Guidance for Industry

Labeling OTC Human Drug Products — Submitting Requests for Exemptions and Deferrals

DRAFT GUIDANCE

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2000
OTC

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This draft guidance, when finalized, will represent the Food and Drug Administration's current thinking on this topic. 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.

If you plan to submit comments on this draft guidance, to expedite FDA review of your comments, please:

- *Clearly explain each issue/concern and, when appropriate, include a proposed revision and the rationale/justification for the proposed change.*
- *Identify specific comments by line number(s); use the PDF version of the document, whenever possible.*

I. INTRODUCTION

This guidance is intended to provide manufacturers, packers, and distributors (hereafter referred to as manufacturers) additional information on submitting requests for exemption from or deferral under ' 201.66(e) of the Agency's regulation on standardized content and format requirements for the labeling of over-the-counter (OTC) human drug products. The guidance provides recommendations on the types of requests the Agency is likely to grant and on the kinds of information that should be included to facilitate the efficient processing of the request.

II. BACKGROUND

In the *Federal Register* of March 17, 1999 (64 FR 13254), the Food and Drug Administration (FDA) published a final regulation (21 CFR 201.66) establishing standardized content and format requirements for the labeling of OTC human drug products. Standardized labeling for OTC drug products is intended

[1]This guidance has been prepared by the Division of Over-the-Counter Drug Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

to make it easier for consumers to read and understand OTC labeling and use OTC drug products safely and effectively.

The new Drug Facts labeling regulation in ' 201.66 covers all OTC human drug and drug-cosmetic products, whether marketed under a new drug marketing application (NDA), abbreviated new drug application (ANDA), or OTC drug monograph (or product not yet the subject of a final OTC drug monograph).

Section 201.66(e) sets forth the procedures for requesting a product-specific exemption from or deferral of the new labeling requirements. As explained in the regulations, the FDA on its own initiative or in response to a written request from a manufacturer may exempt or defer one or more of the specific labeling requirements set forth in ' 201.66(a) through (d) on the basis that the requirement is inapplicable, impracticable, or contrary to public health or safety.

Since the final regulation was issued, the Agency has received a number of inquiries about the exemption provision. Some have asked for guidance on what procedures to follow when requesting an exemption or deferral under ' 201.66(e). Several persons asked how long it will take the Agency to respond to a request for exemption or deferral and what steps they can take to expedite the review of such a request. They also have asked what standards the Agency will apply in reviewing requests for exemption and whether certain types of requests are more likely than others to receive a favorable response from the Agency.

There also have been several questions about possible categories of exemptions that could be handled through an abbreviated process, such as through the submission of a notification to the FDA. One person asked whether an appeal process was available, or whether the Agency's initial decision on a request for exemption or deferral represents final Agency action.

Finally, several manufacturers have expressed concern that the exemption process may require the submission of trade secret or confidential commercial information and that the process in ' 201.66(e) does not provide a mechanism for protecting such information from disclosure.

This guidance is intended to respond to these questions.

III. WHAT PROCEDURES SHOULD I FOLLOW WHEN SUBMITTING AN APPLICATION FOR EXEMPTION?

Section 201.66(e) describes the basic procedures to follow when submitting a request for an exemption from or a deferral of the OTC drug labeling requirements. Generally, the regulation requires the submission of three copies of an *Application for Exemption*, the term to be used for both exemption and deferral requests. Envelopes should be marked "Request for Exemption from 21 CFR 201.66 (OTC Labeling Format)." All three copies should be sent to the following address:

Docket No. 98N-0337
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852.

For products marketed under NDAs or ANDAs, a fourth copy of the request must be sent directly to the applicable marketing application (21 CFR 201.66(e)).

The regulation requires the submission of a separate request for each product. However, various stock keeping units (also known as *shelf keeping units or SKUs*) of the same product may be included in a single request. In such a case, the details presented in an Application for Exemption should be sufficiently individualized for each SKU to allow the Agency to make a determination for each SKU, especially when the labeling differs because of the size or design of the individual packages.

IV. WHAT SHOULD I INCLUDE IN MY APPLICATION FOR EXEMPTION?

The regulation outlines the basic information required in support of each Application for Exemption. Documentation should be included as to why a particular requirement is inapplicable, impracticable, or contrary to public health or safety. In addition, a representation or mock-up of the proposed labeling should be provided, including any additional labeling (outserts), such as labeling used in risers, panel extensions, or other graphical packaging techniques intended to be used with the product.

To facilitate the Agency's review, the Application for Exemption should include:

- A description of the product and the SKUs covered by the Application
- The NDA or ANDA number, if applicable
- If the Application is lengthy, a table of contents or index
- An itemized list of each of the specific provisions under ' 201.66(c) and (d) for which an exemption or deferral is being requested and an explanation why an exemption is appropriate
- A copy of the most recently marketed product labeling, if applicable. For products marketed under an NDA or ANDA, the most recent approved labeling and any additional labeling submitted since the last approved labeling under 21 CFR 314.70(c) or (d) or according to current Agency guidance[2] (including the date of submission of the additional labeling and how that labeling was submitted — e.g., annual report, pending supplement).

