes of this part, the term *medical care* means:

(1) Amounts paid for the diagnosis, cure, mitigation, treatment, or prevention of disease, or amounts paid for the purpose of affecting any structure or function of the body;

(2) Amounts paid for transportation primarily for and essential to medical care referred to in paragraph (c)(1) of this section; and

(3) Amounts paid for insurance covering medical care referred to in paragraphs (c)(1) and (c)(2) of this section.

(d) *Health care practitioner* means a physician or other individual who is a health care provider and licensed under State law to prescribe drugs or devices.

(e) *Health insurance issuer* means an insurance company, insurance service, or insurance organization (including a health maintenance organization, as defined in paragraph (e)(2) of this section) which is licensed to engage in the business of insurance in a State and which is subject to State law which regulates insurance (within the meaning of section 514(b)(2) of the Employee Retirement Income Security Act of 1974 (29 U.S.C. 1144(b)(2))).

(1) Such term does not include a group health plan.

(2) For purposes of this part, the term *health maintenance organization* means:

(i) A Federally qualified health maintenance organization (as defined in section 1301(a) of the Public Health Service Act (42 U.S.C. 300e(a)));

(ii) An organization recognized under State law as a health maintenance organization; or

(iii) A similar organization regulated under State law for solvency in the same manner and to the same extent as such a health maintenance organization.

(f) *Manufacturer* means a person who manufactures a drug or device or who is licensed by such person to distribute or market the drug or device. For purposes of this part, the term may also include the sponsor of the approved, licensed, or cleared drug or device.

(g) *New use* means a use that is not included in the approved labeling of an

approved drug or device, or a use that is not included in the statement of intended use for a cleared device.

(h) A *reference publication* is a publication that:

(1) Has not been written, edited, excerpted, or published specifically for, or at the request of, a drug or device manufacturer;

(2) Has not been edited or significantly influenced by such a manufacturer;

(3) Is not solely distributed through such a manufacturer, but is generally available in bookstores or other distribution channels where medical textbooks are sold;

(4) Does not focus on any particular drug or device of a manufacturer that disseminates information under this part and does not have a primary focus on new uses of drugs or devices that are marketed or are under investigation by a manufacturer supporting the dissemination of information; and

(5) Does not present materials that are false or misleading.

(i) *Scientific or medical journal* means a scientific or medical publication:

(1) That is published by an organization that has an editorial board, that uses 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 that has a publicly stated policy, to which the organization adheres, of full disclosure of any conflict of interest or biases for all authors or contributors involved with the journal or organization;

(2) Whose articles are peer-reviewed and published in accordance with the regular peer-review procedures of the organization;

(3) That is generally recognized to be of national scope and reputation;

(4) That is indexed in the Index Medicus of the National Library of Medicine of the National Institutes of Health; and

(5) That is not in the form of a special supplement that has been funded in whole or in part by one or more manufacturers.

(j) *Supplemental application* means:

(1) For drugs, a supplement to support a new use to an approved new drug application;

(2) For biologics, a supplement to an approved license application;

(3) For devices that are the subject of a cleared 510(k) submission, a new 510(k) submission to support a new use or, for devices that are the subject of an approved premarket approval application, a supplement to support a new use to an approved premarket approval application.

Subpart B—Information To Be Disseminated

§ 99.101 Information that may be disseminated.

(a) A manufacturer may disseminate written information concerning the safety, effectiveness, or benefit of a use not described in the approved labeling for an approved drug or device or in the statement of intended use for a cleared device, provided that the manufacturer complies with all other relevant requirements under this part. Such information shall:

(1) Be about a drug or device that has been approved, licensed, or cleared for marketing by FDA;

(2) Be in the form of:

(i) 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. In addition, the article must be about a clinical investigation with respect to the drug or device and must be considered to be scientifically sound by the experts described above; or

(ii) An unabridged reference publication that includes information about a clinical investigation with respect to the drug or device, which experts qualified by scientific training or experience to evaluate the safety or effectiveness of the drug or device that is the subject of the clinical investigation would consider to be scientifically sound;

(3) Not pose a significant risk to the public health;

(4) Not be false or misleading. FDA may consider information disseminated under this part to be false or misleading if, among other things, the information includes only favorable publications or excludes articles, reference publications, or other information concerning risks and adverse effects that are or may be associated with the new use; and

(5) Not be derived from clinical research conducted by another manufacturer unless the manufacturer disseminating the information has the permission of such other manufacturer to make the dissemination.

