

(mitoxantrone hydrochloride) Injection, EQ 25 mg base/12.5 mL and EQ 30 mg base/15 mL, was withdrawn for reasons of safety or effectiveness. We have carefully reviewed our files for records concerning the withdrawal of NOVANTRONE (mitoxantrone hydrochloride) Injection, EQ 25 mg base/12.5 mL and EQ 30 mg base/15 mL, from sale. We have also independently evaluated relevant literature and data for possible postmarketing adverse events. We have found no information that would indicate that this product was withdrawn from sale for reasons of safety or effectiveness.

Accordingly, the Agency will continue to list NOVANTRONE (mitoxantrone hydrochloride) Injection, EQ 25 mg base/12.5 mL and EQ 30 mg base/15 mL, in the "Discontinued Drug Product List" section of the Orange Book. The "Discontinued Drug Product List" delineates, among other items, drug products that have been discontinued from marketing for reasons other than safety or effectiveness. FDA will not begin procedures to withdraw approval of approved ANDAs that refer to NOVANTRONE Injection. Additional ANDAs for mitoxantrone hydrochloride injection, EQ 25 mg base/12.5 mL and EQ 30 mg base/15 mL, may also be approved by the Agency as long as they meet all other legal and regulatory requirements for the approval of ANDAs. If FDA determines that labeling for this drug product should be revised to meet current standards, the Agency will advise ANDA applicants to submit such labeling.

Dated: April 6, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2011-D-0164]

Draft Guidance for Industry on Safety Labeling Changes; Implementation of the Federal Food, Drug, and Cosmetic Act; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of a draft guidance for industry entitled "Safety Labeling Changes—Implementation of Section

505(o)(4) of the Federal Food, Drug, and Cosmetic Act." The Food and Drug Administration Amendments Act of 2007 (FDAAA) added new provisions to the Federal Food, Drug, and Cosmetic Act (the FD&C Act) authorizing FDA to require certain drug and biological product application holders to make safety related labeling changes based upon new safety information that becomes available after the drug or biological product is approved under the FD&C Act or the Public Health Service Act (the PHS Act). This draft guidance provides information on the implementation of the new provisions, including a description of the types of safety labeling changes that ordinarily might be required under the new legislation, how FDA plans to determine what constitutes new safety information, the procedures involved in requiring safety labeling changes, and enforcement of the requirements for safety labeling changes.

DATES: Although you can comment on any guidance at any time (see 21 CFR 10.115(g)(5)), to ensure that the Agency considers your comment on this draft guidance before it begins work on the final version of the guidance, submit written or electronic comments on the draft guidance by July 12, 2011.

ADDRESSES: Submit written requests for single copies of this guidance to the Division of Drug Information, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 2201, Silver Spring, MD 20993-0002; or the Office of Communication, Outreach and Development (HFM-40), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448. The guidance may also be obtained by mail by calling CBER at 1-800-835-4709 or 301-827-1800. Send one self-addressed adhesive label to assist the office in processing your requests. Submit written comments on the guidance to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.regulations.gov>. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the draft guidance document.

FOR FURTHER INFORMATION CONTACT:

Kristen Everett, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 51, Rm. 6228, Silver Spring, MD 20993-0002, 301-796-5400, or Stephen Ripley, Center for Biologics Evaluation and Research

(HFM-17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-827-6210.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a draft guidance for industry entitled "Safety Labeling Changes—Implementation of Section 505(o)(4) of the Federal Food, Drug, and Cosmetic Act." In the past, FDA has requested that holders of applications for approved products make labeling changes related to safety after approval to address serious risks. FDA learned of the potential for such serious risks from a variety of sources. In most cases, application holders responded to these requests by negotiating appropriate language with FDA staff to address the concerns, and then submitting a supplement or amended supplement to obtain approval of the change. Negotiations were often protracted, and FDA had few tools available at its disposal to end negotiations and require the changes. Congress recognized the limitations of FDA's authority in this area and, in FDAAA, gave FDA new authority to require safety labeling changes in certain circumstances.

