CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 78-202

Name: Budesonide Inhalation Suspension

Sponsor: Apotex Corp.

Approval Date: March 30, 2009

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-202

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-202

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 78-202

Apotex Corp.
U.S. Agent for: Apotex Inc.
Attention: Kiran Krishnan
Associate Director, Regulatory Affairs
2400 North Commerce Parkway, Suite 400
Weston, FL 33326

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated March 31, 2006, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL Unit-dose Ampules.

Reference is also made to your amendments dated August 9, November 5, and November 6, 2007; July 7, August 7, August 27 (two submissions), October 1, November 14, and November 20, 2008; and January 14 (two submissions), and March 18, 2009. We also acknowledge receipt of your correspondence dated August 25, 2006, addressing the patent issues associated with this ANDA.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Pulmicort Respules Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL, of AstraZeneca.

The RLD upon which you have based your ANDA, AstraZeneca's Pulmicort Respules Inhalation Suspension, is subject to periods of patent protection. As noted in the agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book"), U.S. Patent Nos. 6,598,603 (the '603 patent) and 6,899,099 (the '099 patent) will expire (with

pediatric exclusivity added) on June 23, 2019. Your ANDA contains statements under section 505(j)(2)(A)(viii) of the Act that the '603 and '099 patents are method-of-use patents, and that these patents do not claim any indication for which you are seeking approval under this ANDA.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

We note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS, See 505-1(i).

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 2070

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications with a completed Form FDA 2253 at the time of their initial use.

Within 14 days of the date of this letter, submit updated content of labeling [21 CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical in content to the approved labeling. Upon receipt and

verification, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission as "***Miscellaneous Correspondence - SPL for Approved ANDA 78-202***".

Sincerely yours,

{See appended electronic signature page}

Gary Buehler
Director
Office of Generic Drugs
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/

Robert L. West
3/30/2009 09:32:06 AM
Deputy Director, for Gary Buehler

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-202

LABELING REVIEWS

APPROVAL SUMMARY #2
LABELING REVIEW BRANCH

1. APPLICANT INFORMATION:

ANDA Number	78-202
Date of Submission	07 JUL 2008
Applicant	Apotex
Drug Name	Budesonide Inhalation Suspension
Strength(s)	0.25 mg/2mL and 0.5 mg/2mL unit dose ampule, Sterile

LABELS AND LABELING SUMMARY

Containers- Satisfactory July 7, 2008

\\Cdsesub1\evsprod\ANDA078202\0012\m1\us\114-labeling\final-labeling\final-carton-container-labels\ampule---0-5mg2ml.pdf
\\Cdsesub1\evsprod\ANDA078202\0012\m1\us\114-labeling\final-labeling\final-carton-container-labels\ampule---0-25mg2ml.pdf

Foul Pouches- Satisfactory in FPL as of July 7, 2008

\\Cdsesub1\evsprod\ANDA078202\0012\m1\us\114-labeling\final-labeling\final-carton-container-labels\foil-pouch---0-5mg2ml---251268.pdf

\\Cdsesub1\evsprod\ANDA078202\0012\m1\us\114-labeling\final-labeling\final-carton-container-labels\foil-pouch---0-25mg2ml---251290.pdf

Cartons- Satisfactory in FPL as of July 7, 2008

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\\Cdsesub1\evsprod\ANDA078202\0012\m1\us\114-labeling\final-labeling\final-carton-container-labels\carton---0-25mg2ml---246365.pdf

Insert- Satisfactory in FPL on Nov. 20, 2008 with Patient leaflet.

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2. NOTE TO CHEMIST: None

3. MODEL LABELING-This review was based on the labeling NDA- see above.

Reference Listed Drug	
RLD on the 356(h) form	Pulimcort
NDA Number	20-929
RLD established name	Budesonide Inhalation Suspension (Oral)
Firm	Astrazeneca
Currently approved PI	S-032, (b) (4)
AP Date	6/18/07 - 6/19/07

Note: Several pending supplements. We sought concurrence on the ability to carve out once daily dosing. Consult concurred that once daily dosing can be safely carved out 11.17.08 template.

4. PATENTS/EXCLUSIVITIES: [Vol. A1.1 pg.] REFERENCE LISTED DRUG:

Patent Data For NDA 20-929

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4787536	FEB 27,2006 peds Aug 27, 2006			PIII	
6598603	DEC 23,2018 peds Jun 23, 2019	u-529	ONCE DAILY TREATMENT OF ASTHMA WITH NEBULIZED BUDESONIDE	MOU	Carved out consulted
6899099	DEC 23,2018 peds Jun 23, 2019	u-529	" "	MOU	Carved out

Exclusivity Data For NDA 20-929

Code/sup	Expiration	Description	*Labeling impact*
None			

5. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM - Manu by APOTEX in Canada for Apotex in Weston FL

6. CONTAINER/CLOSURE and packaging configurations

   RLD: 1s- cartons of 6 pouches x 5 unit-dose vials:ANDA: 30s (6 pouches with 5 unit dose vials

7. Active and INACTIVE INGREDIENTS

   The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. 1.1, pg.] same as the RLD.

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   USP: store in tight containers
   RLD: store at CRT (20-25) (68-77F). See USP. Store Upright and protect from light
   ANDA: Store at 20-25C (68-77F).[See USP CRT]. Store upright protect from light. Do not freeze

9. DISPENSING STATEMENTS COMPARISON

   USP: Not a USP item; RLD: Respules; ANDA (*Insert*): plastic unit dose ampules

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Date of Review: 12/05/08 Date of Submission: 20 NOV 2008

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cc:

ANDA: 78-202
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
v:\firmsam\apotex\lets&rev\78202ap2labdfsreview
Review

(b) (4)

533.4 mm

SHORT FOLD 71.4 mm | 77 mm | 77 mm | 77 mm | 77 mm | 77 mm | 77 mm

48 mm | 48 mm | 48 mm | 48 mm | 48 mm | 48 mm | 48 mm | 48 mm | 381 mm

Patient's Instructions for Use
℞ **Only**

Budesonide (byoo des' oh nide) Inhalation Suspension
0.25 mg/2 mL and 0.5 mg/2 mL

2 mL ampules containing 0.25 mg or 0.5 mg
FOR INHALATION ONLY.

Please read this leaflet carefully before taking budesonide inhalation suspension. It provides a summary of information about this medication. Following these instructions helps to ensure that you are using the medication correctly.
The medication named budesonide inhalation suspension is intended for inhalation use only with compressed air driven nebulizer systems, also known as jet nebulizers. Do not use with an ultrasonic nebulizer.
For further information, ask your doctor or pharmacist.

