CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-833

STATISTICAL REVIEW(S)

Cobbs

Statistical Review and Evaluation
Clinical

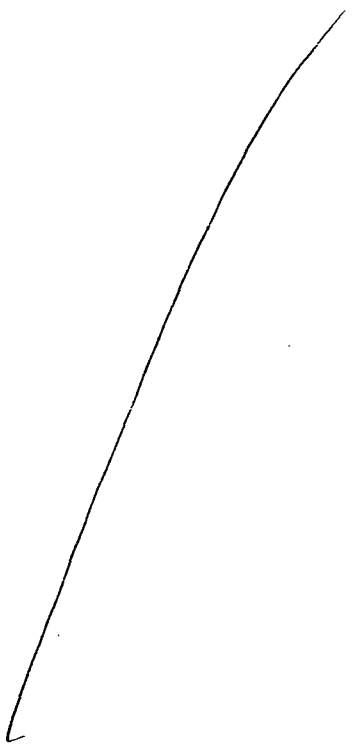
NDA#: 20-833
APPLICANT: Glaxo Wellcome Inc.
NOV 2 4 1999
NAME OF DRUG: Flovent (fluticasone propionate) Diskus
INDICATION: Treatment of Asthma in adults and children greater than 4 years of age
DOCUMENTS REVIEW: Volume 1 dated June 7, 1999 and a correspondence dated October 22, 1999.

This review pertains to a review of the sponsor responses to clinical questions in an Approvable Letter dated March 30, 1999.

The medical officer for this submission is M. Purucker, M.D. (HFD-570).

I. Background

The sponsor submitted an NDA for Flovent Diskus on March 30, 1998. A statistical review of that submission was issued on March 14, 1999. An Approvable letter was sent to the sponsor on March 31, 1999. Flovent Diskus was found to be approvable, but adequate evidence of efficacy of the QD dosing was not felt to be provided. The sponsor



3 Page(s) Withheld

/S/

James R. Gebert, Ph.D.
Mathematical Statistician HFD-715

Concur: Dr. Wilson /S/ 11/27/95

This review contains 5 pages of text.
cc:
Archival NDA 20-833
HFD-570
HFD-570/Dr. Purucker
HFD-570/Mr. Cobbs
HFD-715/Div. File, Chron
HFD-715/Dr. Gebert
HFD-715/Dr. Wilson

Statistical Review and Evaluation
Clinical

MAR 1 4 1999

NDA#:	20-833
APPLICANT:	Glaxo Wellcome Inc.
NAME OF DRUG:	Flovent (fluticasone propionate) Diskus
INDICATION:	Treatment of Asthma in adults and children greater than 4 years of age
DOCUMENTS REVIEW:	Volumes 1.1, 1.28-1.311 and SAS datasets dated March 30, 1998, an unnumbered volume containing datasets dated May 4, 1998, and volumes dated June 5,1998, July 23, 1998 and October 12, 1998.

This review pertains to one oral steroid sparing study (Study FLTA2002) and eight studies in adults and children with asthma.

The medical officer for this submission is M. Purucker, M.D. (HFD-570), with whom this review was discussed.

I. Background

Fluticasone propionate (FP) delivered via meter dose inhaler was approved by the FDA on March 27, 1996 for the maintenance treatment of asthma as prophylactic therapy.

SAS datasets were provided with the application. In reviewing the SAS datasets, this reviewer realized that they did not contain prednisone dosage information from Study FLTA2002. This reviewer requested SAS datasets containing that information in a telephone conversation on April 22, 1998. The sponsor supplied this information in their May 4, 1998 submission.

The following table gives the recommended starting dose and the highest recommended dose of FP inhalation powder (and FP CFC MDI) based on prior anti-asthma therapy.

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Adults and Adolescents		
Bronchodilators Alone	100 mcg twice daily	500 mcg twice daily
Inhaled corticosteroids	100-250 mcg twice daily	500 mcg twice daily
Oral corticosteroids	[redacted] mcg twice daily	1000 mcg twice daily
Children 4 to 11 Years		
Bronchodilators alone	50 mcg twice daily	100 mcg twice daily
Inhaled corticosteroids	50 mcg twice daily	100 mcg twice daily

This program was designed to demonstrate that the MDI and DPI are comparable at the various equivalent dosages, depending upon disease severity, and to test a QD dosing schedule.