(b) For purposes of this part:

(1) 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. Accordingly, a clinical investigation described or discussed in a reprint or copy of an article or in a reference publication must include a description of the study design and conduct, data presentation and analysis, summary of results, and conclusions pertaining to the new use. A clinical investigation presented in a format that does not represent a reasonably comprehensive presentation of the study design, conduct, data, analyses, and conclusions (e.g., letters to the editor, review abstracts, or abstracts of publications) does not qualify for dissemination under this part; and

(2) A reprint or copy of an article or reference publication is ''unabridged' only if it retains the same appearance, form, format, content or configuration as the original article or publication. Such reprint, copy of an article, or reference publication shall not be disseminated with any information that is promotional in nature. A manufacturer may cite a particular discussion about a new use in a reference publication in the explanatory or other information attached to or otherwise accompanying the reference publication under § 99.103.

§ 99.103 Mandatory statements and information.

(a) Any information disseminated under this part shall include:

(1) A prominently displayed statement disclosing:

(i) For a drug, ''This information concerns a use that has not been approved by the Food and Drug Administration and is being disseminated under section 551 *et seq.* of the Federal Food, Drug, and Cosmetic Act.'' For devices, the statement shall read, ''This information concerns a use that has not been approved or cleared by the Food and Drug Administration and is being disseminated under section 551 *et seq.* of the Federal Food, Drug, and Cosmetic Act.'' If the information to be disseminated includes both approved and unapproved uses or cleared and uncleared uses, the manufacturer shall modify the statement to identify the unapproved or uncleared new use. The manufacturer shall permanently affix the statement to the front of each reprint or copy of an article from a scientific or medical journal and to the front of each reference publication disseminated under this part;

(ii) If applicable, the information is being disseminated at the expense of the manufacturer;

(iii) If applicable, the names of any authors of the information who are

employees of, or consultants to, or have received compensation from the manufacturer, or who have a significant financial interest in the manufacturer;

(iv) If applicable, a statement that there are products or treatments that have been approved or cleared for the use that is the subject of the information being disseminated; and

(v) The identification of any person that has provided funding for the conduct of a study relating to the new use of a drug or device for which such information is being disseminated; and

(2) The official labeling for the drug or device;

(3) A bibliography of other articles (that concern reports of clinical investigations both supporting and not supporting the new use) from a scientific reference publication or scientific or medical journal that have been previously published about the new use of the drug or device covered by the information that is being disseminated, unless the disseminated information already includes such a bibliography; and

(4) Any additional information required by FDA. Such information, which shall be attached to the front of the disseminated information, may consist of:

(i) Objective and scientifically sound information pertaining to the safety or effectiveness of the new use of the drug or device and which FDA determines is necessary to provide objectivity and balance. This may include information that the manufacturer has submitted to FDA or, where appropriate, a summary of such information and any other information that can be made publicly available; and

(ii) An objective statement prepared by FDA, based on data or other scientifically sound information, bearing on the safety or effectiveness of the new use of the drug or device.

(b) Except as provided in paragraphs (a)(1)(i) and (a)(4) of this section, the statements, bibliography, and other information required by this section shall be attached to such disseminated information.

(c) For purposes of this section, factors to be considered in determining whether a statement is ''prominently displayed'' may include, but are not limited to, type size, font, layout, contrast, graphic design, headlines, spacing, and any other technique to achieve emphasis or notice. The required statements shall be outlined, boxed, highlighted, or otherwise graphically designed and presented in a manner that achieves emphasis or notice and is distinct from the other information being disseminated.