IMPORTANT POINTS TO REMEMBER ABOUT BUDESONIDE INHALATION SUSPENSION

- Your doctor has prescribed budesonide inhalation suspension. It contains a medication called budesonide, which is a synthetic corticosteroid. It is important that your child take budesonide inhalation suspension using a compressed air driven jet nebulizer as instructed.
- Use this nebulizer therapy as directed at the same time each day, even during symptom-free periods. **DO NOT STOP TREATMENT OR REDUCE THE DOSE EVEN IF YOUR CHILD FEELS BETTER**, unless told to do so by your doctor.
- **DO NOT** let your child inhale more doses or use this medication more often than instructed.
- This medication is intended to help prevent and control asthma symptoms. It is NOT intended to provide rapid relief of breathing difficulties during an asthma attack.
- Your doctor may prescribe additional medication (such as bronchodilators) for emergency relief if an acute asthma attack occurs. Please contact your doctor if:
  - an asthma attack does not respond to the additional medication,
  - your child requires more of the additional medication than usual.
- If your child uses another medication by inhalation, consult your healthcare provider for instructions on when to use it in relation to using budesonide inhalation suspension.
- Budesonide inhalation suspension has not been studied when mixed with other nebulizable medications. Budesonide inhalation suspension should be given separately in the nebulizer.

BEFORE USING BUDESONIDE INHALATION SUSPENSION

Tell your doctor before starting to take this medication if your child:
- Is allergic to budesonide or any other inhaled corticosteroid,
- Is taking any other medications,
- Has any infections,
- Has or had tuberculosis,
- Has osteoporosis,
- Has recently been around anyone with chicken pox or measles,
- Is planning to have surgery,
- Has been taking an oral corticosteroid medicine like prednisone. You may have to follow specific instructions to avoid health risks associated with stopping the use of these types of medicines.

In some circumstances, this medicine may not be suitable and your doctor may wish to prescribe a different medicine. Make sure that your doctor knows what other medicines your child is taking, including prescription and non-prescription medicines, as well as any vitamins or dietary and herbal supplements.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF BUDESONIDE INHALATION SUSPENSION

As with all inhaled corticosteroids, you should be aware of the following side effects:
- **Increased wheezing right after taking budesonide inhalation suspension. Always have a short-acting bronchodilator medicine with you to treat sudden wheezing.** Short-acting bronchodilator medicines help to relax the muscles around the airways in your lungs. Wheezing happens when the muscles around the airways tighten. This makes it hard to breathe. In severe cases, wheezing can stop your breathing and cause death if not treated right away.
- **Immune system effects and higher chance of infections.**
- **Eye problems including glaucoma and cataracts.** Eye examinations should be considered while using budesonide inhalation suspension.
- Your child's growth should be checked regularly while taking budesonide inhalation suspension because of the potential for slowed growth.

Based on clinical trials, the most common side effects reported by patients using budesonide inhalation suspension are:
- Respiratory infections
- Ear infections
- Runny nose

These are not all of the possible side effects of budesonide inhalation suspension. For more information, ask your doctor or pharmacist.

USING BUDESONIDE INHALATION SUSPENSION

Budesonide inhalation suspension should be used with a compressed air driven jet nebulizer following the manufacturer's instructions. The mist produced is then inhaled through either a mouthpiece or face mask. The treatment generally takes five to ten minutes. Treatment is complete when mist no longer comes out of the mouthpiece or face mask. The face mask should be properly adjusted to optimize delivery and to avoid exposing the eyes to the nebulized medication.

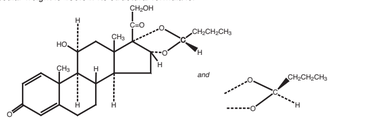
Prescribing Information
℞ **Only**

Budesonide Inhalation Suspension
0.25 mg/2 mL and 0.5 mg/2 mL

For inhalation use via compressed air driven jet nebulizers only (not for use with ultrasonic devices). Not for injection. Read patient instructions before using.

DESCRIPTION

Budesonide, the active component of budesonide inhalation suspension, is a corticosteroid designated chemically as (RS)-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is provided as a mixture of two epimers (22R and 22S). The empirical formula of budesonide is $C_{25}H_{34}O_6$ and its molecular weight is 430.54. Its structural formula is:



Budesonide is a white or almost white, crystalline powder that is practically insoluble in water, sparingly soluble in ethanol, and freely soluble in methylene chloride.

Budesonide inhalation suspension is a sterile suspension for inhalation via jet nebulizer and contains the active ingredient budesonide (micronized), and the inactive ingredients citric acid, edetate disodium dihydrate, polysorbate 80, sodium chloride, sodium citrate, and water for injection. Two dose strengths are available in single-dose ampules: 0.25 mg and 0.5 mg per 2 mL ampule. For budesonide inhalation suspension, like all other nebulized treatments, the amount delivered to the lungs will depend on patient factors, the jet nebulizer utilized, and compressor performance. Using the Pari-LC-Jet Plus Nebulizer/ Pari Master compressor system, under *in vitro* conditions, the mean delivered dose at the mouthpiece (% nominal dose) was approximately 17% at a mean flow rate of 5.5 L/min. The mean nebulization time was 5 minutes or less. Budesonide inhalation suspension should be administered from jet nebulizers at adequate flow rates, via face masks or mouthpieces (see **DOSAGE AND ADMINISTRATION**).

CLINICAL PHARMACOLOGY

Mechanism of Action

Budesonide is an anti-inflammatory corticosteroid that exhibits potent glucocorticoid activity and weak mineralocorticoid activity. In standard *in vitro* and animal models, budesonide has approximately a 200-fold higher affinity for the glucocorticoid receptor and a 1000-fold higher topical anti-inflammatory potency than cortisol (rat croton oil ear edema assay). As a measure of systemic activity, budesonide is 40 times more potent than cortisol when administered subcutaneously and 25 times more potent when administered orally in the rat thymus involution assay.

The activity of budesonide inhalation suspension is due to the parent drug, budesonide. In glucocorticoid receptor affinity studies, the 22R form was two times as active as the 22S epimer. *In vitro* studies indicated that the two forms of budesonide do not interconvert.