It was discovered after the NDA was submitted that studies FLTA 2001 and FLTA 2005 included data from Dr — Dr. — has been put on the disqualified and restricted investigator list and companies have been requested to resubmit analyses excluding his data. This reviewer has reanalyzed the primary efficacy variable excluding his data.

II. Oral Steroid Sparing Study FLTA2002

A. Study Design and Methods of Analysis

This was a randomized, double-blind, parallel-group, placebo controlled, 52 week, multicenter trial. During the 16 weeks of Phase 1, the subjects had their oral prednisone dose reduced if they satisfied reduction criteria given below. During the 36 weeks of Phase 2, subjects were treated with their new maintenance dose of oral prednisone in addition to their randomized treatment. Subjects who dropped out of Phase 1 or Phase 2 could receive open-label FP 1000mcg BID. This review will discuss Phase 1 and, minimally, Phase 2.

To enter the study, subjects must have been using oral corticosteroids for asthma on a daily or every other day basis for at least 6 months preceding Visit 1 and have documentation of attempts to reduce the dose of oral corticosteroid, providing evidence that the subject was currently on a minimum effective dose of prednisone. All subjects must have been taking oral prednisone at a dose between 5-40mg QD (or 10-80mg QOD) for 2 weeks prior to Visit 1. Subjects also had to have a historical demonstration of reversibility ($\geq$15% increase in FEV_1) with bronchodilators. If such documentation of reversibility was absent, the subject had to show reversibility with two puffs of Ventolin to enter the trial. Subjects must also have required the use of inhaled beta-agonist for control of asthma during the 2 weeks immediately preceding Visit 1.

There was a two week screening period following Visit 1. During this two week period, the subject's oral prednisone dose could be increased.

During Phase 1, if a subject required three prednisone bursts, he or she was withdrawn from the double blind study and could begin receiving open-label FP1000mcg BID.

For the prednisone dose to be reduced, subjects had to meet the following asthma stability criteria:

- $FEV_1 \geq$(mean of the highest FEV_1 at Visit 1 and the highest FEV_1 at Visit 2) x 0.80.
- PEFR$\geq$(mean AM PEFR for the 7 days prior to Visit 2) x 0.80.

- Number of nighttime awakenings ≤ (number of nights with awakenings requiring Ventolin use during the 7 days prior to Visit 2) x 1.5. If the number of nights with awakenings prior to Visit 2 was less than 2, a criterion of 3 nights per week was used.
- Ventolin Criterion ≤ (mean Ventolin use, both MDI and nebulized, per 24 hours for the 7 days prior to Visit 2) x 1.5. Each dose (2.5mg) of nebulized Ventolin was considered equal to four actuations of Ventolin Inhalation Aerosol. If the mean Ventolin use prior to Visit 2 was less than 8 actuations per 24 hours, a criteria of 12 actuations per 24 hours was used.

The primary measure of efficacy was the percentage of subjects classified as having 1) 100% reduction, 2) 50%-99% reduction, 3) 1%-49% reduction, 4) no reduction, and 5) any increase. The sponsor stated in the protocol that statistical methods using the rank-order of the oral prednisone change categories would be used to assess treatment-related effects. The sponsor's sample size of 32 subjects per treatment group was calculated assuming that approximately 15% of placebo patients would have 100% reduction and 50% of the subjects in the FP 500mcg BID treatment group would have 100% reduction. This sample size was calculated to give greater than 80% power. The sponsor used Fisher's exact test to test whether there was an overall difference between treatments and whether pairwise the treatments were different in the reduction categories.

B. Results

There were 111 subjects (34 placebo, 41 FP 500mcg BID and 36 FP 1000mcg BID) randomized into the study. Of these 48 subjects (30 placebo, 12 FP 500mcg BID, and 6 FP 1000mcg BID) withdrew during Phase 1. The main reason for withdrawing was lack of efficacy.