[2] See the Agency's guidance for industry, *Changes to an Approved NDA or ANDA* (November 1999).

- For most requests, the FDA recommends that manufacturers submit a labeling mock-up to help illustrate why a labeling requirement may be inapplicable or impracticable for the specific product at issue.

- Labeling mock-ups should be annotated to show all relevant type sizes and styles and any other relevant specifications regarding the labeling or packaging of the product.[3]

The Agency expects to respond only to the specific exemptions or deferrals requested. Applicants are responsible for ensuring that the rest of the product labeling complies with 21 CFR 201.66 and all other relevant statutes and regulations.

V. WHO REVIEWS APPLICATIONS FOR EXEMPTION AND HOW LONG WILL IT TAKE?

The Division of OTC Drug Products will have primary responsibility for reviewing Applications for Exemption. The division=s response to the applicant will be communicated in a letter, a copy of which will be placed in Docket No. 98N-0337.

The time it takes to respond to an Application for Exemption will depend on:

- the completeness of the request (i.e., does the Agency have to contact the applicant for additional information),

- the number of requests received and pending at any particular time and the newness or novelty of the exemption or deferral requested, and

- the availability of staff resources in the division.

In most cases, assuming the Application for Exemption package is complete, the division expects to provide a response within 30 to 60 days for straightforward requests for deferral and for exemption requests that are consistent with previously granted requests. Requests that present new or complex issues are likely to require 120 to 180 days, depending, again, on factors such as resources and the number of requests pending at the same time.

[3] Examples of annotated labeling mock-ups appear in the final regulation document published on March 17, 1999 (64 FR 13254 at 13293 and 13297 to 13303).

VI. WHAT STANDARD WILL THE AGENCY USE TO REVIEW AN APPLICATION?

Under ' 201.66(e), to be granted an exemption, the applicant must demonstrate that the labeling requirement is either inapplicable, impracticable, or contrary to public health or safety. In general, the Agency will review Applications for Exemption on a case-by-case basis.

To date, only a few Applications for Exemption have been submitted. However, as the Agency gains experience with the process, some general principles, common factors, and trends may emerge. In that case, the Agency may develop additional guidance about the types of requests that have or have not been granted and may develop guidance to address other general principles related to OTC drug product labeling.[4]

Based on the few applications that have been received to date, the Agency can provide the following additional information.

A. Applications Based on Insufficient Labeling Space

The Agency has received several Applications for Exemption in which the applicant claims that its product lacks sufficient labeling space to comply with the regulation. As explained in the preamble to the final regulation,[5] the Agency will not routinely grant an exemption for products that claim to be too small to meet the requirements of the regulation. A number of design techniques are available to modify the packaging of products to meet the small package format authorized under ' 201.66(d)(10) (21 CFR 201.66(d)(10)). These techniques include the use of extended panels and risers, peel back or fold out labels, and mounting products on cardboard cards or placards. The Agency expects manufacturers to use alternative design techniques to increase available labeling space so that product labels are easier to read.

Generally, products that are unable to meet the labeling format requirements in the regulation should reconfigure their labeling to meet the final regulation.

However, although the Agency generally is unlikely to grant exemptions based solely on the limits of existing packaging to accommodate the required content and format, the Agency ***will*** consider requests for a deferral of compliance time to allow manufacturers to shift to a larger or alternative package style. Examples of the types of Applications for Exemption the Agency will consider include deferral requests to allow for the installation of new equipment to manufacture a larger size package, or for stability testing on a new, larger, or different size package.

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[4] The draft guidance for industry, *Labeling OTC Human Drug Products Using a Column Format* (November 1999), currently is being finalized.

[5] See the discussion in the final regulation (64 FR 13268).

Manufacturers should make an effort to determine as soon as possible whether they will have to increase the labeling space or package size for each of their products to comply with the regulation. Manufacturers should submit Applications for Exemption for a deferral of compliance time at the earliest possible time. Such a request should contain the applicable information listed in part III above and state whether new labeling or packaging equipment is being ordered or installed with a projected timetable for completion of the new labeling or packaging process. Generally, the Agency does not expect to grant deferrals for more than 12 months for these types of manufacturing changes.

B. Applications Requesting the Use of a Reduced Type Size

The Agency has received several Applications for Exemption from the regulation's minimum 6 point type size requirement. The Agency explained in depth in the preamble to the regulation why the 6 point type is the appropriate minimum standard for OTC drug product labeling. Thus, type size exemptions generally will not be granted.[6] However, as discussed above, the Agency will consider requests for a deferral of compliance time to allow manufacturers to shift to a larger or alternative package style to accommodate the 6 point type size requirement.

