DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV - 5 2001

Alan G. Minsk
Arnall Golden & Gregory, LLP
2800 One Atlantic Center
1201 West Peachtree Street
Atlanta, Georgia 30309-3450

Re: Docket No. 00P-1297/CP2

Dear Mr. Minsk:

This letter is in response to the citizen petition you submitted on May 23, 2000 on behalf of a client. Your request was filed as CP2 under Docket No. 00P-1297 in the Food and Drug Administration's (FDA) Dockets Management Branch. FDA is granting your request with modifications, in order to comply with the Federal Food, Drug, and Cosmetic Act (the Act).

The petition requests FDA to amend 21 C.F.R. § 201.66 to allow an over-the-counter (OTC) drug manufacturer to use the phrase "may contain" or "may also contain" in the inactive ingredient section of the finished drug product labeling to list those inactive ingredients that are different when a finished OTC drug product is obtained from multiple suppliers.

According to your petition, you request this action "to ensure that appropriate disclosures are given regarding ingredients, while allowing the manufacturer the flexibility to source the product from more than one supplier . . . without. . . the expense of maintaining multiple product inventories and costly labeling changes." You state that OTC drug companies often may use multiple suppliers for inactive ingredients in some products in order to maintain an uninterrupted supply of product to their customers and that the specific makeup of composite inactive ingredients can vary slightly from supplier to supplier.

You presented a number of reasons supporting your request for an amendment to the final rule. You state that it would be impracticable to list only the specific inactive ingredients actually present and manufacturers will be forced to either (1) purchase drug product from only one supplier; (2) carry separate inventories of packaging and labeling materials for the same product when slight differences in inactive ingredients exist; or (3) require different suppliers to manufacture to the same formula. Because of the large number of products that potentially could be affected, you conclude that "it will be cumbersome, time-consuming, and draining on the agency limited...resources." You also note that FDA permitted the phrase "may contain" to list inactive ingredients that may or may not be present in a product in response to an Application for Exemption from an OTC drug manufacturer.

FDA uses the term "over-inclusive labeling" to generally describe labeling statements identifying ingredients that may or may not be present in a particular product. FDA believes that over-inclusive inactive ingredient labeling in OTC drug labeling is permissible under the Act, under certain circumstances. Thus, the agency is granting your request with modifications, in order to comply with the Act, as discussed below.

Analysis

In 1997, the Food and Drug Administration Modernization Act (FDAMA) amended § 502(e)(1)(A) of the Act, creating a requirement that inactive ingredients be listed in alphabetical order on the outside retail package of OTC drug products. The new provision in subclause (iii) states 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, on the immediate container, as prescribed in regulation promulgated by the Secretary, except that nothing in this subclause shall be deemed to require that any trade secret be divulged, and except that the requirements of this subclause with respect to alphabetical order shall apply only to nonprescription drugs that are not also cosmetics and that this subclause shall not apply to nonprescription drugs not intended for human use.

In 1999, FDA promulgated final regulations related to the content and format of OTC drug product labeling (OTC labeling rule) (64 FR 13254). The requirement for inactive ingredient listing on OTC drug product labeling was codified at 21 C.F.R. § 201.66(c)(8), as part of this OTC labeling rule.

FDA has examined the statutory and regulatory language and concludes that nothing in § 502(e)(1)(A)(iii), or FDA's OTC labeling rule, prohibits use of over-inclusive OTC drug inactive ingredient labeling. Although there is nothing related to such labeling in the legislative history for § 502(e)(1)(A)(iii), the agency has located no evidence that Congress intended to affect the preexisting voluntary common industry practice of listing inactive ingredient information for OTC drug products in alphabetical order, and utilizing over-inclusive inactive ingredient labeling, as appropriate.[1] Indeed, FDA recognizes that some OTC drug manufacturers used "may contain" or similar language on OTC drug labeling without objection from FDA for nearly 15 years. The agency is not aware of any adverse consequences occurring as a result of over-inclusive inactive ingredient listing. Consequently, there is no reason to believe that over-

[1] The agency notes that although "may contain" listing had been a common industry practice for nearly 15 years, this issue was not raised at any point during the rulemaking process for the OTC labeling rule.

inclusive inactive ingredient listing was meant to be prohibited by § 502(e) of the Act, as amended by FDAMA.