The treatment groups were comparable at baseline in demographic variables, mean prednisone dosage and pulmonary function.

The following table gives the reduction in oral prednisone categories at endpoint (ITT population).

	Placebo n=33*	FP 500 BID n=40*	FP1000 BID n=36
Distribution			
100% reduction	3(9%)	30(75%)	32(89%)
50%-99% reduction	10(30%)	4(10%)	3(8%)
1%-49% reduction	6(18%)	5(13%)	1(3%)
No change	6(18%)	0(0%)	0(0%)
Increase	8(24%)	1(3%)	0(0%)

* One subject in the placebo and FP500 BID groups, did not record a maintenance dose. There was a prednisone burst at endpoint for both of these patients.

Both FP treatments were significantly different from placebo (P<0.001) using Fisher's exact test. The difference between the FP treatments was not significant (P=0.285). Numerically FP1000mcg BID had a higher percentage having 100% reduction.

The mean maintenance dose decreased by 12.0mg and 13.0mg for the FP 500mcg BID and FP 1000mcg BID groups, respectively, compared to 5.19mg for placebo group.

The reduction in oral corticosteroid usage was not at the expense of a deterioration of the secondary parameters. These parameters tended to show a deterioration with placebo, a slight improvement with FP 500mcg BID and more improvement with FP 1000mcg BID. FP 1000mcg BID was significantly better at endpoint than both placebo and FP 500 mcg BID for mean change in FEV_1 prior to AM dose, and mean change in AM and PM PEFR.

Of 59 subjects in the FP groups who went on to Phase 2 of the study, 52 were able to maintain their 100% reduction. The maintenance dose was not recorded for the other 7 subjects.

C. Reviewer's Comments

The sponsor's analysis of oral prednisone reduction categories did not utilize the rank-order of the observations. However, the results would be significant if a rank order procedure such as the Cochran-Mantel-Haenszel test was used.

Although two patients weren't included in the ITT analysis of reduction categories in oral prednisone usage, the p-values comparing FP treatments against placebo are significant, even if a most favorable for placebo and least favorable for FP 500mcg BID assignment is made for these two patients.

This study has demonstrated that FP at 500mcg and 1000mcg BID are oral steroid sparing with greater efficacy for the 1000mcg BID dose in some of the secondary efficacy parameters.

III. Adult and Pediatric Asthma Studies

A. Study Design and Method of Analyses

These were multicenter, randomized, double-blind, placebo-controlled, parallel group studies with a 12 week treatment period and a 7 to 14 day baseline period in patients with asthma. Studies FLTA2001, FLTA2003, FLTA2004, FLTA2005, and FLTA2016 were studies in adults or adolescents. Studies FLTA2006, FLTA2007, and FLTA2008 were in children 4-11 years of age. Subjects were stratified according to whether or not they were taking inhaled corticosteroids or bronchodilator therapy alone, prior to study entry in Studies FLTA2001, FLTA2005, FLTA2016, FLTA2006, FLTA2007, and

FLTA2008. Study FLTA2003 was in patients using bronchodilators alone, whereas Study FLTA2004 was in patients on inhaled corticosteroids.

The purpose of Study FLTA2001 was to compare the Diskus and Diskhaler at the highest recommended dosage for patients not taking oral corticosteroids. Since the sponsor is not going to market the diskhaler, this study loses some relevance to the Diskus program.

To enter the trial the patient had to have a baseline FEV_1 between 50 to 80% of predicted normal (FLTA2016 required a baseline FEV_1 between 45 and 75% of predicted normal). If the children aged 4 to 5 in the pediatric studies were not capable of doing a reproducible FEV_1, their PEFR by [illegible] peak flow meter had to be within 50 to 85% of Polgar predicted PEFR normal. The patients, except for the 4 to 5 year olds, had to have documentation of reversibility (≥ 15% increase in FEV_1) within the past 6 months or ≥ 15% increase in FEV_1 following two puffs of Ventolin.

