

information shall be attached to the front of the disseminated information or, if attached to the back of the disseminated information, its presence shall be made known to the reader by a sticker or notation on the front of the disseminated information and 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 effectiveness of the new use, any other clinical trial information that the manufacturer has relating to the safety 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 reports of clinical experience 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 method of selecting the articles for the bibliography (e.g., the databases or sources and criteria (i.e., subject headings/keywords) 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 that dissemination of information under this part can begin]”; 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 that dissemination of information under this part can begin or no later than such time period as FDA may specify pursuant to

an extension granted under § 99.303(a);” 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 in paragraphs (c)(1) through (c)(3) of this section.

(1) For biological products and devices regulated by the Center for Biologics Evaluation and Research, the Advertising and Promotional Labeling Staff (HFM-602), 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 manufacturer’s

submission, including, where applicable, a certification statement or an application for an exemption.

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

(a) A manufacturer may request, prior to or at the time of making a submission to FDA under § 99.201, that FDA extend the 36-month time period for completing the studies and submitting a supplemental application for the new use that is the subject of the information to be disseminated. Such request must set forth the reasons that such studies cannot be completed and submitted in a supplemental application within 36 months.

(b) A manufacturer who has certified that it will complete the studies necessary to submit a supplemental application for a new use within a specified period of time from the date that dissemination of information under this part can begin under § 99.201(a)(4)(ii), 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. 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:

(i) Evidence 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) Evidence demonstrating that the cost of the study or studies for the new use reasonably exceeds the expected revenue from the new use minus the costs of goods sold and marketing and administrative expenses attributable to the new use of the product. Such evidence shall include:

(A) 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;

(B) The expected patient population for the new use;