DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

September 1, 1999

TRANSMITTED VIA FACSIMILE

Charles A. Rice
President and CEO
Dey Laboratories
2751 Napa Valley Corporate Drive
Napa, CA 94558

RE: ANDA# 74-755
Ipratropium Bromide Inhalation Solution 0.02%
MACMIS ID# 7412

# WARNING LETTER

Dear Mr. Rice:

This Warning Letter concerns Dey Laboratories' (Dey) promotional materials and activities for the marketing of Dey's generic brand of Ipratropium Bromide Inhalation Solution 0.02%. The Division of Drug Marketing, Advertising, and Communications (DDMAC) has determined that Dey is disseminating a Pharmacotherapy journal article reprint "Preservatives in Nebulizer Solution: Risks without Benefit", by Beasley, Fishwick, Miles, and Hendeles (1998;18:130-139) that makes false or misleading statements about a competitor's FDA-approved prescription drug product. Specifically, the article states or suggests that "Atrovent" (ipratropium bromide) Inhalation Solution contains the preservative benzalkonium chloride (BAC) and leads to bronchoconstriction. In fact, Atrovent marketed in the US has never contained BAC. Dey disseminated the Beasley article even though it was aware of the false or misleading statement about its competitor's product.

Based on our review, we conclude that Dey's dissemination of this false or misleading journal article reprint is in violation of the Federal Food, Drug, and Cosmetic Act ("Act"). See 21 USC §§ 331(a),(b) and 352(a), and applicable regulations. Dey has misbranded its own generic ipratropium bromide inhalation solution by making false or misleading

representations about a competitive product (21 CFR 201.6(a)). Because the reprint Dey disseminated is false or misleading, the Warning Letter is not in conflict with the Court's order in Washington Legal Foundation v. Henney et al., Civ. No. 94-1306 (D.D.C. July 28, 1999).

**Misleading Representations About A Competitor's Product**

Dey markets prescription drugs including bronchodilators such as ipratropium bromide inhalation solution. Dey's ipratropium product competes with an ipratropium product marketed by Boehringer Ingelheim under the name "Atrovent." As part of its activities to promote its products, Dey disseminated the Beasley article to physicians, hospitals, pharmacies, and trade show attendees.

On March 5, 1999, DDMAC sent Dey a written inquiry about the dissemination of this promotional labeling. On March 15, 1999, Dey responded and acknowledged that it disseminated the article between May 1998 and March 1999. Dey's response referenced written and verbal company communications instructing Dey's sales force on the use of this reprint in promotion. Although Dey's sales training materials noted that the Atrovent referenced in the article is a different formulation than the product available in the US, and that the US Atrovent does not contain BAC, these important contextual messages were not stated by the authors in the 1998 reprint. Nor, according to Dey's response, were these important contextual messages communicated by Dey, either by written information accompanying the reprint or by voluntary declarations of Dey sales representatives to its customers receiving the reprint.

It appears from Dey's response to DDMAC's inquiry about dissemination of this reprint that Dey recognized that, in the absence of disclosing the appropriate context, the potential existed for such a misleading representation. Nonetheless, Dey promoted this misleading suggestion of "Atrovent's" compromised safety and efficacy to healthcare professionals without proactively providing a corrective message.

Furthermore, the authors and publisher of this 1998 article recognized the need to correct its misleading impression. In April 1999, they published the following clarification (Pharmacotherapy 1999;19(4):473-474):

> We would like to clarify two issues related to our article previously published in this journal.... First, in reviewing the effects of the inclusion of the preservatives benzalkonium chloride (BAC) and edetic acid (EDTA) in nebulizer solutions, we detailed the studies of ipratropium bromide nebulizer solution that contained both of these agents. We refer to a series of studies published in the late 1980s in which it was shown that inhalation of Atrovent nebulizer solution (the commercially available ipratropium bromide nebulizer solution that contained BAC 0.25 mg/ml and EDTA 0.5 mg/ml) by asthmatic patients may cause marked bronchoconstriction, while inhalation of the ipratropium bromide solution that did

not contain the preservatives resulted in a significantly greater bronchodilator effect. As a direct result of these studies, the preservative-containing Atrovent nebulizer solution was gradually withdrawn from some markets around the world and replaced by preservative-free Atrovent nebulizer solution. **With respect to the United States, the Atrovent nebulizer solution containing preservatives was never licensed for use. The preservative-free Atrovent nebulizer solution was introduced into the United States in 1993 and represents the currently available Atrovent nebulizer solution. Table 1 details the availability of Atrovent nebulizer solutions with and without BAC and EDTA in various countries throughout the world. (Emphasis added).**

**Conclusion and Recommendations**

Dey's dissemination of the 1998 Pharmacotherapy article suggesting that the US formulation of Atrovent contains the preservative BAC resulting in possible compromised safety and efficacy, promoted false or misleading impressions about this competitive product. Dey's use of any other materials with the same misrepresentation is also false or misleading. Accordingly, Dey should propose an action plan to disseminate corrective messages about this issue to all healthcare providers, institutions, and organizations who received this violative information.

This corrective action plan should also include:

A. Immediately ceasing the use of this reprint in any Dey-related promotion and the dissemination of any information, verbal or printed, that contains false or misleading information suggesting that the US formulation of Atrovent contains BAC or any other preservative.

B. A written statement of Dey's intent to comply with "A" above.

C. Submit a proposed "Dear Healthcare Provider" letter that will correct the false or misleading information you disseminated.

D. Provide a complete list of all advertising and promotional labeling materials that you intend to continue using.

The Dear Healthcare Provider letter should be submitted to DDMAC for review. After agreement is reached on the content and audience, the letter should be disseminated by direct mail to all healthcare providers who received the violative promotion.

Dey's response should be received no later than September 15, 1999. If Dey has any questions or comments, please contact Thomas W. Abrams, R.Ph., M.B.A. or Leah Palmer, Pharm.D. by facsimile at (301) 594-6771, or at the Food and Drug Administration, Division of Drug Marketing, Advertising, and Communications, HFD-40, Rm 17-B-20,

5600 Fishers Lane, Rockville, MD 20857. We remind you that only written communications are considered official.

In all future correspondence regarding this particular matter, please refer to MACMIS ID# 7412 in addition to the NDA number.

Sincerely,

Norman A. Drezin, R.Ph., JD
Acting Director
Division of Drug Marketing,
Advertising, and Communications