Patients had to have a diagnosis of chronic asthma with either bronchodilator therapy alone and/or inhaled corticosteroid therapy during the past 6 months.

After randomization, subjects returned to the clinic at treatment weeks 1, 2, 3, 4, 6, 8, 10 and 12. At these visits spirometry was performed. In the pediatric studies, all patients performed a PEFR by [illegible] peak flow meter at the clinic visits. If a patient dropped out for lack of efficacy, a terminal visit was arranged, if possible, where spirometry was obtained.

Patients recorded in a daily diary their A.M. and P.M. PEFR using a [illegible] peak flow meter, puffs of Ventolin used for relief of asthma symptoms, number of nighttime awakenings due to asthma that required using Ventolin, and an asthma symptom score using a 4-point scale with 0 indicating no symptoms to 3 indicating that symptoms were continuous and interfered with activities and/or sleep. (Subjects in Study FLTA2001 did not rate overall symptoms but were asked to rate wheeze, cough, and shortness of breath each using the same 4-point scale. The sponsor averaged these three symptoms to create an overall symptom assessment in that study).

The primary analysis discussed in this review is an analysis of variance of changes in FEV_1 (or percent-predicted PEFR for children) at endpoint, which included factors: treatment, investigator and treatment-by-investigator interaction. If the overall p-value was significant, the sponsor did pairwise analyses with the same model, but only including the two treatments compared. The full model containing all treatments usually gave unestimable functions for treatment differences; the pairwise analyses always provided a p-value for treatment effect.

B. Results

1. Adult Studies

a.) Study FLTA2001

There were 213 patients (70 placebo, 64 Diskus FP 500mcg BID, 79 Diskhaler FP 500mcg BID) enrolled into the study at 15 centers. Data from an additional 16 patients (Dr ~ center) were dropped prior to analysis and unblinding due to concerns about reliability of their data. Of these 213 patients, 155 (33 (47%) placebo, 54 (84%) Diskus, 68 (86%) diskhaler) completed the study. There were 33 patients (25 placebo, 3 Diskus, and 5 Diskhaler) who withdrew for lack of efficacy.

The treatment groups were comparable at baseline in demographic variables and pulmonary function.

The table below provides the mean changes at endpoint in FEV_1 prior to A.M. dose and p-values comparing both FP treatments with placebo. Two patients who had only baseline values are not included in the analysis below.

Treatment Mean Changes in Liters (Standard Errors)			P-Values		
Placebo N=69	Diskus 500 BID N=63	Diskhaler 500 BID N=79	Placebo vs Diskus	Placebo vs Diskhaler	Diskus vs Diskhaler
0.03 (0.07)	0.52 (0.05)	0.41(0.05)	<0.001	<0.001	0.172

Efficacy was also seen for both FP devices for A.M. and P.M. PEFR, overall daily symptoms and total Ventolin usage.

If the data from Dr. — is deleted in the analysis of endpoint predose A.M. changes in FEV_1 the following results are obtained.

Treatment Mean Changes in Liters (Standard Errors)			P-Values		
Placebo N=62	Diskus 500 BID N=59	Diskhaler 500 BID N=73	Placebo vs Diskus	Placebo vs Diskhaler	Diskus vs Diskhaler
0.06 (0.07)	0.52 (0.06)	0.40(0.06)	<0.001	<0.001	0.206

Excluding the data from Dr — did not change results.

b.) Study FLTA2003

There were 299 patients (73 placebo, 73 Diskus FP 100mcg BID, 77 Diskus FP 200 QD, and 76 BDP 168mcg BID) enrolled into the study at 25 centers. Patients were on bronchodilator therapy alone. Of these 299 patients, 215 [38 (52%) placebo, 57 (78%) Diskus 100mcg BID, 64 (83%) Diskus 200mcg QD, and 56(74%) BDP 168mcg BID] completed the study. There were 41 patients (19 placebo, 5 FP 100mcg BID, 7 FP 200mcg QD, and 10 BDP) who withdrew for lack of efficacy.

The treatment groups were comparable at baseline in demographic variables and pulmonary function.