The precise mechanism of corticosteroid actions on inflammation in asthma is not well known. Inflammation is an important component in the pathogenesis of asthma. Corticosteroids have been shown to have a wide range of inhibitory activities against multiple cell types (eg, mast cells, eosinophils, neutrophils, macrophages, and lymphocytes) and mediators (eg, histamine, eicosanoids, leukotrienes, and cytokines) involved in allergic- and non-allergic-mediated inflammation. The anti-inflammatory actions of corticosteroids may contribute to their efficacy in asthma.

Studies in asthmatic patients have shown a favorable ratio between topical anti-inflammatory activities and systemic corticosteroid effects over a wide dose range of inhaled budesonide in a variety of formulations and delivery systems including an inhalation-driven, multi-dose dry powder inhaler and the inhalation suspension for nebulization. This is explained by a combination of a relatively high local anti-inflammatory effect, extensive first pass hepatic degradation of orally absorbed drug (85-95%) and the low potency of metabolites (see below).

Pharmacokinetics

Absorption: In asthmatic children 4-6 years of age, the total absolute bioavailability (ie, lung + oral) following administration of budesonide inhalation suspension via jet nebulizer was approximately 6% of the labeled dose.

In children, a peak plasma concentration of 2.6 nmol/L was obtained approximately 20 minutes after nebulization of a 1 mg dose. Systemic exposure, as measured by AUC and C_{max}, is similar for young children and adults after inhalation of the same dose of budesonide inhalation suspension.

Distribution: In asthmatic children 4-6 years of age, the volume of distribution at steady-state of budesonide was 3 L/kg, approximately the same as in healthy adults. Budesonide is 85-90% bound to plasma proteins, the degree of binding being constant over the concentration range (1-100 nmol/L) achieved with, and exceeding, recommended doses. Budesonide showed little or no binding to corticosteroid-binding globulin. Budesonide rapidly equilibrated with red blood cells in a concentration independent manner with a blood/plasma ratio of about 0.8.

Metabolism: *In vitro* studies with human liver homogenates have shown that budesonide is rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4) catalyzed biotransformation have been isolated and identified as 16α-hydroxyprednisolone and 6β-hydroxybudesonide. The corticosteroid activity of each of these two metabolites is less than 1% of that of the parent compound. No qualitative difference between the *in vitro* and *in vivo* metabolic patterns has been detected. Negligible metabolic inactivation was observed in human lung and serum preparations.

Excretion/Elimination: Budesonide is primarily cleared by the liver. Budesonide is excreted in urine and feces in the form of metabolites. In adults, approximately 60% of an intravenous radiolabeled dose was recovered in the urine. No unchanged budesonide was detected in the urine.

In asthmatic children 4-6 years of age, the terminal half-life of budesonide after nebulization is 2.3 hours, and the systemic clearance is 0.5 L/min, which is approximately 50% greater than in healthy adults after adjustment for differences in weight.

Special Populations: No differences in pharmacokinetics due to race, gender, or age have been identified.

Hepatic Insufficiency: Reduced liver function may affect the elimination of corticosteroids. The pharmacokinetics of budesonide were affected by compromised liver function as evidenced by a doubled systemic availability after oral ingestion. The intravenous pharmacokinetics of budesonide were, however, similar in cirrhotic patients and in healthy adults.

Nursing Mothers: The disposition of budesonide when delivered by inhalation from a dry powder inhaler at doses of 200 or 400 mcg twice daily for at least 3 months was studied in eight lactating women with asthma from 1 to 6 months postpartum. Systemic exposure to budesonide in these women appears to be comparable to that in non-lactating women with asthma from other studies. Breast milk obtained over eight hours post-dose revealed that the maximum concentration of budesonide for the 400 and 800 mcg doses was 0.39 and 0.78 nmol/L, respectively, and occurred within 45 minutes after dosing. The estimated oral daily dose of budesonide from breast milk to the infant is approximately 0.007 and 0.014 mcg/kg/day for the two dose regimens used in this study, which represents approximately 0.3% to 1% of the dose inhaled by the mother. Budesonide levels in plasma samples obtained from five infants at about 90 minutes after breast-feeding (and about 140 minutes after drug administration to the mother) were below quantifiable levels (<0.02 nmol/L in four infants and <0.04 nmol/L in one infant) (see **PRECAUTIONS**, ***Nursing Mothers***).

Pharmacodynamics

The therapeutic effects of conventional doses of orally inhaled budesonide are largely explained by its direct local action on the respiratory tract. To confirm that systemic absorption is not a significant factor in the clinical efficacy of inhaled budesonide, a clinical study in adult patients with asthma was performed comparing 400 mcg budesonide administered via a pressurized metered dose inhaler with a tube spacer to 1400 mcg of oral budesonide and placebo. The study demonstrated the efficacy of inhaled budesonide but not orally ingested budesonide despite comparable systemic levels.

Improvement in the control of asthma symptoms following inhalation of budesonide inhalation suspension can occur within 2-8 days of beginning treatment, although maximum benefit may not be achieved for 4-6 weeks.

Budesonide administered via a dry powder inhaler has been shown in various challenge models (including histamine, methacholine, sodium metabisulfite, and adenosine monophosphate) to decrease bronchial hyperresponsiveness in asthmatic patients. The clinical relevance of these models is not certain.

Pre-treatment with budesonide administered 1600 mcg daily (800 mcg twice daily) via a dry powder inhaler for 2 weeks reduced the acute (early-phase reaction) and delayed (late-phase reaction) decrease in FEV_1 following inhaled allergen challenge.

The effects of budesonide inhalation suspension on the hypothalamic-pituitary-adrenal (HPA) axis were studied in three, 12-week, double-blind, placebo-controlled studies in 293 pediatric patients, 6 months to 8 years of age, with persistent asthma. For most patients, the ability to increase cortisol production in response to stress, as assessed by the short cosyntropin (ACTH) stimulation test, remained intact with budesonide inhalation suspension treatment. In a subgroup of children age 6 months to 2 years (n=21) treated with a total daily dose of budesonide inhalation suspension up to 1 mg or placebo, the mean change from baseline in ACTH-stimulated cortisol levels showed a decline in peak stimulated cortisol at 12 weeks compared to an increase in the placebo group. These mean differences were not statistically significant compared to placebo. Another 12 week study was conducted in 141 pediatric patients 6 to 12 months of age with mild to moderate asthma or recurrent/persistent wheezing. All patients were treated with a total daily dose of either 0.5 mg or 1 mg of budesonide inhalation suspension or placebo. A total of 28, 17, and 31 patients in the budesonide inhalation suspension 0.5 mg, 1 mg, and placebo arms respectively, had an evaluation of serum cortisol levels post-ACTH stimulation both at baseline and at the end of the study. The mean change from baseline to Week 12 ACTH-stimulated minus basal plasma cortisol levels did not indicate adrenal suppression in patients treated with budesonide inhalation suspension versus placebo. However, 7 patients in this study (4 of whom received budesonide inhalation suspension 0.5 mg, 2 of whom received budesonide inhalation suspension 1 mg and 1 of whom received placebo) showed a shift from normal baseline stimulated cortisol level (≥500 nmol/L) to a subnormal level (<500 nmol/L) at Week 12. In 4 of these patients receiving budesonide inhalation suspension, the cortisol values were near the cutoff value of 500 nmol/L.