§ 99.105 Recipients of information.

A manufacturer disseminating information on a new use under this part may only disseminate that information to a health care practitioner; a pharmacy benefit manager; a health insurance issuer; a group health plan; or a Federal or State government agency.

Subpart C—Manufacturer's Submissions, Requests, and Applications

§ 99.201 Manufacturer's submission to the agency.

(a) Sixty days before disseminating any written information concerning the safety, effectiveness, or benefit of a new use for a drug or device, a manufacturer shall submit to the agency:

(1) An identical copy of the information to be disseminated, including any information (e.g., the bibliography) and statements required under § 99.103;

(2) Any other clinical trial information which the manufacturer has relating to the safety or effectiveness of the new use, any reports of clinical experience pertinent to the safety of the new use, and a summary of such information. For purposes of this part, clinical trial information includes, but is not limited to, published papers and abstracts, even if not intended for dissemination, and unpublished manuscripts, abstracts, and data analyses from completed or ongoing investigations. The information and reports required under this paragraph shall include case studies, retrospective reviews, epidemiological studies, adverse event reports, and any other material concerning adverse effects or risks reported for or associated with the new use. If the manufacturer has no knowledge of clinical trial information relating to the safety or effectiveness of the new use or reports of clinical experience pertaining to the safety of the new use, the manufacturer shall provide a statement to that effect;

(3) An explanation of the manufacturer's search strategy in selecting the articles for the bibliography (e.g., the databases and criteria used to generate the bibliography and the time period covered by the bibliography); and

(4) If the manufacturer has not submitted a supplemental application for the new use, one of the following:

(i) If the manufacturer has completed studies needed for the submission of a supplemental application for the new use:

(A) A copy of the protocol for each completed study or, if such protocol was submitted to an investigational new drug application or an investigational device exemption, the number(s) for the investigational new drug application or investigational device exemption covering the new use, the date of submission of the protocol(s), the protocol number(s), and the date of any amendments to the protocol(s); and

(B) A certification stating that, ''On behalf of [insert manufacturer's name], I certify that [insert manufacturer's name] has completed the studies needed for the submission of a supplemental application for [insert new use] and will submit a supplemental application for such new use to the Food and Drug Administration no later than [insert date no later than 6 months from date of the initial dissemination of information under this part];'' or

(ii) If the manufacturer has planned studies that will be needed for the submission of a supplemental application for the new use:

(A) The proposed protocols and schedule for conducting the studies needed for the submission of a supplemental application for the new use. The protocols shall comply with all applicable requirements in parts 312 of this chapter (investigational new drug applications) and 812 of this chapter (investigational device exemptions). The schedule shall include the projected dates on which the manufacturer expects the principal study events to occur (e.g., initiation and completion of patient enrollment, completion of data collection, completion of data analysis, and submission of the supplemental application); and

(B) A certification stating that, ''On behalf of [insert manufacturer's name], I certify that [insert manufacturer's name] will exercise due diligence to complete the clinical studies necessary to submit a supplemental application for [insert new use] and will submit a supplemental application for such new use to the Food and Drug Administration no later than [insert date no later than 36 months from date of the initial dissemination of information under this part];'' or

(iii) An application for exemption from the requirement of a supplemental application; or

(5) If the manufacturer has submitted a supplemental application for the new use, a cross-reference to that supplemental application.

(b) The manufacturer's attorney, agent, or other authorized official shall sign the submission and certification statement or application for exemption. If the manufacturer does not have a place of business in the United States, the submission and certification statement or application for exemption shall contain the signature, name, and address of the manufacturer's attorney,

agent, or other authorized official who resides or maintains a place of business in the United States.

