CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

NDA 21077/S-052

Trade Name: ADVAIR DISKUS

Generic Name: fluticasone propionate and salmeterol inhalation powder

Sponsor: Glaxo Group Limited d/b/a GlaxoSmithKline

Approval Date: 06/17/2014

Indication: ADVAIR DISKUS is a combination product containing a corticosteroid and a LABA indicated for: Treatment of asthma in patients 4 years and older; maintenance treatment of airflow obstruction and reducing exacerbations in patients with chronic obstructive pulmonary disease (COPD). Important limitation: Not indicated for the relief of acute bronchospasm.

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APPLICATION NUMBER:

NDA 21077/S-052

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APPLICATION NUMBER:

NDA 21077/S-052

APPROVAL LETTER

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20121/S-043, 20833/S-029, 21077/S-052, 21254/S-022, and 21433/S-024

APPROVAL LETTER

Glaxo Group Limited d/b/a GlaxoSmithKline
Attention: Purnima Narang
Assistant Director, CMC Regulatory Affairs
Five Moore Drive, PO Box 13398
Research Triangle Park, NC 27709

Dear Ms. Narang:

Please refer to your Supplemental New Drug Applications (sNDA) dated and received February 18, 2014, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA#	Supplement#	Product Description
20121	S-043	Flonase® (fluticasone propionate) Nasal Spray
20833	S-029	Flovent® Diskus (fluticasone propionate) Inhalation Powder
21077	S-052	Advair® Diskus (fluticasone propionate/salmeterol) Inhalation Powder
21254	S-022	Advair® HFA (fluticasone propionate/salmeterol) Inhalation Aerosol
21433	S-024	Flovent® HFA (fluticasone propionate) Inhalation Aerosol

We acknowledge receipt of your amendment dated May 15, 2014.

These "Prior Approval" supplemental applications provide for revision to particle size distribution acceptance limits for micronised fluticasone propionate.

We have completed our review of these supplemental new drug applications. These supplements are approved.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Youbang Liu, Regulatory Project Manager, at (301) 796-1926.

Sincerely,

{See appended electronic signature page}

Ramesh Raghavachari, Ph.D.
Branch Chief, Branch IX
Division of New Drug Quality Assessment III
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RAMESH RAGHAVACHARI
06/17/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

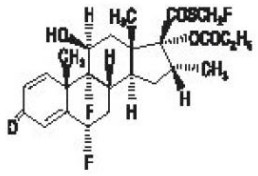
NDA 21077/S-052

CHEMISTRY REVIEW(S)

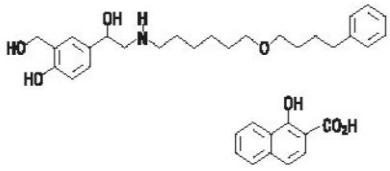
Chemistry Review:# 1	**1. Division:** ONDQA-DPARP	**2. NDA Number:** *(a)* NDA 20-121 S043; *(b)* NDA 20-833 S029; (c) NDA21-077 S052 *(d)* NDA 21-254 S022; *(e)* NDA21-433 S024;
3. Name and Address of Applicant: GlaxoSmithKline LLC 980 Great West Road Brentford, Middlesex, UK, TW89GS		**4. Supplement(s):** PAS **Number:** NDA 20-121 S043 (lead) **Date(s):** 02/18/2014
5. Name of Drug (6. non-proprietary name): *(a)* FLONASE® Aqueous Nasal Spray (Fluticasone propionate); *(b)* FLOVENT Diskus (Fluticasone propionate): *(c)* ADVAIR Diskus® (Fluticasone propionate/salmeterol); *(d)* ADVAIR® HFA Inhalation Aerosol (Fluticasone propionate/salmeterol); *(e)* FLOVENT® HFA Inhalation Aerosol (Fluticasone propionate);		
7. Supplement Provides for: New acceptance criteria for PSD of micronized Fluticasone propionate		**8. Amendment(s):** 05/15/2014
9. Pharmacological Category: See drug product information	**10. How Dispensed:** R_x	**11. Related Documents:**
12. Dosage Form: inhalation spray or nasal spray	**13. Potency:** See drug product information	