The effects of budesonide inhalation suspension at doses of 0.5 mg twice daily, and 1 mg and 2 mg twice daily (2 times and 4 times the highest recommended total daily dose, respectively) on 24-hour urinary cortisol excretion were studied in 18 patients between 6 to 15 years of age with persistent asthma in a cross-over study design (4 weeks of treatment per dose level). There was a dose-related decrease in urinary cortisol excretion at 2 and 4 times the recommended daily dose. The two higher doses of budesonide inhalation suspension (1 and 2 mg twice daily) showed statistically significantly reduced (43-52%) urinary cortisol excretion compared to the run-in period. The highest recommended dose of budesonide inhalation suspension, 1 mg total daily dose, did not show statistically significantly reduced urinary cortisol excretion compared to the run-in period.

Budesonide inhalation suspension, like other inhaled corticosteroid products, may impact the HPA axis, especially in susceptible individuals, in younger children, and in patients given high doses for prolonged periods.

CLINICAL TRIALS

Three double-blind, placebo-controlled, parallel group, randomized U.S. clinical trials of 12-weeks duration each were conducted in 1018 pediatric patients, 6 months to 8 years of age, with persistent asthma of varying disease duration (2 to 107 months) and severity. Doses of 0.25 mg and 0.5 mg administered twice daily were compared to placebo to provide information about appropriate dosing to cover a range of asthma severity. A Pari-LC-Jet Plus Nebulizer (with a face mask or mouthpiece) connected to a Pari Master compressor was used to deliver budesonide inhalation suspension to patients in the 3 U.S. controlled clinical trials. The co-primary endpoints were nighttime and daytime asthma symptom scores (0-3 scale). Each of the doses discussed below were studied in one or two, but not all three of the U.S. studies.

Results of the 3 controlled clinical trials for recommended dosages of budesonide inhalation suspension (0.25 mg to 0.5 mg twice daily, up to a total daily dose of 1 mg) in patients, 12 months to 8 years of age, are presented below. Compared to placebo, budesonide inhalation suspension significantly decreased both nighttime and daytime symptom scores of asthma at doses of 0.25 mg twice daily, and 0.5 mg twice daily. Symptom reduction in response to budesonide inhalation suspension occurred across gender and age. Budesonide inhalation suspension significantly reduced the need for bronchodilator therapy at all the doses studied.

Improvements in lung function were associated with budesonide inhalation suspension treatment in the subgroup of patients capable of performing lung function testing. Significant improvements were seen in FEV_1 [budesonide inhalation suspension 0.5 mg twice daily] and morning PEF [budesonide inhalation suspension 0.25 mg twice daily; 0.5 mg twice daily] compared to placebo.

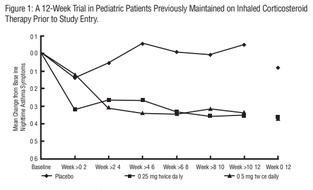
A numerical reduction in nighttime and daytime symptom scores (0-3 scale) of asthma was observed within 2-8 days, although maximum benefit was not achieved for 4-6 weeks after starting treatment. The reduction in nighttime and daytime asthma symptom scores was maintained throughout the 12 weeks of the double-blind trials.

Patients Previously Maintained on Inhaled Corticosteroids

The efficacy of budesonide inhalation suspension at doses of 0.25 mg and 0.5 mg twice daily was evaluated in 133 pediatric asthma patients, 4 to 8 years of age, previously maintained on inhaled corticosteroids (mean FEV_1 79.5% predicted; mean baseline nighttime asthma symptom scores of the treatment groups ranged from 1.04 to 1.18; mean baseline dose of beclomethasone dipropionate of 265 mcg/day, ranging between 42 to 1008 mcg/day; mean baseline dose of triamcinolone acetonide of 572 mcg/day, ranging between 200 to 1200 mcg/day). The changes from baseline to Weeks 0-12 in nighttime asthma symptom scores are shown in Figure 1. Nighttime asthma symptom scores were significantly improved in patients treated with budesonide inhalation suspension compared to placebo. Similar improvements were also observed for daytime asthma symptom scores.

Budesonide inhalation suspension at a dose of 0.5 mg twice daily significantly improved FEV_1, and both doses (0.25 mg and 0.5 mg twice daily) significantly increased morning PEF, compared to placebo.

Figure 1: A 12-Week Trial in Pediatric Patients Previously Maintained on Inhaled Corticosteroid Therapy Prior to Study Entry.

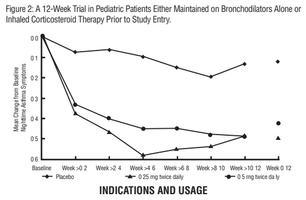


Patients Either Maintained on Bronchodilators Alone or Inhaled Corticosteroid Therapy

The efficacy of budesonide inhalation suspension at doses of 0.25 mg twice daily and 0.5 mg twice daily, was evaluated in pediatric patients 12 months to 8 years of age (mean baseline nighttime asthma symptom scores of the treatment groups ranged from 1.13 to 1.31). Approximately 70% were not previously receiving inhaled corticosteroids. The changes from baseline to Weeks 0-12 in nighttime asthma symptom scores are shown in Figure 2. Budesonide inhalation suspension at doses of 0.25 mg and 0.5 mg twice daily, significantly improved nighttime asthma symptom scores compared to placebo. Similar improvements were also observed for daytime asthma symptom scores.

Budesonide inhalation suspension at a dose of 0.5 mg twice daily significantly improved FEV_1, and at doses of 0.25 mg and 0.5 mg twice daily significantly improved morning PEF, compared to placebo.

Figure 2: A 12-Week Trial in Pediatric Patients Either Maintained on Bronchodilators Alone or Inhaled Corticosteroid Therapy Prior to Study Entry.



INDICATIONS AND USAGE

Budesonide inhalation suspension is indicated for the maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age.

Budesonide inhalation suspension is NOT indicated for the relief of acute bronchospasm.

