



**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Parts 201 and 343**

**[Docket No. FDA-1977-N-0025]**

**Partial Withdrawal of Proposed Amendment to the Tentative Final Monograph for Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Use**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notification of partial withdrawal.

**SUMMARY:** The Food and Drug Administration (FDA or the Agency) is announcing a partial withdrawal of a proposed rule published in the *Federal Register* of August 21, 2002 (2002 proposed rule). The proposed rule, if finalized, would have amended FDA's tentative final monograph (TFM) for over-the-counter (OTC) internal analgesic, antipyretic, and antirheumatic (IAAA) drug products to include ibuprofen as a generally recognized as safe and effective (GRASE) analgesic/antipyretic active ingredient for OTC use. FDA is withdrawing this proposed rule due to changes in our understanding of ibuprofen since FDA issued the proposed rule. FDA is not withdrawing those portions of the 2002 proposed rule to amend its regulations to include consistent pregnancy and allergy warnings for OTC IAAA drug products containing nonsteroidal anti-inflammatory active ingredients.

**DATES:** As of [INSERT DATE OF PUBLICATION IN THE *FEDERAL REGISTER*], FDA withdraws the proposed additions to §§ 343.3 and 343.10, and proposed revisions to §§ 343.20 and 343.50 published on August 21, 2002 (67 FR 54139).

**ADDRESSES:** For access to the docket to read background documents or comments received, go to <https://www.regulations.gov> and insert the docket number found in brackets in the heading of this document into the “Search” box and follow the prompts, and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

**FOR FURTHER INFORMATION CONTACT:** Kevin Lorick, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, Rm. 5413, Silver Spring, MD 20993-0002, 301-796-6696, Kevin.Lorick@fda.hhs.gov.

**SUPPLEMENTARY INFORMATION:**

I. Background

In the *Federal Register* of November 16, 1988 (53 FR 46204), FDA published a proposed rule in the form of a TFM that proposed conditions under which OTC IAAA drug products would be generally recognized as safe and effective and not misbranded. On August 21, 2002 (67 FR 54139), FDA published a proposed rule that would have amended that TFM to include ibuprofen as a proposed GRASE analgesic/antipyretic active ingredient for OTC use. The 2002 proposed rule, if finalized, would have allowed manufacturers to market ibuprofen drug products for OTC use without submission of a new drug application (NDA), if all conditions of the monograph and other requirements were satisfied. At that time, ibuprofen drug products were marketed OTC under NDAs or abbreviated new drug applications (ANDAs) approved by FDA. This is still the case today--all ibuprofen drug products in the OTC marketplace are covered by NDAs or ANDAs. FDA is not aware of any ibuprofen drug products marketed under the TFM.

In the same 2002 proposed rule, the Agency proposed to update FDA regulations in 21 CFR part 201 to include consistent pregnancy and allergy warnings for OTC IAAA drug products containing nonsteroidal anti-inflammatory active ingredients. This proposal, if

finalized, would update pregnancy, allergy, and asthma statements required in the labeling of certain IAAA products. FDA is not withdrawing that part of the proposed rule.

On September 20, 2002, FDA held a meeting of the Nonprescription Drugs Advisory Committee to discuss safety issues related to the use of aspirin and other OTC nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen.<sup>1</sup> Safety issues discussed included stomach bleeding. As a result of this meeting and subsequent FDA review of the data and additional comments submitted to the public docket (see Docket No. FDA-1977-N-0025), all OTC ibuprofen products marketed under NDAs and ANDAs bear warnings about gastrointestinal bleeding. Warnings state that the risk of bleeding is higher in persons who are age 60 or older, have stomach ulcers or bleeding problems, take a blood thinning (anticoagulant) or steroid drug, take other drugs containing prescription or nonprescription nonsteroidal anti-inflammatory drugs (NSAIDs), have three or more alcoholic drinks every day, or who take more or for a longer time than directed. These requirements are codified under 21 CFR 201.326(a)(2).

On February 10 and 11, 2014, FDA held a joint meeting of the Arthritis Advisory Committee and the Drug Safety and Risk Management Advisory Committee to discuss cardiovascular safety issues related to the use of NSAIDs, including ibuprofen.<sup>2</sup> Safety issues included increased risk of heart attack and stroke that may be worsened with using too much NSAID or using NSAIDs for longer than recommended. Thus, FDA sent letters on August 18, 2016, to all manufacturers of ibuprofen requesting supplements to their applications to update labels with this new safety information. All OTC ibuprofen products now include label warnings against increased risk of heart attack and stroke with the use of NSAIDs other than aspirin.

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<sup>1</sup> <https://www.fda.gov/ohrms/dockets/ac/cder02.htm#NonprescriptionDrugs>.

<sup>2</sup> <https://wayback.archive-it.org/7993/20170404145443/https://www.fda.gov/AdvisoryCommittees/Calendar/ucm380871.htm>.

To help ensure the continued utility of the consumer labeling as it relates to the safety of nonprescription ibuprofen drug products, FDA carefully monitors adverse event reporting.

The safety issues that have arisen subsequent to the 2002 proposed rule have caused the Agency to question whether ibuprofen can be “generally recognized as safe and effective” for use as an active ingredient in OTC IAAA drug products. For this reason, the Agency is withdrawing the 2002 proposed amendments to 21 CFR part 343. Our withdrawal of the 2002 proposed amendment to the IAAA TFM has no effect on the continued approval and marketing of the NDA and ANDA OTC ibuprofen drug products. As noted above, FDA has addressed the safety issues associated with ibuprofen through the NDA and ANDA safety framework, which is different from the safety framework for drugs marketed under the OTC monograph framework.

FDA is not withdrawing those portions of the 2002 proposed rule to amend its regulations to include consistent pregnancy and allergy warnings for OTC IAAA drug products containing nonsteroidal anti-inflammatory active ingredients.

## II. Partial Withdrawal of the Proposed Rule

For the reasons described in this document, FDA is withdrawing portions of the 2002 proposed rule, which would have amended the OTC IAAA TFM.

Dated: May 8, 2018.

Leslie Kux,

Associate Commissioner for Policy.

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