14. Chemical Name and Structure:

Fluticasone propionate: *S*-(fluoromethyl) 6α,9-difluoro-11β,17-dihydroxy-16α-methyl-3-oxoandrosta-1,4-diene-17β- carbothioate



*S*almeterol: 4-hydroxy-α -[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol, 1-hydroxy-2-naphthalenecarboxylate



15. Comments:

- The supplement provides for new specifications for micronized fluticasone propionate, which is the drug substance in every drug product included in this bundled supplement.
- A new acceptance criteria for particle size distribution was proposed based on analysis of stability data.
- An information request was sent 05/02/2014 requesting that the acceptance criteria for both release and stability specifications be the same and that a legend be provided with the submitted tables.
- An amendment was received on 05/15/2014 with a revised acceptance criteria

16. Conclusion: This supplement is recommended for approval from CMC perspective

17. Name:	**Signature:**	**Date:**
Erika Englund, Ph.D., Chemist		
18. Concurrence:	**Signature:**	**Date:**
Ramesh Raghavachari, Ph.D., Branch Chief, Br., IX, ONDQA		

Drug Product Information

NDA 20-121 FLONASE® Aqueous Nasal Spray (Fluticasone propionate)

1. Approved 10/19/1994 for the relief of symptoms of seasonal or perennial rhinitis
2. FLONASE Nasal Spray, 50 mcg is an aqueous suspension of fluticasone propionate for topical administration to the nasal mucosa by means of a metering, atomizing spray pump
3. FLONASE Nasal Spray also contains microcrystalline cellulose and carboxymethylcellulose sodium, dextrose, 0.02% w/w benzalkonium chloride, polysorbate 80, and 0.25% w/w phenylethyl alcohol, and has a pH between 5 and 7.
4. Each actuation delivers 50 mcg of fluticasone propionate in 100 mg of formulation
5. Each 16-g bottle of FLONASE Nasal Spray provides 120 metered sprays

NDA 20-833 FLOVENT Diskus (Fluticasone propionate)

1. Approved 09/29/2000 for the maintenance treatment of asthma
2. It is available in 50, 100 or 250 mcg strengths
3. Flovent Diskus is an orange plastic inhaler which contains a foil blister strip of powder formulation.
4. Each blister on the strip contains a white powder mix of micronized fluticasone propionate (50, 100, or 250 mcg) in 12.5 mg of formulation containing lactose monohydrate (which contains milk proteins).
5. After the inhaler is activated, the powder is dispersed into the airstream created by the patient inhaling through the mouthpiece

NDA 21-077 Advair Discus (Fluticasone propionate/salmeterol)

1. Approved 08/24/2000 for the treatment of asthma in patients aged 4 years and older and maintenance treatment of COPD
2. Advair Discus is available in the following strengths: 100/50, 250/50 and 500/50 (fluticasone propionate mcg /salmeterol mcg inhalation powder)
3. It is administered as 1 inhalation twice daily
4. The inhaler contains a foil blister strip of powder formulation for oral inhalation

NDA 21-254 ADVAIR® HFA Inhalation Aerosol (Fluticasone propionate/salmeterol)

1. Approved 06/08/2006 and indicated for the treatment as asthma
2. Advair HFA is available in the following strengths: 45/ 21, 115/ 21, 230/21 (fluticasone propionate mcg/salmeterol mcg)
3. It is administered twice daily every day by the orally inhaled route
4. ADVAIR HFA is supplied in 8 and 12 g pressurized aluminum canisters containing 60 and 120 metered inhalations, respectively
5. Each unit contains a microcrystalline suspension of fluticasone propionate (micronized) and salmeterol xinafoate (micronized) in propellant HFA-134a (1,1,1,2-tetrafluoroethane). It contains no other excipients.

NDA 21-433 FLOVENT® HFA Inhalation Aerosol (Fluticasone propionate)

1. Approved 05/14/2004 for the maintenance treatment of asthma in patients 12 years of age and older
2. It is available in 44, 110, and 220 mcg/actuation strengths
3. The highest recommended dosage is 440 mcg twice daily
4. FLOVENT HFA 44 mcg is supplied in 10.6-g pressurized aluminum canisters, and FLOVENT HFA 110 mcg and FLOVENT HFA 220 mcg are supplied in 12-g pressurized aluminum canisters.