CONTRAINDICATIONS

Budesonide inhalation suspension is contraindicated as the primary treatment of status asthmaticus or other acute episodes of asthma where intensive measures are required.

Hypersensitivity to budesonide or any of the ingredients of this preparation contraindicates the use of budesonide inhalation suspension.

WARNINGS

Particular care is needed for patients who are transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in asthmatic patients during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. After withdrawal from systemic corticosteroids, a number of months are required for recovery of hypothalamic-pituitary-adrenal (HPA)-axis function.

Patients who have been previously maintained on 20 mg or more per day of prednisone (or its equivalent) may be most susceptible, particularly when their systemic corticosteroids have been almost completely withdrawn.

During this period of HPA-axis suppression, patients may exhibit signs and symptoms of adrenal insufficiency when exposed to trauma, surgery, infection (particularly gastroenteritis) or other conditions associated with severe electrolyte loss. Although budesonide inhalation suspension may provide control of asthma symptoms during these episodes, in recommended doses it supplies less than normal physiological amounts of corticosteroid systemically and does NOT provide the mineralocorticoid activity that is necessary for coping with these emergencies.

During periods of stress or a severe asthma attack, patients who have been withdrawn from systemic corticosteroids should be instructed to resume oral corticosteroids (in large doses) immediately and to contact their physicians for further instructions. These patients should also be instructed to carry a warning card indicating that they may need supplementary systemic corticosteroids during periods of stress or a severe asthma attack.

Patients requiring oral corticosteroids should be weaned slowly from systemic corticosteroid use after transferring to budesonide inhalation suspension. Lung function (FEV_1 or AM PEF), beta-agonist use, and asthma symptoms should be carefully monitored during withdrawal of oral corticosteroids. In addition to monitoring asthma signs and symptoms, patients should be observed for signs and symptoms of adrenal insufficiency such as fatigue, lassitude, weakness, nausea and vomiting, and hypotension.

Transfer of patients from systemic corticosteroid therapy to budesonide inhalation suspension may unmask allergic or other immunologic conditions previously suppressed by the systemic corticosteroid therapy, eg, rhinitis, conjunctivitis, eosinophilic conditions, eczema, and arthritis (see **DOSAGE AND ADMINISTRATION**).

Patients who are on drugs which suppress the immune system are more susceptible to infection than healthy individuals. Chicken pox and measles, for example, can have a more serious or even fatal course in susceptible pediatric patients or adults on immunosuppressant doses of corticosteroids. In pediatric or adult patients who have not had these diseases, or who have not been properly vaccinated, particular care should be taken to avoid exposure. How the dose, route, and duration of corticosteroid administration affects the risk of developing a disseminated infection is not known. The contribution of the underlying disease and/or prior corticosteroid treatment to the risk is also not known.

The clinical course of chicken pox or measles infection in patients on inhaled corticosteroids has not been studied. However, a clinical study has examined the immune responsiveness of asthma patients 12 months to 8 years of age who were treated with budesonide inhalation suspension (see **PRECAUTIONS, Pediatric Use**).

If a patient on immunosuppressant doses of corticosteroids is exposed to chicken pox, therapy with varicella zoster immune globulin (VZIG) or pooled intravenous immunoglobulin (IVIG), as appropriate, may be indicated. If exposed to measles, prophylaxis with pooled intramuscular immunoglobulin (IG) may be indicated. (See the respective package inserts for complete VZIG and IG prescribing information.) If chicken pox develops, treatment with antiviral agents may be considered.

Budesonide inhalation suspension is not a bronchodilator and is not indicated for the rapid relief of acute bronchospasm or other acute episodes of asthma.

As with other inhaled asthma medications, bronchospasm, with an immediate increase in wheezing, may occur after dosing. If acute bronchospasm occurs following dosing with budesonide inhalation suspension, it should be treated immediately with a fast-acting inhaled bronchodilator. Treatment with budesonide inhalation suspension should be discontinued and alternate therapy instituted.

Patients should be instructed to contact their physician immediately when episodes of asthma not responsive to their usual doses of bronchodilators occur during treatment with budesonide inhalation suspension.

PRECAUTIONS

General

During withdrawal from oral corticosteroids, some patients may experience symptoms of systemically active corticosteroid withdrawal, eg, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement of respiratory function (see **DOSAGE AND ADMINISTRATION**).

Because budesonide is absorbed into the circulation and may be systemically active, particularly at higher doses, suppression of HPA function may be associated when budesonide inhalation suspension is administered at doses exceeding those recommended (see **DOSAGE AND ADMINISTRATION**), or when the dose is not titrated to the lowest effective dose. Since individual sensitivity to effects on cortisol production exists, physicians should consider this information when prescribing budesonide inhalation suspension.

Because of the possibility of systemic absorption of inhaled corticosteroids, patients treated with budesonide inhalation suspension should be observed carefully for any evidence of systemic corticosteroid effects. Particular care should be taken in observing patients post-operatively or during periods of stress for evidence of inadequate adrenal response.

It is possible that systemic corticosteroid effects such as hypercorticism, reduced bone mineral density, and adrenal suppression may appear in a small number of patients, particularly at higher doses. If such changes occur, budesonide inhalation suspension should be reduced slowly, consistent with accepted procedures for management of asthma symptoms and for tapering of systemic corticosteroids.

Orally inhaled corticosteroids, including budesonide, may cause a reduction in growth velocity when administered to pediatric patients. A reduction in growth velocity may occur as a result of inadequate control of asthma or from use of corticosteroids for treatment. The potential effects of prolonged treatment on growth velocity should be weighed against the clinical benefits obtained and the risks associated with alternative therapies. To minimize the systemic effects of orally inhaled corticosteroids, including budesonide inhalation suspension, each patient should be titrated to his/her lowest effective dose (see **PRECAUTIONS, Pediatric Use**).

Although patients in clinical trials have received budesonide inhalation suspension on a continuous basis for periods of up to 1 year, the long-term local and systemic effects of budesonide inhalation suspension in human subjects are not completely known. In particular, the effects resulting from chronic use of budesonide inhalation suspension on developmental or immunological processes in the mouth, pharynx, trachea, and lung are unknown.

In clinical trials with budesonide inhalation suspension, localized infections with *Candida albicans* occurred in the mouth and pharynx in some patients. The incidences of localized infections of *Candida albicans* were similar between the placebo and budesonide inhalation suspension treatment groups. If these infections develop, they may require treatment with appropriate antifungal therapy and/or discontinuance of treatment with budesonide inhalation suspension.