Practical Application Of Over-inclusive Labeling For OTC Drug Products

Because § 502(e)(1)(A)(iii) of the Act requires inactive ingredients to be listed in alphabetical order, use of "may contain" or "may also contain" labeling, in the manner specifically requested in your citizen petition would, as a practical matter, most likely violate the Act. This is because it may be impossible for those alternative ingredients following the "may contain" clause to maintain an alphabetical order. FDA, however, believes that over-inclusive inactive ingredient labeling may be accomplished consistent with the Act by placing those ingredients that may or may not be contained in the OTC drug product in the inactive ingredient listing, as set forth in 21 C.F.R. § 201.66(c)(8), with an asterisk placed next to those ingredients.[2] The asterisk would then be reprinted at the end or bottom of the inactive ingredient section of the "Drug Facts" box, with the notation "contains one or more of these ingredients."[3,4]

Although the agency has concluded that this approach to over-inclusive inactive ingredient labeling would be consistent with § 502(e)(1)(A)(iii) of the Act, the agency cautions that overzealous use of over-inclusive inactive ingredient listing could cause products to be misbranded and/or adulterated under other provisions of the Act. Too many alternative ingredients could be misleading and may cause consumer confusion. Therefore, FDA intends to issue guidance to the industry listing suggested parameters for the use of over-inclusive inactive ingredient listing. Such parameters may include limiting the number of ingredients associated with the asterisk. At some point, the list could get so long that the inactive ingredient listing is comprised mostly of ingredients that may not be present in the product. Another parameter may be limiting the type of ingredients associated with the asterisk (e.g., binders, fillers, lubricants, and colors.) For example, FDA is not sure if sweeteners or flavors should be included, since

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[2] For example: "*acacia, *dextrose, sucrose, *xanthum gum" or "acacia*, dextrose*, sucrose, xanthum gum*". FDA may issue future guidance on labeling formats and other issues related to matters discussed in this letter.

[3] For example, for product labeling that uses the standard format set forth in § 201.66, left justify the statement at the end of the inactive ingredient section: "*contains one or more of these ingredients". For product labeling that uses the modified format set forth in § 201.66(d)(10), the statement should appear at the end of the inactive ingredient section with 2 square "ems" between last inactive ingredient listed and the statement "*contains one or more of these ingredients". See § 201.66(d)(4). FDA may issue future guidance on labeling formats and other issues related to matters discussed in this letter.

[4] FDA views the phrase "contains one or more of these ingredients" preferable to the phrase "may contain" or "may also contain." The latter type of over-inclusive inactive ingredient labeling has the potential to mislead consumers, in that such statements do not advise whether any of the ingredients following the statement definitively appear in the product. On the other hand, "contains one or more of these ingredients" informs the consumer that at least one of the alternative ingredients referred to by the phrase is present in the product.

these are important characteristic traits that consumers look for in a product. Similarly, certain regulations specifically require, or propose to require, disclosure of certain ingredients that for public health reasons should be affirmatively listed in the labeling (e.g., ingredients with specific allergenic or dietary concerns.)[5] These types of ingredients would be unsuitable for over-inclusive inactive ingredient listing. Additionally, in order to provide consumers with the opportunity to find out if in fact an ingredient is in the lot number of the product that they purchased or are about to purchase, FDA believes that the optional information in 21 C.F.R. § 201.66(c)(9) ("Questions?" or "Questions or comments?" followed by the telephone number of a source to answer questions about the product) should specifically be included in labeling that uses over-inclusive inactive ingredient listing. The guidance also may contain direction regarding the graphical placement and size of the asterisk and related statement.

If you have any suggestions or comments regarding guidance parameters for the use of this type of inactive ingredient listing, please provide them to Docket No. 00P-1297, with a copy to the Division of OTC Products in the Center for Drug Evaluation and Research, as soon as possible for consideration. Be assured that if you do not have an opportunity to provide suggestions before the draft guidance is issued, you will have an opportunity to comment prior to FDA issuing a final guidance.

Procedural Request

You request that FDA amend the OTC labeling rule at 21 C.F.R. § 201.66 to permit "may contain" listing for inactive ingredients. The agency does not believe that an amendment, or any rulemaking, is necessary to effectuate over-inclusive labeling in the inactive ingredient section of OTC drug product labeling if such labeling follows the format set forth in this letter. As mentioned above, FDA does not believe that the language in § 502(e)(1)(A)(iii), 21 C.F.R. § 201.66(c)(8), or § 201.66 in general, would preclude this type of listing.

Conclusion

For the reasons stated above, FDA is granting, in principle, your citizen petition, with modifications that the agency believes are required to ensure that over-inclusive inactive ingredient labeling complies with the Act. OTC drug product labeling may include certain ingredients in the inactive ingredient listing that may be contained in the product. This can be accomplished by placing an asterisk next to the ingredients that may or may not be in the product and inserting the phrase "contains one or more of these ingredients" at the bottom or end of the inactive ingredients section in the "Drug Facts" box. The agency will provide guidance to industry listing suggested parameters that could prevent the product from being deemed

[5] *See e.g.*, 21 C.F.R. § 201.64 (sodium disclosure requirement); 21 C.F.R. § 201.21(b)(aspartame disclosure requirement); 61 FR 17807 (proposed calcium, magnesium, and potassium disclosure requirement).

misbranded or adulterated under the Act due to inappropriate use of the asterisk listing.

If you have any comments, please reference the docket number above and submit them to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, Maryland, 20852.

I hope this information is helpful.

Sincerely yours,

Dennis E. Baker
Associate Commissioner
for Regulatory Affairs