Deputy Division Director Summary Review

Application:	NDA 20-548, (b) (4) 8-018
Sponsor:	GlaxoSmithKline
Product:	Flovent Inhalation Aerosol
Date:	June 3, 2003

Background

This supplemental NDA is submitted for the purpose of describing two pediatric studies that were performed in (partial) response to a Written Request (WR) for Flovent® (fluticasone propionate) Inhalation Aerosol. This product is a CFC (chlorfluorocarbon) based formulation of Flovent®. These studies were two of seven total studies ultimately performed by the sponsor and submitted to us in response to the WR. Exclusivity was granted on February 25, 2003 because the sponsor completed all of the studies outlined in the WR.

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Overview of Clinical Data

The medical officer reviewed two clinical studies (FMS30058 and FMS30059). These were 12-week, placebo-controlled, double-blind studies of safety and efficacy of Flovent®. FMS30058 enrolled children 2 to 4 years of age, while FMS30059 enrolled children 6 months up to 2 years of age. A total of 332 patients were enrolled in FSM30058 with n=111 randomized to Flovent 44 mcg BID, n=108 randomized to Flovent 88 mcg BID, and n=113 randomized to placebo. A total of 211 patients were enrolled in FMS30059 with n=69 randomized to Flovent 88 mcg BID, n=73 randomized to Flovent 44 mcg BID, and n=69 to placebo.

Unexpectedly, serum fluticasone concentrations were detected in ten "placebo" patients in study FMS30058 and in three "placebo" patients in study FSM 30059. Clearly, patients treated with placebo should not have detectable serum fluticasone levels. The serum concentrations of fluticasone in these subjects were comparable to serum levels that were obtained in (presumably) treated subjects. These 13 patients came from a variety of study sites. The applicant was queried about this aberrancy, but no explanation could be provided.

Expectedly, serum fluticasone concentrations were not detected in all "treated" patients. Since fluticasone has a very low oral bioavailability, serum levels are often undetectable in treated subjects. For example, fluticasone plasma concentrations were detected in only 49% and 31% of Flovent 44 mcg and Flovent 88 mcg treated subjects, respectively. Unfortunately, therefore, the interpretation of the safety and efficacy data from this randomized controlled trial becomes all the more problematic.

It is known that 13 patients in the placebo arm had fluticasone levels detected in their serum and this raised concern. If the reviewers could have been assured that this problem was limited to only these 13 patients, a revised analysis excluding those could have been performed (b) (4) Unfortunately, such reassurance from the applicant was not made available to the Division despite our request.

Data integrity therefore became a major concern in these studies and interpretation of definitive safety and efficacy results was not possible. Reviewers could not be assured that the 13 placebo patients truly received placebo, nor could they be assured that this problem was not more widespread. It could not be determined whether there was an error in patient randomization (with patients receiving incorrect randomized treatment) or if

this was a laboratory error (with lab samples between patients being mixed up). Without a clear explanation of this finding, the entire database became suspect (b) (4)

Clinical Action

(b) (4) Information from the performed clinical studies (b) (4) call into question the integrity of the provided data. In order to address these concerns the applicant should either:

- Repeat the clinical studies and provide reliable data OR
- Explain the finding of fluticasone propionate levels in placebo-treated patients in studies FMS30058 and FMS30059 and provide a reliable set of data from which meaningful conclusions may be drawn.

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Marianne Mann, M.D.
Deputy Director, DPADP

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