The table below provides the mean changes at endpoint in FEV_1 prior to A.M. dose and p-values comparing both FP treatments with placebo. Two placebo patients are not included in the analysis below because they had only baseline values.

Treatment Mean Changes in Liters (Standard Errors)				P-Values			
Placebo N=71	Diskus 100 BID N=73	Diskus 200 QD N=77	BDP BID N=76	Placebo vs Diskus 100 BID	Placebo vs Diskus 200QD	Placebo vs BDP	Diskus 100 BID vs Diskus 200QD
0.21 (0.07)	0.49 (0.05)	0.37 (0.06)	0.48 (0.06)	<0.001	0.054	0.002	0.112

The p-values (placebo versus diskus 100mcg BID or placebo versus Diskus 200mcg QD) above were not adjusted for multiple comparisons. Any adjustment would make the 200 mcg QD dose even less significant.

The FP 100mcg BID diskus was also significant for A.M. and P.M. PEFR, overall daily symptoms and Ventolin usage. The FP 200mcg QD diskus was significant for A.M. and P.M. PEFR and Ventolin usage.

c.) Study FLTA2004

There were 271 patients (69 placebo, 65 Diskus FP 100mcg BID, 65 Diskus FP 200 QD, and 72 BDP 168mcg BID) enrolled into the study at 26 centers. Patients were on inhaled corticosteroids. Of these 271 patients, 152 [26 (38%) placebo, 42 (65%) Diskus 100mcg BID, 36 (55%) Diskus 200mcg QD, and 48(67%) BDP 168mcg BID] completed the study. There were 78 patients (33 placebo, 12 FP 100mcg BID, 21 FP 200mcg QD, 12 BDP) who withdrew for lack of efficacy.

The treatment groups were comparable at baseline in demographic variables and pulmonary function.

The table below provides the mean changes at endpoint in FEV_1 prior to A.M. dose and p-values comparing both FP treatments with placebo.

Treatment Mean Changes in Liters (Standard Errors)				P-Values			
Placebo N=69	Diskus 100 BID N=65	Diskus 200 QD N=65	BDP BID N=72	Placebo vs Diskus 100 BID	Placebo vs Diskus 200QD	Placebo vs BDP	Diskus 100 BID vs Diskus 200QD
-0.08 (0.06)	0.27 (0.06)	0.11 (0.07)	0.26 (0.07)	<0.001	0.055	0.002	0.079

The p-values (placebo versus diskus 100mcg BID or placebo versus Diskus 200mcg QD) above were not adjusted for multiple comparisons. Any adjustment would make the 200 mcg QD dose even less significant.

The FP 100mcg BID diskus was also significant for A.M. and P.M. PEFR, overall daily symptoms and Ventolin usage. The FP 200mcg QD diskus was significant for overall daily symptoms and ventolin usage.

d.) Study FLTA2005

There were 253 patients (84 placebo, 86 FP 250mcg BID, 83 FP 500mcg QD) enrolled into the study at 16 centers. Of these 253 patients, 158 (31(37%) placebo, 74 (86%) FP 250mcg BID, and 53 (64%) FP 500mcg QD) completed the study. There were 73 patients (45 placebo, 7 FP 250mcg BID, 21 FP 500 mcg QD) who withdrew for lack of efficacy.

The treatment groups were comparable at baseline in demographic variables and pulmonary function.

The table below provides the mean changes at endpoint in FEV_1 prior to A.M. dose and p-values comparing both FP treatments with placebo. Two patients were not included in the analysis below because they had only baseline values.

Treatment Mean Changes in Liters (Standard Errors)			P-Values		
Placebo N=83	FP 250 mcg BID N=86	FP 500 mcg QD N=82	Placebo vs FP 250 mcg BID	Placebo vs FP 500mcg QD	FP 250mcg BID vs FP 500 mcg QD
-0.15 (0.05)	0.42 (0.05)	0.14(0.05)	<0.001	<0.001	<0.001

Both FP 250mcg BID and FP 500 mcg QD were significant for AM and PM PEFR, Overall daily symptoms and Ventolin usage. Both Ventolin usage and endpoint FEV_1 prior to A.M. dose showed the BID dosage superior to the QD dosage.

