DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

DEC - 9 1998

TRANSMITTED VIA FACSIMILE

Ms. Michele M. Hardy
Director, Advertising Policy
Regulatory Affairs
Glaxo Wellcome Inc.
5 Moore Drive
P.O. Box 13398
Research Triangle Park, NC 27709

Re: NDA# 20-548
Flovent (fluticasone propionate) Inhalation Aerosol
44 mcg, 110 mg, 220 mcg
MACMIS ID#: 7239

Dear Ms. Hardy:

This letter concerns promotional activities and materials disseminated by Glaxo Wellcome Inc. (GW) for Flovent (fluticasone propionate) Inhalation Aerosol (MDI). Some of these issues were previously discussed in 1997 and 1998 correspondence between the Division of Drug Marketing, Advertising, and Communications (DDMAC) and GW.

As part of a September 1998 Flovent promotional program entitled, "Reduce Asthma Inflammation Now" or "RAIN", a monograph reference material presented a slide presentation that included comparative bioavailability claims. These comparative pharmacokinetic presentations (see below) contain unsubstantiated implied superiority claims, that lack fair balance, or are otherwise misleading.

1. Page 10 monograph text: "The oral bioavailability of Flovent is negligible (<1%) and substantially lower than that of beclomethasone dipropionate Beclovent or triamcinolone acetonide." (References: 18/Data on File, 20/Johnson, 1996)

The first claim of negligible (<1%) bioavailability, an implied safety superiority claim, is not substantiated by the referenced citations, and it misrepresents the total systemic absorption profile for Flovent because the claim lacks fair balance. According to the Pharmacokinetics: Absorption section of the Flovent approved product labeling, although the drug's oral bioavailability is negligible (<1%), "[i]n contrast, the majority of the fluticasone propionate delivered to the lung is systemically absorbed. The systemic bioavailability of [Flovent]

averaged about 30% of the dose delivered from the actuator." DDMAC previously addressed this issue in various contexts with GW in letters dated, April 24, 1997 and April 8, 1998. On these and subsequent occasions, GW committed to revising pertinent Flovent promotional materials to be consistent with the approved product labeling and to delete any safety superiority claims based on clinical pharmacology data that were not substantiated by substantial evidence (i.e., adequate and well-controlled studies).

2. Page 18 monograph/bioavailability chart slide 25
(Reference: Johnson, 1996 citing Derendorf and Zaborny):

	Oral	Inhaled	Total
Flovent (fluticasone propionate) Inhalation Aerosol	<1.0%	30.0%	~30.0%
Flovent Rotadisk (fluticasone propionate inhalation powder)	<1.0%	13.5%	~13.5%
beclomethasone dipropionate	<20.0%	~20.0%	~40.0%
triamcinolone acetonide	22.5%	21.5%	~44.0%

In slide 25, the second claim is a comparative bioavailability chart between Flovent, Flovent Rotadisk, beclomethasone dipropionate, and triamcinolone acetonide (TAA), based on pharmacokinetic data. This slide again makes an unsubstantiated safety superiority claim that has not been demonstrated by substantial evidence and presents an inaccurate and misleading comparison (e.g., see the TAA bioavailability profile).

The TAA bioavailability slide profile presentation is misleading for several reasons. First, the TAA that was the subject of the Johnson review article reference was an intravenous formulation of the phosphate salt of TAA (and at doses exceeding the highest approved dose for this compound). Because the phosphate salt is not considered as interchangeable or predictive of the commercially available compound, Azmacort (triamcinolone acetonide) Inhalation Aerosol, the actual total systemic bioavailability is misrepresented by GW. Thus, the TAA/Azmacort formulation mean value that represents the total systemic exposure from all routes of absorption is not 44% as presented in GW's chart, but is rather 25%.

Second, depending on the listed inhaled corticosteroid, the chart inappropriately combines results from various study designs for oral systemic bioavailability of a swallowed dose. GW's resulting presentation is misleading because of inaccurate calculations. For instance, the data presented for Flovent/Flovent Rotadisk is correctly based on an indirect assessment

methodology, while the data presented for TAA is incorrectly based on a direct assessment methodology. If the TAA oral bioavailability had been calculated based on the same direct method, the percentage would be 10.6%, as is stated in the Azmacort approved product labeling, rather than 22.5% as is represented in slide 25. In addition, the numbers cited for TAA are based upon an inappropriate comparator, the TAA phosphate ester.

Third, the chart inappropriately and misleadingly adds together oral and inhaled bioavailabilities to generate inaccurate "total bioavailability" calculations. The inhaled route already represents the total percentage of a dose detectable in the blood stream because it represents the sum of all absorption sites (oral, swallowed, buccal, etc...) and is the highest possible value. Therefore, these values are not additive, and it is scientifically and mathematically inaccurate to add oral to inhaled bioavailability to generate "total bioavailability." Thus, this chart contains favorable data from nonclinical studies in a way that suggests they have clinical significance when in fact no such clinical significance has been demonstrated.

For the above discussed reasons, these comparative pharmacokinetic claims falsely or misleadingly imply that Flovent has superior clinical safety to the other listed orally inhaled corticosteroids in treating asthma, when such clinical superiority has not been demonstrated by substantial evidence.

GW should immediately cease its dissemination and use of all promotional materials for Flovent and Flovent Rotadisk that contain the same or similar violations. GW should respond in writing no later than December 23, 1998, and should include a list of similarly violative materials and a description of its method of discontinuing its use. GW's response should be directed to the undersigned 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, Maryland 20857. DDMAC reminds GW that only written communications are considered official.

In future correspondence regarding this particular matter, please refer to MACMIS ID# 7239 in addition to the NDA number.

Sincerely,

Joan Hankin, JD
Regulatory Review Officer
Division of Drug Marketing,
Advertising and Communications