DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

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David L. Rosen, R.Ph., J.D.
McDermott, Will & Emery
600 Thirteenth Street, N.W.
Washington, DC 20005-3096

Re: Docket No. 01P-0253/CP1

Dear Mr. Rosen:

This letter responds to your citizen petition dated May 25, 2001, you request the Food and Drug Administration (FDA) to amend 21 CFR Part 341 (Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter (OTC) Human Use), specifically for OTC antitussive drug products to include a chewing gum dosage form for the active ingredient menthol as a topical antitussive drug. Also, you request FDA to amend 21 CFR 341.3(c) to add "or when released from a chewing gum" as a new dosage form to the definition for topical antitussive drug, and 21 CFR 341.76(d)[1] to include directions for the new proposed chewing gum dosage formulation. The grounds for your petition were primarily based upon the data that you submitted.

You seek to amend the antitussive monograph to encourage the development and sale of new and innovative methods for the delivery of drug products. You contended that the release mechanism for chewing gum is identical to lozenges, which are included as a dosage form for menthol in the monograph, and that chewing gum is a safe and effective delivery system. Your proposed directions for the gum dosage form are similar to the directions for a lozenge in § 341.74(d)(2)(iii) of the monograph. You submitted data to support the contention that the gum dosage form releases an amount of menthol equivalent to that released by a lozenge, and that the rate and extent of release are comparable to those of menthol-containing lozenges. You also pointed out that other chewing gum drug products are available for OTC use, e.g., Nicorette, Biotene Dental Gum, and Aspergum.

We are not aware of the marketing of a chewing gum dosage form with menthol as an active ingredient in an OTC antitussive drug product before the start of the OTC drug review on May 11, 1972. You indicate in your petition that this will be a new and innovative method for drug delivery. Your label of Cough Suppressant Gum Sugar-Free states that it is a "new patented" cough suppressant gum. Monographs are intended only for OTC drugs that are generally recognized among qualified experts as safe and effective.

Although it is not the purpose of the OTC drug review, the Agency encourages the development of new and innovative methods for the delivery of drug products. It does this in

[1] Although 21 CFR 341.76(c)(2)(iv) is cited in the petition, we believe 341.76(d) was the intended section.

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many ways, most particularly by allowing for the submission of new drug applications for any product that is not generally recognized as safe and effective. Menthol as a topical antitussive chewing gum can be submitted as an NDA deviation under 21 CFR 330.11. This product is limited to an NDA deviation because assurance is needed that an individual piece of gum containing 17 mg. of menthol releases the intended monograph dosage quantity of 5 mg. of menthol in 20 minutes.

We do not agree that the release mechanism for chewing gum is identical to lozenges. Although both a lozenge and chewing gum release menthol in a manner to act on the nerve receptors within the respiratory tract, we consider the gum dosage form to have a different release mechanism requiring chewing as opposed to dissolution or disintegrating slowly in the mouth as defined in the United States Pharmacopeia (USP) for a lozenge. We also find that your submitted data are insufficient to demonstrate that the rate and extent of release of menthol for chewing gum are comparable to that of a menthol-containing lozenge. The data submitted are limited to in-vitro release and, moreover, there was no explanation as to how this study was conducted. Therefore, without sufficient detail of the study these data are deficient and uninterpretable.

For approval of an NDA deviation, we would need acceptable data showing a correlation between the in-vitro data and actual in-vivo extractions (how much menthol is released from the chewing gum into the human mouth), and data on an in-vivo determination of menthol release from the gum product compared to a similar product, e.g., a lozenge. To assist you in assembling information, submitting samples and presenting data to support analytical methodologies for this antitussive chewing gum dosage form, please see the guidance document entitled "Guidance for Industry, Analytical Procedures and Methods Validation, Chemistry, Manufacturing and Controls Documentation." This guidance can be obtained at http://www.fda.gov/cder/guidance/2396dft.pdf. In addition, you may find helpful an article relating to the conduct of in-vitro drug release testing of a medicated chewing gum by Kvist, C., et al. entitled "Apparatus for studying in vitro drug release from medicated chewing gums" in *International Journal of Pharmaceutics*, 189:57-65 (1999).

With regard to the other chewing gum products that you cited, Nicorette received an NDA approval. Aspergum is subject to the internal analgesic tentative final monograph and was in the OTC marketplace at the start of the OTC drug review. It may continue to be marketed and is subject to the risk that the internal analgesic final monograph will not include the gum dosage form for aspirin. Biotene Dental Gum is not the subject of an approved NDA and is not in the OTC drug review.

If your client plans to pursue an NDA deviation, we strongly recommend a meeting to discuss the type of information and studies that would be needed to support the application. The studies may need to be done under an IND. Ms. Babette Merritt, Project Manager, at 301-827-2301 is the contact person to arrange such a meeting.

If you have any questions or comments regarding the above information, with the exception of the submission of data in support of an NDA deviation, please refer to the docket and comment numbers noted above and submit all inquiries in triplicate to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

We hope this information will be helpful.

Sincerely yours,

Dennis E. Baker.
Associate Commissioner
for Regulatory Affairs