If the data from Dr. ——— is deleted in the analysis of endpoint predose AM changes in FEV_1 the following results are obtained.

Treatment Mean Changes in Liters (Standard Errors)			P-Values		
Placebo N=78	FP 250 mcg BID N=81	FP 500 mcg QD N=75	Placebo vs FP 250 mcg BID	Placebo vs FP 500mcg QD	FP 250mcg BID vs FP 500 mcg QD
-0.15 (0.05)	0.42 (0.05)	0.11(0.05)	<0.001	<0.001	<0.001

Excluding the data from Dr. ——— did not change the results.

e.) Study FLTA2016

There were 330 patients (84 placebo, 79 FP 100mcg QD, 81 FP 200mcg QD, and 86 FP 500mcg QD) enrolled into the study at 21 centers. Of these 330 patients, 205 [41(49%) placebo, 45 (57%) FP 100mcg QD, 53 (65%) FP 200mcg QD, and 66(77%) FP 500mcg QD] completed the study. There were 92 patients (37 placebo, 23 FP 100mcg QD, 20 FP 200mcg QD, 12 FP 500mcg QD) who withdrew for lack of efficacy.

The treatment groups were comparable at baseline in demographic variables and pulmonary function.

The table below provides the mean changes at endpoint in FEV_1 prior to A.M. dose and p-values comparing both FP treatments with placebo. Two patients were not included because they had only baseline values. The overall P-value was not significant (p=0.185).

Treatment Mean Changes in Liters (Standard Errors)				P-Values		
Placebo N=83	Diskus 100 QD N= 79	Diskus 200 QD N=80	Diskus 500 QD N=86	Placebo vs Diskus 100 QD	Placebo vs Diskus 200QD	Placebo vs Diskus 500 QD
0.11 (0.06)	0.20 (0.06)	0.27 (0.06)	0.30 (0.06)	0.222	0.392	0.029

The p-values above were not adjusted for multiple comparisons. Any adjustment would make the QD doses less significant.

Some significance was seen in secondary efficacy analyses. Both FP 100mcg QD and FP 500mcg QD were significant in A.M. and P.M. PEFR, overall daily symptoms and ventolin usage. FP 200 mcg QD was significant in P.M. PEFR and ventolin usage.

2. Pediatric Studies

a.) Study FLTA2006

This study enrolled 437 children (86 placebo, 90 Diskus 50 BID, 87 Diskus 100 BID, 91 Diskhaler 50 BID and 83 Diskhaler 100 BID) at 34 centers. Of the 437 subjects enrolled, 319 (39 (45%) placebo, 69(77%) diskus 50BID, 71(82%) Diskus 100BID, 77 (85%) Diskhaler 50BID, and 63(76%) Diskhaler 100BID) completed the study. There were 78 patients (40 placebo, 13 Diskus 50 BID, 7 Diskus 100 BID, 5 Diskhaler 50 BID, 13 Diskhaler 100 BID) who withdrew for lack of efficacy.

Treatment groups were comparable at baseline in demographic and baseline pulmonary function.

The table below provides the mean changes at endpoint in clinic percent-predicted PEFR prior to A.M. dose and p-values comparing both FP treatments with placebo. Four patients are not included in the analyses below. One because the patient had only baseline values and three because the patients had no clinic PEFR at endpoint visit. (The sponsor had used FEV_1 to determine endpoint visit. The three patients had FEV_1 determinations but no PEFR at that visit.)