Inhaled corticosteroids should be used with caution, if at all, in patients with active or quiescent tuberculosis infection of the respiratory tract, untreated systemic fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex.

Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported following the inhaled administration of corticosteroids.

Information for Patients

Patients being treated with budesonide inhalation suspension should receive the following information and instructions. The information is intended to aid the patient in the safe and effective use of the medication. It is not a disclosure of all possible adverse or intended effects. For instructions on the proper use of budesonide inhalation suspension and to attain the maximum improvement in asthma symptoms, the patient or the parent/guardian of the patient should receive, read, and follow the accompanying patient information and instructions carefully.

- Patients should take budesonide inhalation suspension at regular intervals twice a day as directed, since its effectiveness depends on regular use. The patient should not alter the prescribed dosage unless advised to do so by the physician.
- The effects of mixing budesonide inhalation suspension with other nebulizable medications have not been adequately assessed. Budesonide inhalation suspension should be administered separately in the nebulizer.
- Budesonide inhalation suspension is not a bronchodilator, and its use is not intended to treat acute life-threatening episodes of asthma.
- Budesonide inhalation suspension should be administered with a jet nebulizer connected to a compressor with an adequate air flow, equipped with a mouthpiece or suitable face mask. The face mask should be properly adjusted to optimize delivery and to avoid exposing the eyes to the nebulized medication (see **DOSAGE AND ADMINISTRATION**).
- Ultrasonic nebulizers are not suitable for the adequate administration of budesonide inhalation suspension and, therefore, are not recommended (see **DOSAGE AND ADMINISTRATION**).
- Rinsing the mouth with water after each treatment may decrease the risk of development of local candidiasis. Corticosteroid effects on the skin can be avoided if the face is washed after the use of a face mask.
- Improvement in asthma control following treatment with budesonide inhalation suspension can occur within 2-8 days of beginning treatment, although maximum benefit may not be achieved for 4-6 weeks after starting treatment. If the asthma symptoms do not improve in that time frame, or if the condition worsens, the patient or the patient's parent/guardian should be instructed not to increase the dosage, but to contact the physician.
- Patients should not stop the use of budesonide inhalation suspension abruptly without consulting with their prescribing physician.

PERF.

GLUE

Budesonide Inhalation Suspension
0.25 mg/2 mL and 0.5 mg/2 mL

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Budesonide Inhalation Suspension
0.25 mg/2 mL and 0.5 mg/2 mL

GLUE

10 mm inside margins

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DOSAGE

Patients should take budesonide inhalation suspension at regular intervals twice a day, as directed, since its effectiveness depends on regular use.

Improvement in the control of asthma symptoms with budesonide inhalation suspension can occur within 2-8 days. It may take up to 4-6 weeks before maximum improvement is seen.

If your child misses a dose by more than several hours, just take the next regularly scheduled dose when it is due. **DO NOT DOUBLE** the dose.

HOW TO USE BUDESONIDE INHALATION SUSPENSION

1. Assemble the nebulizer according to the instructions supplied by the manufacturer.
2. Open the sealed aluminum foil envelope and remove one (1) single-dose ampule from the strip (Figure 1). Record the date that you open the foil on the envelope in the space provided.

   Place the unused ampules remaining on the strip back into the aluminum foil envelope before storing. This will protect the medication from light. **Budesonide inhalation suspension should be stored in an upright position at 20-25°C (68-77°F) [see USP Controlled Room Temperature]. Do not refrigerate or freeze.**
3. Gently shake the ampule using a circular motion as shown in Figure 2.
4. Hold the ampule upright without squeezing and open by twisting off the top (Figure 3).
5. Place the open end of the ampule into the nebulizer cup and slowly squeeze out all of the contents as shown in Figure 4.
6. If using a face mask, make sure that the mask fits tightly so that the mist does not get into the child's eyes. Turn on the compressor to begin nebulizing the medication. Use the nebulizer as directed.

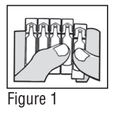


Figure 1

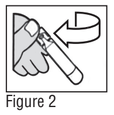


Figure 2

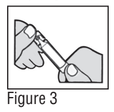


Figure 3

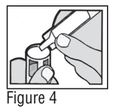


Figure 4

Continue the treatment with budesonide inhalation suspension until mist is no longer coming out of the mouthpiece/face mask (usually about 5 to 10 minutes).

7. Throw away the empty ampule. See the **CLEANING OF EQUIPMENT** and **STORING YOUR BUDESONIDE INHALATION SUSPENSION** sections for additional information.

NOTE:

1. As with other inhaled corticosteroids, rinse your child's mouth with water after each dose to reduce the risk of developing thrush.
2. Wash your child's face after treatment to avoid possible skin irritation.

CLEANING OF EQUIPMENT

The nebulizer cup and the mouthpiece or the face mask should be cleaned according to the instructions supplied by the manufacturer.

STORING YOUR BUDESONIDE INHALATION SUSPENSION

Budesonide inhalation suspension should be stored in an upright position at 20-25°C (68-77°F) [see USP Controlled Room Temperature] in the aluminum foil envelope to protect from light. Do not freeze.

When the foil envelope is opened, the unused ampules should be used within 2 weeks. After opening the aluminum foil package, the unused ampules should be returned to the foil envelope to protect them from light. Any individually opened ampule must be used promptly.

Remember to record the date you open the foil on the envelope in the space provided.

Store budesonide inhalation suspension, like all medications, in a secure place out of the reach of children.

FURTHER INFORMATION ABOUT BUDESONIDE INHALATION SUSPENSION

This leaflet does not contain the complete information about this medication. If you have any questions, you should ask your doctor or pharmacist.

You may want to read this leaflet again. Please DO NOT THROW IT AWAY until you have finished the medication.

REMEMBER: This medication has been prescribed for your child by your doctor. DO NOT give this medication to anyone else.

USE THIS PRODUCT AS DIRECTED, UNLESS INSTRUCTED TO DO OTHERWISE BY YOUR DOCTOR.

If your child is exposed to chicken pox or measles, consult your doctor.