(c) The manufacturer shall send three copies of the submission and certification statement or application for exemption to FDA. The outside of the shipping container shall be marked as ''Submission for the Dissemination of Information on an Unapproved/New Use.'' The manufacturer shall send the submission and certification statement or application for exemption to the appropriate FDA component listed below:

(1) For biological products and devices regulated by the Center for Biologics Evaluation and Research, the Advertising and Promotional Labeling Staff (HFM–202), Center for Biologics Evaluation and Research, Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852;

(2) For human drug products, the Division of Drug Marketing, Advertising, and Communications (HFD–40), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857; or

(3) For medical devices, the Promotion and Advertising Policy Staff (HFZ–302), Office of Compliance, Center for Devices and Radiological Health, Food and Drug Administration, 2098 Gaither Rd., Rockville, MD 20850.

(d) The 60-day period shall begin when FDA receives a complete submission, including, where applicable, a certification statement or application for exemption. 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.

§ 99.203 Request to extend the time for completing planned studies.

(a) A manufacturer who has certified that it will complete the studies necessary to submit a supplemental application for a new use within 36 months from the date of initial dissemination of information under this part, but later finds that it will be unable to complete such studies and submit a supplemental application within that time period may request an extension of time from FDA.

(b) The manufacturer, in its request for extension, shall identify the product, the new use, and shall:

(1) Describe the study or studies that cannot be completed on time and explain why the study or studies cannot be completed on time;

(2) Describe the current status of the incomplete study or studies and summarize the work conducted, including the dates on which principal events concerning the study or studies occurred; and

(3) Estimate the additional time needed to complete the studies and submit a supplemental application. The requested extension shall not exceed an additional 24 months.

(c) The manufacturer shall send three copies of the request for extension to the same FDA office that received the manufacturer's initial submission and certification statement. The outside of the envelope shall be marked as ''Request for Time Extension—Dissemination of Information on an Unapproved Use.''

§ 99.205 Application for exemption from the requirement to file a supplemental application.

(a) In certain circumstances, described in paragraph (b) of this section, a manufacturer may submit an application for an exemption from the requirement to submit a supplemental application for a new use for purposes of disseminating information on that use.

(b) The manufacturer's application for an exemption shall identify the basis for the proposed exemption and shall include materials demonstrating that it would be economically prohibitive or that it would be unethical to conduct the studies necessary to submit a supplemental application for the new use.

(1) If the basis for the manufacturer's application for exemption is that it would be economically prohibitive to incur the costs necessary to submit a supplemental application for a new use, the manufacturer shall, at a minimum, provide evidence:

(i) Explaining why existing data characterizing the safety and effectiveness of the drug or device, including data from the study described in the information to be disseminated, are not adequate to support the submission of a supplemental application for the new use. Such evidence shall include an analysis of all data relevant to the safety and effectiveness of the use, a summary of those data, and any documentation resulting from prior discussions with the agency concerning the adequacy of the existing data; and

(ii) Demonstrating that the estimated cost of the studies needed for the approval of the new use would 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 that there are not less expensive ways to obtain the needed information. Such evidence shall include:

(A) A description of the current and projected U.S. patient population for the product and an estimate of the current and projected economic benefit to the manufacturer from its use. Such estimate shall assume that the total potential market for the drug or device is equal to the prevalence of the disease(s) or condition(s) that the drug or device will be used to treat and involve the following considerations:

(*1*) The estimated market share for the drug or device during any exclusive market period, a summary of any exclusive market period for the product, and an explanation of the basis for the estimate;

(*2*) A projection of and justification for the price at which the drug or device will be sold; and

(*3*) Comparisons with sales of similarly situated drugs or devices, where available.

(B) A description of the additional studies that the manufacturer believes are necessary to support the submission of a supplemental application for the new use, including documentation from prior discussions, if any, with the agency concerning the studies that would be needed, and an estimate of the projected costs for such studies;

(C) An attestation by a responsible individual of the manufacturer verifying that the estimates included with the submission are accurate and were prepared in accordance with generally accepted accounting procedures. The data underlying and supporting the estimates shall be made available to FDA upon request.