5. Each canister contains 120 metered inhalations and is fitted with a counter and a dark orange oral actuator with a peach strapcap

Chemistry Review

NDA 20-121 S043 is the lead supplement in this bundle and the only supplement with full supporting information in module 3. The other supplements in this bundle contain a cross – reference to NDA 20-121 for drug substance information.

Previously, NDA 20-121 S035 provided for the use of the (b) (4) instrumentation for the measurement of particle size distribution (PSD) of micronized fluticasone propionate. The new instrumentation covered a wider range of particle sizes (0.02-2000 µm) than the previously approved instrumentation (0.1-80 µm) and a new acceptance criteria was proposed based on the release batch data only. The percent of particles by weight (b) (4), Raymond Frankewich, Ph.D. reviewed supplement 35 and found it adequate on November 26, 2005.

NDA 20-121 S043 provides for new particle size distribution acceptance criteria based on analysis of historical stability batches from the GSK sites in Ware, UK and Evreux, France. GSK stated that stability batches were inadvertently omitted from the original assessment of the acceptance criteria in supplement 35. A justification for the proposed specifications was also submitted. These bundled supplements do not provide for any other changes to the drug substance or drug products.

3.2.S.4.1 Specification

The originally proposed specifications submitted in this supplement provided for different acceptance criteria for the release and stability specifications. An information request was sent for updated specifications that provided for the same acceptance criteria for both the release and stability specifications. The following information request was sent on 05/02/2014:

> *The different acceptance criteria for the release and stability specifications are not acceptable for the US market. Refer to ICH Q6A. Submit one set of acceptance criteria for both the release and stability specifications.*

The specifications from the IR response received on 05/15/2014 are copied below.

Table 1 Approved and Proposed Particle Size Distribution Specifications for Micronized Fluticasone Propionate

	Approved Acceptance Criteria	Proposed Acceptance Criteria
Median Particle Size (MPS) (μm)	(b) (4)	(b) (4)
Particles by weight (b) (4)		
Particles by weight		
Particles by weight		

There were no other changes to the other approved specifications. This is adequate.

Evaluation: Adequate
The 05/15/2014 amendment provided for the same acceptance criteria for both the release and stability specifications. This is adequate.

3.2.S.4.5 Justification of Specification
The proposed specifications were based on analysis of the historical stability batches. This is consistent with ICH Q6A, which recommends the use of data from stability studies for the establishment of acceptance criteria. The sponsor states that there were some changes in the observed particle size (b) (4) and (b) (4) over the shelf life of the product, but these changes were not significant enough to warrant a change in the acceptance criteria for these two ranges. Two tables were provided in section 3.2.S.4.5 showing the stability trend in Median Particle Size (MPS) and Particle Size Distribution (PSD) (b) (4) during 60 months of stability studies, but there was no legend provided. The following information request was sent on 05/02/2014:

> *Provide a legend that relates the colors in the graph to the batch numbers in Figures 1 and 2 in section 3.2.S.4.5. In addition, provide the source of these batches (Ware, UK, or Evreux).*

The graphs with legends are copied below. A table was also provided in Appendix 1 that showed the raw data for these graphs.

Figure 1 **Stability Trend for Particles less than (b) (4) (up to 60 months) for Ware, UK and Evreux, France Batches**

(b) (4)

Figure 2 **Stability Trend for Median Particle Size (up to 60 months) for Ware, UK and Evreux, France Batches**

(b) (4)

A total of 45 batches were evaluated in the tables above. The changes in the batches from Evreux (blue) were more pronounced than the batches from Ware (black). Of note, only the batches from Evreux went out of specification (OOS) during the stability studies. 10 out of the 25 batches from Evreux were OOS during stability studies. One batch was OOS at month 9, and nine batches were OOS at month 18 or later. All of the batches that were OOS for MPS, were also OOS for particle size (b) (4)

GSK is proposing to change the acceptance criteria for % of particles (b) (4) based on the stability batches shown above. At release, all batches were within specification for the original % of particles (b) (4) acceptance criteria of (b) (4) specification. However, by month 24 one batch was OOS with (b) (4) for % of particles (b) (4). All batches would have been within specification at all time points with the proposed (b) (4) specification. This change in acceptance criteria is considered low risk because the maximum allowed percentage of particles below (b) (4) has not increased and is still (b) (4). The review of supplement 35 by Raymond Frankewich, Ph.D. highlighted that the percentage of particles below (b) (4) should be kept to a minimum.