Treatment Mean Changes in Percent (Standard error)					P-Values			
Placebo N=85	FP 50 BID N= 88	FP 100 BID N=87	Disk-Haler 50 BID N=91	Disk-Haler 100 BID N=82	Placebo vs FP 50 BID	Placebo vs FP 100BID	FP 50 vs Disk-Haler 50	FP 100 Vs Disk-Haler 100
7.64 (2.23)	19.55 (1.98)	19.50 (2.13)	22.57 (2.21)	23.18 (2.53)	<0.001	0.002	0.315	0.245

The Diskus 100 mcg BID, Diskhaler 50 mcg BID, and Diskhaler 100 mcg BID were significant in A.M. and P.M. PEFR, overall daily symptoms and Ventolin usage. The Diskus 50 mcg BID was significant for A.M. and P.M. PEFR and Ventolin usage.

b.) Study FLTA2007

There were 262 patients (83 placebo, 88 FP 50mcg BID, 91 FP 100mcg QD) enrolled into the study at 19 centers. Of these 262 patients, 169 (44(53%) placebo, 63 (72%) FP 50mcg BID, and 62 (68%) FP 100mcg QD) completed the study. There were 69 patients

(29 placebo, 17 FP 50mcg BID, and 23 FP 100mcg QD) who withdrew for lack of efficacy.

The treatment groups were comparable at baseline in demographic variables and pulmonary function.

The table below provides the mean changes at endpoint in percent-predicted PEFR prior to A.M. dose and p-values comparing both FP treatments with placebo. The overall p-value was not significant p=0.130. There were four patients not included in the analysis below. Three because they had only baseline determinations and one because there was no PEFR determinations at the endpoint determination (determined from FEV_1 assessment).

Treatment Mean Changes in Percent (Standard Errors)			P-Values		
Placebo	FP 50 mcg BID	FP 100 mcg QD	Placebo vs FP 50 mcg BID	Placebo vs FP 100mcg QD	FP 50mcg BID vs FP 100 mcg QD
N=80	N=87	N=91			
5.85 (2.30)	16.97 (2.25)	10.54 (2.22)	0.038	0.389	0.270

FP 50 mcg BID and FP 100 mcg QD were significant for P.M. PEFR. FP 50 mcg BID was also significant for ventolin usage but the overall p-value was not significant.

c.) Study FLTA2008

There were 242 patients (78 placebo, 80 FP 100mcg BID, 84 FP 200mcg QD) enrolled into the study at 21 centers. Of these 242 patients, 142 (32(41%) placebo, 58 (73%) FP 100mcg BID, and 52 (73%) FP 200mcgQD) completed the study. There were 83 patients (42 placebo, 16 FP 100 mcg BID and 25 FP 200mcg QD) who withdrew for lack of efficacy.

The treatment groups were comparable at baseline in demographic variables and pulmonary function.

The table below provides the mean changes at endpoint in Percent-Predicted PEFR prior to A.M. dose and p-values comparing both FP treatments with placebo. The overall p-value was not significant p=0.229.

Treatment Mean Changes in Percent (Standard Errors)			P-Values		
Placebo	FP 100 mcg BID	FP 200 mcg QD	Placebo vs FP 100 mcg BID	Placebo vs FP 200mcg QD	FP 100mcg BID vs FP 200 mcg QD
N=78	N=80	N=84			
7.90 (2.53)	15.86 (2.29)	13.03 (2.60)	0.011	0.554	0.650

Both FP 100mcg BID and FP 200 mcg QD were significant for A.M. and P.M. PEFR and overall daily symptoms. FP 100 mcg BID was also significant for ventolin usage.

IV. Overall Comments

Study FLTA2002 showed the oral steroid sparing ability of FP 500mcg BID and FP 1000mcg BID.

Study FLTA2001 showed the efficacy of FP 500mcg BID given by Diskus. It was relatively comparable to the FP 500mcg BID Diskhaler.

Study FLTA2003 showed that FP 100mcg BID was effective in patients taking bronchodilators alone. Study FLTA2004 showed that FP 100mcg BID was effective in patients taking inhaled corticosteroids. Studies FLTA2006 and FLTA2007 showed that FP 50mcg BID was effective in children. Although some variables were found to be different from placebo for QD dosing, QD dosing was not effective for the primary efficacy variable and, numerically, was not as effective as BID dosing.

The studies showed that the Diskus formulation and the MDI formulation of Flovent could have similar dosage recommendations.