C. Applications Relating to the Listing of Inactive Ingredients

Section 751 of the Food and Drug Administration Modernization Act (FDAMA) of 1997 amended section 502(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352(e)) to state that a drug is misbranded unless its label bears the established name of each inactive ingredient listed in alphabetical order on the outside container of the retail package and, if determined to be appropriate by the Secretary (of Health and Human Services), on the immediate container, as prescribed in regulation promulgated by the Secretary. The requirements for alphabetical order apply only to nonprescription drugs that are not also cosmetics. The listing of inactive ingredients for nonprescription drugs that are also cosmetics should appear in descending order of predominance (see 21 CFR 201.66(c)(8)).

At this time, the regulations in 21 CFR 201.66 are the implementing regulations for FDAMA section 751. The division has denied those Applications that have requested an exemption from the statutory and regulatory requirement to list inactive ingredients.

The division, however, has approved one Application for Exemption relating to the composition of the list of inactive ingredients. In that case, a distributor obtained bulk tablets of a product (marketed under the OTC drug monograph system) from three different suppliers whose formulations contained different inactive ingredients. The distributor requested that it be allowed to use a single label containing the phrase Amay contain@ to list all of the inactive ingredients in the three tablets, some of which would or would not be present in the actual marketed product.

[6] For a further discussion of the 6 point minimum font size, see petition responses in Docket Nos. 98N-0337 and 99P-4617 from William K. Hubbard, FDA, to the Cosmetic, Toiletry, and Fragrance Association and to Covington & Burling on behalf of the Consumer Healthcare Products Association, dated February 4, 2000.

The division approved this request, allowing the three inactive ingredients common to all three formulas to follow the words *Inactive ingredients* as provided in ' 201.66(c)(8), and the remaining inactive ingredients from the three formulas to follow the words *may contain*. The division added that the labeling for this product should contain the information listed in ' 201.66(c)(9) so that any consumer who has questions about the inactive ingredient information has a telephone number to call for information.

VII. CAN I APPEAL AN EXEMPTION DECISION?

If an applicant disagrees with the division=s decision on an Application for Exemption, the applicant should contact the division for further clarification or explanation. Applicants who are unable to resolve the matter satisfactorily at the division level and who wish to appeal a decision should follow the procedures in Agency guidance.[7] A sponsor also may informally raise a procedural or administrative matter with CDER's ombudsman (see 21 CFR 314.103).

VIII. WHAT ABOUT CONFIDENTIAL INFORMATION?

The Agency has been asked several times about the possibility of revealing confidential information during the exemption process. The exemption and deferral process under ' 201.66(e) is considered a matter of public record.[8] Applications for exemption are submitted to a public docket, and the division=s decision (a statement of the basis for its decision) is likewise expected to be placed in the public docket.[9]

The Agency believes that, in the majority of cases, the documentation supporting an Application for Exemption should not require the submission of information that may be considered privileged or confidential, or that otherwise may be protected from public disclosure. For example, the contents of the labeling of an already-marketed product generally would not be considered privileged or confidential, nor would the placement of that information into the new required labeling format be expected, as a general matter, to reveal privileged or confidential information.

The Agency encourages applicants to remove, or redact, information that is not essential to the request for exemption or deferral. Trade names and promotional statements in labeling mock-ups may be redacted if such information is not essential to the request. For example, information on the principal display panel may not need to be included for the Agency to evaluate Drug Facts labeling that appears only on the back and/or side panels of a package. Applicants also may mask unessential information

[7] Guidance for industry on Formal Dispute Resolution: Appeals Above the Division Level (February 2000).

[8] See the preamble to the regulation at 64 FR 13268.

[9] The Agency=s general practices and procedures for the submission of documents to the Dockets Management Branch are set forth in 21 CFR 10.20.

using random characters to take the place of text that the applicant considers to be confidential. However, the use of random characters should include an appropriate mixture of characters to cover approximately the same amount of labeling space that the actual text would occupy.

An Application for Exemption may also be submitted by authorized representatives of the individual manufacturer, as described in 21 CFR 10.20(b).

If an applicant believes that trade secret or confidential commercial or financial information (as those terms are defined in 21 CFR 20.61(a) and (b)) may be needed to support an Application for Exemption, the applicant should consult with the division before submitting its Application. The division may be able to help the applicant determine whether the information is necessary, or how it can be submitted to the public docket in a more general, disclosable form. For example, in several Applications for Exemption submitted to date, the applicants requested confidentiality for information concerning (1) an average increase in the cost of the product resulting from a specific labeling alternative, (2) what would need to be done to existing equipment to implement a specific labeling alternative, or (3) the sales figures for a product marketed in several different ways (loose without a blister card outer package, and with an outer blister card or carton). In most cases, the financial information is unlikely to have a bearing on the Agency=s response to the exemption request. The analysis of impacts in the final regulation already considered the fact that there will be cost increases to some manufacturers to comply with the new labeling requirements and that some products will need to be repackaged.[10]

[10]See the *Federal Register* of March 17, 1999, 64 FR 13276 to 13285.