Title IX, section 901 of FDAAA (Pub. L. 110-85) amended the FD&C Act by adding new section 505(o)(4) (21 U.S.C. 355(o)(4)). Section 505(o)(4) authorizes FDA to require, and if necessary, order labeling changes if FDA becomes aware of new safety information that FDA believes should be included in the labeling of certain prescription drug and biological products approved under section 505 of the FD&C Act or section 351 of the PHS Act (42 U.S.C. 262). Specifically, section 505(o)(4) of the FD&C Act applies to prescription drug products with an approved new drug application (NDA) under section 505(b) of the FD&C Act, biological products with an approved biologics license application (BLA) under section 351 of the PHS Act, or prescription drug products with an approved abbreviated new drug application (ANDA) under section 505(j) of the FD&C Act if the reference listed drug (RLD) with an approved NDA is not currently marketed. FDAAA imposes timeframes for application holders to submit and FDA staff to review such changes, and gives FDA new enforcement tools to bring about timely and appropriate labeling changes. This draft guidance provides information on the implementation of the new provisions, including a description of the types of safety labeling changes that ordinarily

might be required under the new legislation, how FDA plans to determine what constitutes new safety information, the procedures involved in requiring safety labeling changes, and enforcement of the requirements for safety labeling changes.

This draft guidance is being issued consistent with FDA's good guidance practices regulation (21 CFR 10.115). The draft guidance, when finalized, will represent the Agency's current thinking on the implementation of section 901 of FDAAA on safety labeling changes. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes and regulations.

II. Comments

Interested persons may submit to the Division of Dockets Management (see ADDRESSES) either electronic or written comments regarding this document. It is only necessary to send one set of comments. It is no longer necessary to send two copies of mailed comments. Identify comments with the docket number found in brackets in the heading of this document. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

III. Paperwork Reduction Act of 1995

Under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520), Federal agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information that they conduct or sponsor. "Collection of information" is

defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes Agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA, 44 U.S.C. 3506(c)(2)(A), requires Federal agencies to provide a 60-day notice in the **Federal Register** for each proposed collection of information before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing this notice of the proposed collection of information set forth in this document.

With respect to the collections of information associated with this draft guidance that were not previously approved by OMB, described below, FDA invites comments on the following topics: (1) Whether the proposed information collected is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimated burden of the proposed information collected, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information collected; and (4) ways to minimize the burden of information collected on the respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

This draft guidance provides information on the implementation of section 901 of FDAAA, which authorizes FDA to require certain drug and biological product application holders to make safety related labeling changes based upon new safety information that becomes available after

the drug or biological product is approved under the FD&C Act or the PHS Act. FDA plans to request safety labeling changes by sending a notification letter to the application holder. Under section 505(o)(4)(B), the application holder must respond to FDA's notification by submitting a labeling supplement or notifying FDA that the applicant does not believe the labeling change is warranted and submitting a statement detailing the reasons why the application holder does not believe a change is warranted (a rebuttal statement).

The submission of rebuttal statements may result in the collection of information that is not already approved by OMB. Based on FDA's experience thus far with safety labeling changes requirements under section 505(o)(4), FDA estimates that approximately six application holders will elect to submit approximately one rebuttal statement each year and that each rebuttal statement will take approximately 6 hours to prepare.

In addition, in the draft guidance, the agency states that new labeling prepared in response to a safety labeling change notification should be available on the application holder's Web site within 10 calendar days of approval, which may result in the collection of information that is not already approved by OMB. FDA estimates that approximately 197 application holders will post new labeling one time each year in response to a safety labeling change notification and that the posting of the labeling will take approximately 4 hours to prepare.

FDA estimates the burden of the collections of information that have not already been approved by OMB, is as follows:

TABLE 1—ESTIMATED ANNUAL REPORTING BURDEN ¹

	Number of respondents	Number of responses per respondent	Total responses	Hours per response	Total hours
Rebuttal statement	6	1	6	6	36
Total					36

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

TABLE 2—ESTIMATED ANNUAL THIRD PARTY DISCLOSURE BURDEN ¹

Type of submission	Number of respondents	Annual frequency per disclosure	Total annual disclosures	Hours per disclosure	Total hours
Post approved labeling on application holder's Web site ...	197	1	197	4	788

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

This draft guidance also refers to previously approved collections of

information. Specifically, the draft guidance describes: Labeling

supplements for NDAs, ANDAs, and BLAs submitted under 21 CFR 314.70,

314.71, 314.97 and 601.12; and the content and format of prescription drug labeling submitted under 21 CFR 201.56 and 201.57. These collections of information are subject to review by OMB under the PRA act and are approved under OMB control numbers 0910-0001, 0910-0338, and 0910-0572. Section V of the draft guidance refers to the guidance entitled "Formal Dispute Resolution: Appeals Above the Division Level," which describes collections of information approved under OMB control number 0910-0430.