(2) If the basis for the manufacturer's application for exemption is that it would be unethical to conduct the studies necessary for the supplemental application for a new use, the manufacturer shall provide evidence:

(i) Explaining why existing data characterizing the safety and effectiveness of the drug or device, including data from the study described in the information to be disseminated, are not adequate to support the submission of a supplemental application for the new use. Such evidence shall include an analysis of all data relevant to the safety and effectiveness of the new use, a summary of those data, and any documentation resulting from prior discussions with the agency concerning the adequacy of the existing data; and

(ii) Explaining why it would be unethical to conduct the further studies that would be necessary for the approval of the new use. Such evidence shall establish that, notwithstanding the

insufficiency of available data to support the submission of a supplemental application for the new use, the data are persuasive to the extent that withholding the drug or device in a controlled study (e.g., by providing no therapy, a placebo, an alternative therapy, or an alternative dose) would pose an unreasonable risk of harm to human subjects. For purposes of determining what is unethical under this part an unreasonable risk of harm would ordinarily arise only when the new use appears to affect mortality or irreversible morbidity. In assessing the appropriateness of conducting studies to support the new use, the manufacturer may provide evidence showing that the new use is broadly accepted as current standard medical treatment or therapy. The manufacturer shall also address the possibility of conducting studies in different populations or of modified design (e.g., adding the new therapy to existing treatments or using an alternative dose if monotherapy studies could not be conducted).

Subpart D—FDA Action on Submissions, Requests, and Applications

§ 99.301 Agency action on a submission.

(a) *Submissions.* Within 60 days after receiving a submission under this part, FDA may:

(1) Determine that the manufacturer does not comply with the requirements under this part and that, as a result, the manufacturer shall not disseminate any information under this part;

(2) Request additional information or documents to assist the agency in determining whether the information to be disseminated complies with the requirements under this part. This may include, but is not limited to, copies of articles listed by the manufacturer in its bibliography;

(3) Determine that the information submitted regarding a new use fails to provide data, analyses, or other written matter that is objective and balanced. If FDA makes such a determination, the agency:

(i) Shall provide to the manufacturer notice and an opportunity for a meeting regarding the agency's determination;

(ii) May require the manufacturer to disseminate additional information, including information which the manufacturer has submitted to FDA or, where appropriate, a summary of such information or any other information that can be made publicly available, which, in the agency's opinion:

(A) Is objective and scientifically sound;

(B) Pertains to the safety or effectiveness of the new use; and

(C) Is necessary to provide objectivity and balance; and

(iii) May require the manufacturer to disseminate an objective statement prepared by FDA that is based on data or other scientifically sound information available to the agency and bears on the safety or effectiveness of the drug or device for the new use; and

(4) Require the manufacturer to maintain records that will identify individual recipients of the information that is to be disseminated.

(b) *Protocols/Studies.* Within 60 days after receiving a submission under this part, FDA shall:

(1) If the manufacturer has planned studies that will be needed for the submission of a supplemental application for the new use, review the manufacturer's proposed protocols and schedule for completing such studies and determine whether the proposed protocols are adequate and whether the proposed schedule for completing the studies is reasonable. FDA shall notify the manufacturer if it determines that the proposed protocols are adequate and the proposed schedule for completing the studies is reasonable. Until such notification, the manufacturer shall not disseminate any information under this part; or

(2) If the manufacturer has completed studies that the manufacturer believes would be an adequate basis for the submission of a supplemental application for the new use, 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. FDA shall notify the manufacturer if it determines that the completed studies are inadequate, based on a preliminary review, to support the filing of a supplemental application for the new use or are not complete. Upon such notification, the manufacturer shall not disseminate any information under this part.

§ 99.303 Extension of time for completing planned studies.

(a) Upon review of a drug or device manufacturer's proposed protocol and schedule for conducting studies needed for the submission of a supplemental application for a new use, FDA may determine that such studies cannot be completed and submitted within 36 months. The agency may exercise its discretion in extending the time period for completing the studies and submitting a supplemental application.

(b) The manufacturer may, in writing, request that FDA extend the time period for conducting studies needed for the submission of a supplemental application for a new use and submitting a supplemental application to FDA. FDA may grant or deny the request or, after consulting the manufacturer, grant an extension different from that requested by the manufacturer. Extensions under this paragraph shall not exceed 24 months.