Figure 3 **Correlation Between Percentage of Particles Less than (b) (4) and Median Particle Size (GSK, Ware, UK and GSK, Evreux, France Batches)**

A shift in the percentage of particles for any size can impact the median particle size. As the % PSD (b) (4) decreased over time, there was a linear increase in the MPS mean. GSK stated that due to the correlation between MPS and %PSD (b) (4), the proposed change in MPS criterion, from (b) (4) to (b) (4), reflects the change observed in the distribution profile of particles less than (b) (4) and its corresponding effect on MPS.

Overall Evaluation: Adequate

The acceptance criteria for the proposed specifications was based on the analysis of historical batches of drug substance, which is consistent with the recommendation from ICH Q6A for the establishment of acceptance criteria. The previously approved specifications only considered the release batches of drug substance. Stability data from the Ware and Evreux GSK sites was submitted in support of the new acceptance criteria. There was greater variability in results from the drug substance batches from Evreux than Ware. Only the batches from Evreux were out of specification during the stability studies, but the batches from Ware were at the limits for the acceptance criteria. Based on the analysis of the stability data, the proposed specifications are adequate from CMC perspective.

Nanotechnology Submission Report Form

Nanotechnology is absent.

Report # (For WG internal use)	
Application and submission number (*e.g.*, I-XXXXXX-P-XXXX)	(a) NDA 20-121 S043; (b) NDA 20-833 S029; (c) NDA21-077 S052 (d) NDA 21-254 S022; (e) NDA21-433 S024;
Who has identified the product as a potential for containing nanomaterials? (i.e. Sponsor or CVM)	Nanotechnology not present
Is this a modification of an approved product or another investigational product? If so, what has been modified?	No
Please describe the nanomaterials (*e.g.*, poloxamer 188 micelle with emulsified active, particle size 30 -50 nm, or nanocrystal suspension, particle size 130 – 160 nm, etc.)	None
Does the new formulation have unique properties including effects via engineering of the constituent on the nanoscale? If so, explain.	No

Other information worth recording (*e.g.*, INAD or NADA # of a corresponding product w/o nanomaterials)	No
Reviewer Name, Date, HFV code	Erika Elaine Englund, PhD

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ERIKA E ENGLUND
05/29/2014

RAMESH RAGHAVACHARI
05/29/2014

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 21077/S-052

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 20121/S-043, 20833/S-029, 21077/S-052,
21254/S-022, and 21433/S-024

ACKNOWLEDGEMENT --
PRIOR APPROVAL SUPPLEMENT

Glaxo Group Limited d/b/a GlaxoSmithKline
Attention: Purnima Narang
Assistant Director, CMC Regulatory Affairs
Five Moore Drive, PO Box 13398
Research Triangle Park, NC 27709

Dear Ms. Narang:

We have received your Supplemental New Drug Applications (sNDA) dated and received February 18, 2014 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

NDA#	Supplement#	Product Description
20121	S-043	Flonase® (fluticasone propionate) Nasal Spray
20833	S-029	Flovent® Diskus (fluticasone propionate) Inhalation Powder
21077	S-052	Advair® Diskus (fluticasone propionate/salmeterol) Inhalation Powder
21254	S-022	Advair® HFA (fluticasone propionate/salmeterol) Inhalation Aerosol
21433	S-024	Flovent® HFA (fluticasone propionate) Inhalation Aerosol

These "Prior Approval" supplemental applications propose revision to particle size distribution acceptance limits for micronised fluticasone propionate.

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on April 19, 2014, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 18, 2014.

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Pulmonary, Allergy and Rheumatology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, see http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm.

If you have questions, call me, at (301) 796-1926.

Sincerely,

{See appended electronic signature page}

Youbang Liu
Regulatory Project Manager
Division III of New Drug Quality Assessment
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

YOUBANG LIU
03/21/2014