Manufactured by:	Manufactured for:
Apotex Inc.	Apotex Corp.
Toronto, Ontario	Weston, FL
Canada M9L 1T9	33326

246362 November 2008

- Patients whose chronic systemic corticosteroids have been reduced or withdrawn should be instructed to carry a warning card indicating that they may need supplemental systemic corticosteroids during periods of stress or an asthma attack that does not respond to bronchodilators.
- As always, care should be taken to avoid exposure to persons with chicken pox and measles. If exposure to such a person occurs, and the child has not had chicken pox or been properly vaccinated, a physician should be consulted without delay (see **WARNINGS**, and **PRECAUTIONS, Pediatric Use**).
- Long-term use of inhaled corticosteroids, including budesonide, may increase the risk of some eye problems (cataracts or glaucoma). Regular eye examinations should be considered.
- Patients or their parents/guardians considering use of budesonide inhalation suspension should consult with their physician if they are allergic to budesonide or any other orally inhaled corticosteroid.
- Physicians should be informed of other medications patients are taking as budesonide inhalation suspension may not be suitable in some circumstances and the physician may wish to use a different medicine.
- Budesonide inhalation suspension should be stored upright at 20-25°C (68-77°F) [see USP Controlled Room Temperature] and protected from light. Budesonide inhalation suspension should not be refrigerated or frozen.
- When an aluminum foil envelope has been opened, the shelf life of the unused ampules is two weeks when protected from light. The date the envelope was opened should be recorded on the envelope in the space provided.
- After opening the aluminum foil envelope, the unused ampules should be returned to the envelope to protect them from light. Any individually opened ampules must be used promptly.
- For proper usage of budesonide inhalation suspension and to attain maximum improvement, the accompanying Patient's Instructions for Use should be read and followed.

Drug Interactions

In clinical studies, concurrent administration of budesonide and other drugs commonly used in the treatment of asthma has not resulted in an increased frequency of adverse events. The main route of metabolism of budesonide, as well as other corticosteroids, is via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4). After oral administration of ketoconazole, a potent inhibitor of CYP3A4, the mean plasma concentration of orally administered budesonide increased. Concomitant administration of other known inhibitors of CYP3A4 (eg, itraconazole, clarithromycin, erythromycin, etc.) may inhibit the metabolism of, and increase the systemic exposure to, budesonide. Care should be exercised when budesonide is coadministered with long-term ketoconazole and other known CYP3A4 inhibitors. Omeprazole did not have effects on the pharmacokinetics of oral budesonide, while cimetidine, primarily an inhibitor of CYP1A2, caused a slight decrease in budesonide clearance and a corresponding increase in its oral bioavailability.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term studies were conducted in rats and mice using oral administration to evaluate the carcinogenic potential of budesonide.

In a two-year study in Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of gliomas in male rats at an oral dose of 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis). No tumorigenicity was seen in male and female rats at respective oral doses up to 25 and 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis). In two additional two-year studies in male Fischer and Sprague-Dawley rats, budesonide caused no gliomas at an oral dose of 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis). However, in the male Sprague-Dawley rats, budesonide caused a statistically significant increase in the incidence of hepatocellular tumors at an oral dose of 50 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis). The concurrent reference corticosteroids (prednisolone and triamcinolone acetonide) in these two studies showed similar findings.

In a 91-week study in mice, budesonide caused no treatment-related carcinogenicity at oral doses up to 200 mcg/kg (less than the maximum recommended daily inhalation dose in adults and children on a mcg/m² basis).

Budesonide was not mutagenic or clastogenic in six different test systems: Ames *Salmonella*/ microsome plate test, mouse micronucleus test, mouse lymphoma test, chromosome aberration test in human lymphocytes, sex-linked recessive lethal test in *Drosophila melanogaster*, and DNA repair analysis in rat hepatocyte culture.

In rats, budesonide had no effect on fertility at subcutaneous doses up to 80 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m² basis). However, it caused a decrease in prenatal viability and viability in the pups at birth and during lactation, along with a decrease in maternal body-weight gain, at subcutaneous doses of 20 mcg/kg and above (less than the maximum recommended daily inhalation dose in adults on a mcg/m² basis). No such effects were noted at 5 mcg/kg (less than the maximum recommended daily inhalation dose in adults on a mcg/m² basis).

Pregnancy

Teratogenic Effects: Pregnancy Category B - As with other corticosteroids, budesonide was teratogenic and embryocidal in rabbits and rats. Budesonide produced fetal loss, decreased pup weights, and skeletal abnormalities at subcutaneous doses of 25 mcg/kg in rabbits (less than the maximum recommended daily inhalation dose in adults on a mcg/m² basis) and 500 mcg/kg in rats (approximately 4 times the maximum recommended daily inhalation dose in adults on a mcg/m² basis). In another study in rats, no teratogenic or embryocidal effects were seen at inhalation doses up to 250 mcg/kg (approximately 2 times the maximum recommended daily inhalation dose in adults on a mcg/m² basis).

Experience with oral corticosteroids since their introduction in pharmacologic, as opposed to physiologic, doses suggests that rodents are more prone to teratogenic effects from corticosteroids than humans.

Studies of pregnant women, however, have not shown that inhaled budesonide increases the risk of abnormalities when administered during pregnancy. The results from a large population-based prospective cohort epidemiological study reviewing data from three Swedish registries covering approximately 99% of the pregnancies from 1995-1997 (ie, Swedish Medical Birth Registry; Registry of Congenital Malformations; Child Cardiology Registry) indicate no increased risk for congenital malformations from the use of inhaled budesonide during early pregnancy. Congenital malformations were studied in 2014 infants born to mothers reporting the use of inhaled budesonide for asthma in early pregnancy (usually 10-12 weeks after the last menstrual period), the period when most major organ malformations occur. The rate of recorded congenital malformations was similar compared to the general population rate (3.8% vs. 3.5%, respectively). In addition, after exposure to inhaled budesonide, the number of infants born with orofacial clefts was similar to the expected number in the normal population (4 children vs. 3.3, respectively).

These same data were utilized in a second study bringing the total to 2534 infants whose mothers were exposed to inhaled budesonide. In this study, the rate of congenital malformations among infants whose mothers were exposed to inhaled budesonide during early pregnancy was not different from the rate for all newborn babies during the same period (3.6%).

Despite the animal findings, it would appear that the possibility of fetal harm is remote if the drug is used during pregnancy. Nevertheless, because the studies in humans cannot rule out the possibility of harm, budesonide inhalation suspension should be used during pregnancy only if clearly needed.

Non-teratogenic Effects: Hypoadrenalism may occur in infants born of mothers receiving corticosteroids during pregnancy. Such infants should be carefully observed.