(c) FDA may grant a manufacturer's request for an extension if FDA determines that the manufacturer has acted with due diligence to conduct the studies needed for the submission of a supplemental application for a new use and to submit such a supplemental application to FDA in a timely manner and that, despite such actions, the manufacturer needs additional time to complete the studies and submit the supplemental application.

(d) If FDA extends the time period for completing the studies and submitting a supplemental application under paragraph (a) of this section or grants a manufacturer's request for an extension under paragraph (c) of this section, the manufacturer shall submit a new certification under § 99.201(a)(4)(ii)(B) that sets forth the timeframe within which clinical studies will be completed and a supplemental application will be submitted to FDA.

§ 99.305 Exemption from the requirement to file a supplemental application.

(a) Within 60 days after receipt of an application for an exemption from the requirement of a supplemental application, FDA shall approve or deny the application.

(1) If FDA does not act on the application for an exemption within the 60-day period, the application for an exemption shall be deemed to be approved.

(2) If an application for an exemption is deemed to be approved, FDA may, at any time, terminate such approval if it determines that the requirements for granting an exemption have not been met. FDA shall notify the manufacturer if the approval is terminated.

(b) In reviewing an application for an exemption, FDA shall consider the materials submitted by the manufacturer and may consider any other appropriate information, including, but not limited to, any pending or previously approved applications for exemption submitted by the manufacturer.

(c) FDA may grant an application for an exemption if FDA determines that:

(1) It would be economically prohibitive for the manufacturer to incur the costs necessary to submit a supplemental application for a new use, which at a minimum requires:

(i) That existing data characterizing the safety and effectiveness of the drug

or device, including data from the study described in the information to be disseminated are not adequate to support the submission of a supplemental application for the new use; and

(ii) 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; or

(2) It would be unethical to conduct clinical studies needed to support the submission of a supplemental application for the new use because:

(i) Existing data characterizing the safety and effectiveness of the drug or device, including data from the study described in the information to be disseminated are not adequate to support the submission of a supplemental application for the new use; and

(ii) Although available evidence would not support the submission of a supplemental application for the new use, the data are persuasive to the extent that withholding the drug or device in a controlled study would pose an unreasonable risk of harm to human subjects and no studies in different populations or of modified design can be utilized. In determining whether it would be unethical to conduct clinical studies, the agency shall consider, in addition to the persuasiveness of available evidence of effectiveness, whether the new use of the drug or device is broadly accepted as current standard medical treatment or therapy.

Subpart E—Corrective Actions and Cessation of Dissemination

§ 99.401 Corrective actions and cessation of dissemination of information.

(a) *FDA actions based on post dissemination data.* If FDA receives data after a manufacturer has begun disseminating information on a new use and, based on that data, determines that the new use that is the subject of information disseminated under this part may not be effective or may present a significant risk to public health, FDA shall consult the manufacturer and, after such consultation, take appropriate action to protect the public health. Such action may include ordering the manufacturer to cease disseminating information on the new use and to take appropriate corrective action.

(b) *FDA actions based on information disseminated by a manufacturer.* If FDA determines that a manufacturer is disseminating information that does not comply with the requirements under this part, FDA may:

(1) Provide to the manufacturer an opportunity to bring itself into compliance with the requirements under this part if the manufacturer's noncompliance constitutes a minor violation of these requirements; or

(2) Order the manufacturer to cease dissemination of information and to take corrective action. FDA shall issue such an order only after it has:

(i) Provided notice to the manufacturer regarding FDA's intent to issue an order to cease dissemination; and

(ii) Provided to the manufacturer an opportunity for a meeting. FDA shall not provide an opportunity for a meeting if the manufacturer certified that it will submit a supplemental application for the new use within 6 months of initial dissemination and the noncompliance involves a failure to submit such supplemental application.