/S/

James R. Gebert, Ph.D.
Mathematical Statistician HFD-715

Concur: Dr. Wilson /S/ 2/4/99

Dr. Nevius /S/ 1/4/99

This review contains 12 pages of text.

cc:
Archival NDA 20-833
HFD-570
HFD-570/Dr. Prucker
HFD-570/Mr. Hilfiker
HFD-715/Div. File,Chron
HFD-715/Dr. Gebert
HFD-715/Dr. Wilson

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES
(STABILITY)

Date	SEP 28 2000
NDA #	20-883
Applicant	Glaxo Wellcome
Name of Drug	Flovent Diskus (50, 100, and 250 μg/blister)
Indication	
Document Reviewed	▫ Vol. 15.2, Chemistry, manufacturing, and Controls Section ▫ Data named Flovent Stability on 3.25 diskette: ▫ \Flovent Stability\P50data.xls ▫ \Flovent Stability\P100data.xls ▫ \Flovent Stability\P250data.xls ▫ \Flovent Stability\P50casc.xls ▫ \Flovent Stability\P100casc.xls ▫ \Flovent Stability\P250casc.xls
Statistical Reviewer	Ted J. Guo, Ph.D., Div II/OEB, HFD-715
Chemist	Dale Koble, Ph.D., Division of Pulmonary Drug Products (ODE II, HFD-570)
Key Words	Stability

Summary

The evaluation of sponsor's stability analysis has determined that the expiry-dating periods for Flovent Diskus are ——— for packages 50 and 100 µg per blister; ——— for package 250 µg per blister. These estimated expiry-dating periods are longer than those proposed by the sponsor: 18 months for 50/100 µg per blister and 24 months for 250 µg per blister.

These analyses evaluate the batches packaged in 50, 100, and 250 µg per blister; stored under 25°C/60%RH; and sponsor-defined specification limits for ———

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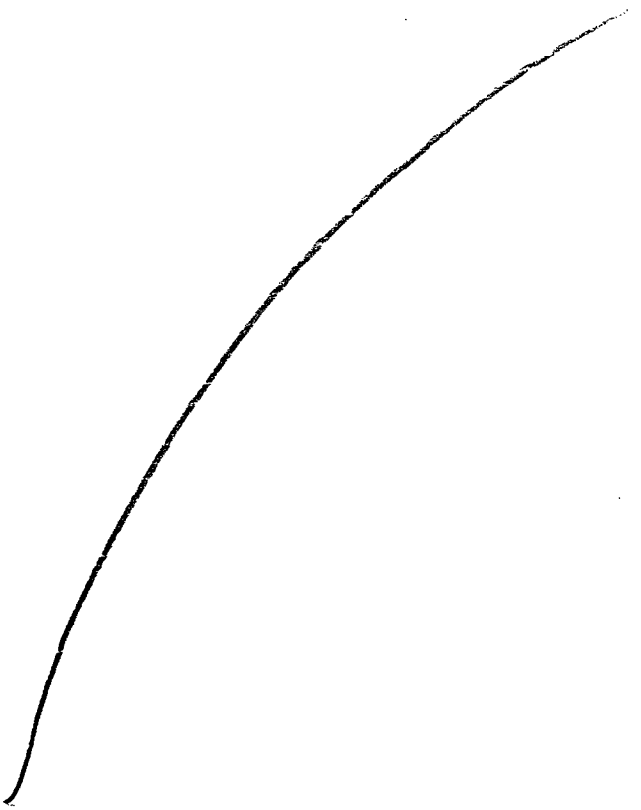
Conclusion

This reviewer concluded that the estimated expiry-dating periods were ——— for packages 50 and 100 µg per blister; and ——— ; for package 250 µg per blister (Table 17). These estimates may be useful in comparison with the sponsor's proposed periods: Eighteen months for Flovent at 50 and 100 µg/blisters and twenty-four months for Flovent at 250 µg/blister.

Table 17. Summary of selected stability analyses



File name: FloventStab.doc

Signoff Page

Reviewer: Ted Guo, Ph.D. /S/ 9/28/00
Concur: Steve Wilson, Ph.D. /S/ 9/28/00

CC:
Archival NDA 20-883

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HFD-570/ Dale Koble

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