IV. Electronic Access

Persons with access to the Internet may obtain the document at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>, or <http://www.regulations.gov>.

Dated: April 7, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-1998-D-0281]

Guidance for Industry and Food and Drug Administration Staff; 30-Day Notices, 135-Day Premarket Approval Supplements and 75-Day Humanitarian Device Exemption Supplements for Manufacturing Method or Process Changes; Availability

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is announcing the availability of the guidance entitled "30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes." This document provides guidance on the type of changes to an approved application that FDA believes may qualify for submission as 30-day notices, the type of information to submit in a 30-day notice, and the user fees associated with these submissions. The guidance document is immediately in effect, but it remains subject to comment in accordance with the

Agency's good guidance practices (GGP).

DATES: Submit either electronic or written comments on this guidance at any time. General comments on Agency guidance documents are welcome at any time.

ADDRESSES: Submit written requests for single copies of this guidance to the Division of Small Manufacturers, International, and Consumer Assistance, Center for Devices and Radiological Health (CDRH), Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 4613, Silver Spring, MD 20993-0002; or to the Office of Communication, Outreach and Development (HFM-40), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448. Send one self-addressed adhesive label to assist that office in processing your request. See the **SUPPLEMENTARY INFORMATION** section for electronic access to the guidance.

Submit electronic comments on the guidance to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT:

For devices regulated by CDRH: Anastacia Bilek, Center for Devices and Radiological Health, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 66, Rm. 3656, Silver Spring, MD 20993-0002, 301-796-5588.

For devices regulated by CBER: Stephen Ripley, Center for Biologics Evaluation and Research (HFM-17), Food and Drug Administration, 1401 Rockville Pike, Suite 200N, Rockville, MD 20852, 301-827-6210.

SUPPLEMENTARY INFORMATION:

I. Background

FDA is announcing the availability of a guidance for industry entitled "30-Day Notices, 135-Day Premarket Approval (PMA) Supplements and 75-Day Humanitarian Device Exemption (HDE) Supplements for Manufacturing Method or Process Changes." This guidance is being issued consistent with FDA's GGP regulation (§ 10.115 (21 CFR 10.115)). This guidance is being implemented without prior public comment because the Agency has determined that prior public participation is not feasible or appropriate (§ 10.115(g)(2)). The Agency made this determination because statutory provisions regarding medical device user fees under the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Pub. L. 110-85) are

in effect and being implemented, and guidance is needed to help effect such implementation. Although this guidance is immediately in effect, it remains subject to comment in accordance with the Agency's GGP regulation.

The Medical Device User Fee and Modernization Act of 2002 (MDUFMA) (Pub. L. 107-250) amended the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. *et seq.*) to authorize FDA to collect user fees for the review of certain premarket submissions (See section 708 of the FD&C Act (21 U.S.C. 379j)). FDAAA further amended the FD&C Act to extend FDA's authority to collect medical device user fees through September 30, 2012, and added 30-day notices to the types of premarket submissions subject to user fees (21 U.S.C. 379j(a)(2)(A)(vi)). For additional information on the MDUFMA, please see <http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceUserFeeandModernizationActMDUFMA/default.htm>.

This guidance supersedes the previous guidance document entitled "30-Day Notices and 135-Day PMA Supplements for Manufacturing Method or Process Changes, Guidance for Industry and CDRH," that published in the **Federal Register** of February 25, 1998 (63 FR 9570). This guidance describes the user fees authorized, updates the previous guidance to clarify the process for submitting a 30-day notice, and provides additional information on the types of changes that may be submitted. The previous guidance did not include information on HDEs even though certain modifications to a manufacturing procedure or method of manufacture for HDEs are subject to the 30-day notice provisions. The current guidance includes this information.

The guidance represents the Agency's current thinking on 30-day notices, 135-day PMA supplements and 75-Day HDE supplements for manufacturing method or process changes. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute and regulations.

II. Paperwork Reduction Act of 1995

This guidance refers to previously approved collections of information found in FDA regulations. These collections of information are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501-