(c) *FDA actions based on a manufacturer's supplemental application.* FDA may order a manufacturer to cease disseminating information under this part and to take corrective action if:

(1) In the case of a manufacturer that has submitted a supplemental application for the new use, FDA determines that the supplemental application does not contain adequate information for approval of the new use;

(2) In the case of a manufacturer that has certified that it will submit a supplemental application for the new use within 6 months, the manufacturer has not, within the 6-month period, submitted a supplemental application for the new use;

(3) In the case of a manufacturer that has certified that it will submit a supplemental application for the new use within 36 months or within such time as FDA has determined to be appropriate under § 99.303(a) or (c), such manufacturer has not submitted the supplemental application within the certified time or, FDA, after an informal hearing, has determined that the manufacturer is not acting with due diligence to initiate or complete the studies necessary to support a supplemental application for the new use; or

(4) In the case of a manufacturer that has certified that it will submit a supplemental application for the new use within 36 months or within such time as FDA has determined to be appropriate under § 99.303(a) or (c), the manufacturer has discontinued or terminated the clinical studies that would be necessary to support a supplemental application for a new use.

(d) *Effective date of orders to cease dissemination.* An order to cease dissemination of information shall be effective upon date of issuance by FDA, unless otherwise stated in such order.

(e) *Cessation of dissemination by a noncomplying manufacturer.* A manufacturer that begins to disseminate information in compliance with this part, but subsequently fails to comply with this part, shall immediately cease disseminating information under this part. A manufacturer that discontinues, terminates, or fails to conduct with due diligence clinical studies that it certified it would complete under § 99.201(a)(4)(ii) shall be deemed not in compliance with this part. A manufacturer shall notify FDA if it ceases dissemination under this paragraph.

§ 99.403 Termination of approvals of applications for exemption.

(a) FDA may, at any time, terminate the approval of an application for an exemption from the requirement to file a supplemental application if:

(1) The application for an exemption had been deemed to be approved because the agency had not acted on the application within 60 days after its receipt by FDA;

(2) The manufacturer is disseminating written information on the new use; and

(3) FDA determines that it would be economically or ethically possible for the manufacturer to conduct the clinical studies needed to submit a supplemental application for the new use.

(b) If FDA terminates a deemed approval of an application for an exemption under paragraph (a) of this section, FDA also may:

(1) Order the manufacturer to cease disseminating information; and

(2) Order the manufacturer to take action to correct the information that has been disseminated if FDA determines that the new use described in the disseminated information would pose a significant risk to public health.

(c) FDA shall notify the manufacturer if it terminates the deemed approval of an application for an exemption under paragraph (a) of this section. If FDA also issues an order to cease dissemination of information, the manufacturer shall comply with the order no later than 60 days after its receipt.

(d) FDA may, at any time, terminate the approval of an application for an exemption from the requirement to file a supplemental application for a new use if, after consulting with the manufacturer that was granted such

exemption, FDA determines that the manufacturer no longer meets the requirements for an exemption on the basis that it is economically prohibitive or unethical to conduct the studies needed to submit a supplemental application for the new use.

(e) If FDA terminates an approval of an application for an exemption under paragraph (d) of this section, the manufacturer must, within 60 days of being notified by FDA that its exemption approval has been terminated, file a supplemental application for the new use that is the subject of the information being disseminated under the exemption, certify, under § 99.201(a)(4)(i) or (a)(4)(ii) that it will file a supplemental application for the new use, or cease disseminating information on the new use. FDA may require a manufacturer that ceases the dissemination of information on the new use to undertake corrective action.

§ 99.405 Applicability of labeling, adulteration, and misbranding authority.

The dissemination of information relating to a new use for a drug or device may constitute labeling, evidence of a new intended use, adulteration, or misbranding of the drug or device if such dissemination fails to comply with section 551 of the Federal Food, Drug, and Cosmetic Act (the act) and the requirements of this part. A manufacturer's failure to exercise due diligence in submitting the clinical studies that are necessary for the approval of a new use that is the subject of information disseminated under this part or in beginning or completing such clinical studies shall be deemed a failure to comply with section 551 of the act and the requirements of this part.

Subpart F—Recordkeeping and Reports

§ 99.501 Recordkeeping and reports.

(a) A manufacturer disseminating information under this part shall:

(1) Maintain records sufficient to allow the manufacturer to take corrective action as required by FDA. The manufacturer shall make such records available to FDA, upon request, for inspection and copying. Such records shall either:

(i) Identify, by name, those persons receiving the disseminated information; or

(ii) Identify, by category, the recipients of the disseminated information, unless FDA requires the manufacturer to retain records identifying individual recipients of the disseminated information. Manufacturers whose records identify recipients by category only shall:

(A) Identify subcategories of recipients where appropriate (e.g., oncologists, pediatricians, obstetricians, etc.); and

(B) Ensure that any corrective action to be taken will be sufficiently conspicuous to individuals within that category of recipients;

(2) Maintain an identical copy of the information disseminated under this part; and

(3) Upon the submission of a supplemental application to FDA, notify the appropriate office identified in § 99.201(c) of this part.

(b) A manufacturer disseminating information on a new use for a drug or device shall, on a semiannual basis, submit to the FDA office identified in § 99.201(c) of this part:

(1) A list containing the titles of articles and reference publications relating to the new use of drugs or devices that the manufacturer disseminated to a health care practitioner, pharmacy benefit manager, health insurance issuer, group health plan, or Federal or State government agency. The list shall cover articles and reference publications disseminated in the 6-month period preceding the date on which the manufacturer provides the list to FDA;

(2) A list identifying the categories of health care practitioners, pharmacy benefit managers, health insurance issuers, group health plans, or Federal or State government agencies that received the articles and reference publications in the 6-month period described in paragraph (b)(1) of this section. The list shall also identify which category of recipients received a particular article or reference publication;

(3) A notice and summary of any additional clinical research or other data relating to the safety or effectiveness of the new use, and, if the manufacturer possesses such clinical research or other data, a copy of the research or data. Such other data may include, but is not limited to, new articles published in scientific or medical journals, reference publications, and summaries of adverse effects that are or may be associated with the new use;

(4) If the manufacturer is conducting studies necessary for the submission of a supplemental application, periodic progress reports on these studies. Such reports shall describe the studies' current status (i.e., progress on patient enrollment, any significant problems that could affect the manufacturer's ability to complete the studies, and expected completion dates). If the manufacturer discontinues or terminates a study before completing it, the manufacturer shall, as part of the next periodic progress report, state the reasons for such discontinuation or termination; and

(5) If the manufacturer was granted an exemption from the requirement to submit a supplemental application for the new use, any new or additional information that relates to whether the manufacturer continues to meet the requirements for such exemption. This information may include, but is not limited to, new or additional information regarding revenues from the product that is the subject of the dissemination and new or additional information regarding the persuasiveness of the data on the new use, including information regarding whether the new use is broadly accepted as current standard medical treatment or therapy.

(c) A manufacturer shall maintain a copy of all information, lists, records, and reports required or disseminated under this part for 3 years after it has ceased dissemination of such information and make such documents available to FDA for inspection and copying.

Dated: May 29, 1998.

Michael A. Friedman,

Lead Deputy Commissioner for the Food and Drug Administration.

Donna E. Shalala,

Secretary of Health and Human Services.

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DEPARTMENT OF DEFENSE

Office of the Secretary

32 CFR Part 286

[DoD 5400.7–R]

RIN 0790–AG58

DoD Freedom of Information Act Program Regulation

AGENCY: Office of the Secretary, Department of Defense (DoD).

ACTION: Proposed rule.

SUMMARY: This proposed rule conforms to the requirements of the Electronic Freedom of Information Act Amendments of 1996. This proposed revision reflects substantial and administrative changes since May 1997, as a result of DoD reorganization. The proposal also provides guidance to DoD on implementation of this amended law.

DATES: Comments must be received by August 7, 1998.