Nursing Mothers

Budesonide, like other corticosteroids, is secreted in human milk. Data with budesonide delivered via dry powder inhaler indicates that the total daily oral dose of budesonide in breast milk to the infant is approximately 0.3% to 1% of the dose inhaled by the mother (see **CLINICAL PHARMACOLOGY, Pharmacokinetics, *Special Populations, Nursing Mothers***). No studies have been conducted in breastfeeding women with budesonide inhalation suspension; however, the dose of budesonide available to the infant in breast milk, as a percentage of the maternal dose, would be expected to be similar. Budesonide inhalation suspension should be used in nursing women only if clinically appropriate. Prescribers should weigh the known benefits of breastfeeding for the mother and the infant against the potential risks of minimal budesonide exposure in the infant.

Pediatric Use

Safety in pediatric patients six months to 12 months of age has been evaluated. Safety and effectiveness in pediatric patients 12 months to 8 years of age have been established (see **CLINICAL PHARMACOLOGY, Pharmacodynamics, CLINICAL TRIALS** and **ADVERSE REACTIONS**).

It has been reported a study in pediatric patients 6 to 12 months of age with mild to moderate asthma or recurrent/persistent wheezing. All patients were randomized to receive either budesonide inhalation suspension or placebo. Adrenal axis function was assessed with an ACTH stimulation test at the beginning and end of the study, and mean changes from baseline in this variable did not indicate adrenal suppression in patients who received budesonide inhalation suspension versus placebo. However, on an individual basis, 7 patients in this study (6 in the budesonide inhalation suspension treatment arms and 1 in the placebo arm) experienced a shift from having a normal baseline stimulated cortisol level to having a subnormal level at Week 12 (see **CLINICAL PHARMACOLOGY, Pharmacodynamics**). Pneumonia was observed more frequently in patients treated with budesonide inhalation suspension than in patients treated with placebo, (N = 2, 1, and 0) in the budesonide inhalation suspension 0.5 mg, 1 mg, and placebo groups, respectively.

A dose dependent effect on growth was also noted in this 12-week trial. Infants in the placebo arm experienced an average growth of 3.7 cm over 12 weeks compared with 3.5 cm and 3.1 cm in the budesonide inhalation suspension 0.5 mg and 1 mg arms respectively. This corresponds to estimated mean (95% CI) reductions in 12-week growth velocity between placebo and budesonide inhalation suspension 0.5 mg of 0.2 cm (-0.6 to 1.0) and between placebo and budesonide inhalation suspension 1 mg of 0.6 cm (-0.2 to 1.4). These findings support that the use of budesonide inhalation suspension in infants 6 to 12 months of age may result in systemic effects and are consistent with findings of growth suppression in other studies with inhaled corticosteroids.

Controlled clinical studies have shown that inhaled corticosteroids may cause a reduction in growth velocity in pediatric patients. In these studies, the mean reduction in growth velocity was approximately one centimeter per year (range 0.3 to 1.8 cm per year) and appears to be related to dose and duration of exposure. This effect has been observed in the absence of laboratory evidence of hypothalamic-pituitary-adrenal (HPA)-axis suppression, suggesting that growth velocity is a more sensitive indicator of systemic corticosteroid exposure in pediatric patients than some commonly used tests of HPA-axis function. The long-term effects of this reduction in growth velocity associated with inhaled corticosteroids, including the impact on final adult height, are unknown. The potential for "catch up" growth following discontinuation of treatment with inhaled corticosteroids has not been adequately studied.

In a study of asthmatic children 5-12 years of age, those treated with budesonide administered via a dry powder inhaler 200 mcg twice daily (n=311) had a 1.1-centimeter reduction in growth compared with those receiving placebo (n=418) at the end of one year; the difference between these two treatment groups did not increase further over three years of additional treatment. By the end of four years, children treated with the budesonide dry powder inhaler and children treated with placebo had similar growth velocities. Conclusions drawn from this study may be confounded by the unequal use of corticosteroids in the treatment groups and inclusion of data from patients attaining puberty during the course of the study.

The growth of pediatric patients receiving inhaled corticosteroids, including budesonide inhalation suspension, should be monitored routinely (eg, via stadiometry). The potential growth effects of prolonged treatment should be weighed against clinical benefits obtained and the risks and benefits associated with alternative therapies. To minimize the systemic effects of inhaled corticosteroids, including budesonide inhalation suspension, each patient should be titrated to his/her lowest effective dose.

An open-label non-randomized clinical study examined the immune responsiveness of varicella vaccine in 243 asthma patients 12 months to 8 years of age who were treated with a total daily dose of budesonide inhalation suspension up to 1 mg (n=151) or non-corticosteroid asthma therapy (n=92) (ie, beta$_2$-agonists, leukotriene receptor antagonists, cromones). The percentage of patients developing a seroprotective antibody titer of ≥5.0 (gpELISA value) in response to the vaccination was similar in patients treated with budesonide inhalation suspension (85%) compared to patients treated with non-corticosteroid asthma therapy (90%). No patient treated with budesonide inhalation suspension developed chicken pox as a result of vaccination.

Geriatric Use

Of the 215 patients in 3 clinical trials of budesonide inhalation suspension in adult patients, 65 (30%) were 65 years of age or older, while 22 (10%) were 75 years of age or older. No overall differences in safety were observed between these patients and younger patients, and other reported clinical or medical surveillance experience has not identified differences in responses between the elderly and younger patients.

ADVERSE REACTIONS

The following adverse reactions were reported in pediatric patients treated with budesonide inhalation suspension.

The incidence of common adverse reactions is based on three double-blind, placebo-controlled, U.S. clinical trials in which 945 patients, 12 months to 8 years of age, (98 patients ≥12 months and <2 years of age; 225 patients ≥2 and <4 years of age; and 622 patients ≥4 and ≤8 years of age) were treated with budesonide inhalation suspension or vehicle placebo. The incidence and nature of adverse events reported for budesonide inhalation suspension was comparable to that reported for placebo. The following table shows the incidence of adverse events in U.S. controlled clinical trials, regardless of relationship to treatment, in patients previously receiving bronchodilators and/or inhaled corticosteroids. This population included a total of 605 male and 340 female patients.

Adverse Events with ≥ 3% Incidence Reported by Patients on Budesonide Inhalation Suspension

Adverse Events	Vehicle Placebo (n=227) %	Budesonide Inhalation Suspension Total Daily Dose 0.5 mg (n=223) %	1 mg (n=317) %
Respiratory System Disorder			
Respiratory Infection	36	35	38
Rhinitis	9	11	12
Coughing	5	9	8
Resistance Mechanism Disorders			
Otitis Media	11	11	9
Viral Infection	3	5	3
Moniliasis	2	3	4
Gastrointestinal System Disorders			
Gastroenteritis	4	5	5
Vomiting	3	4	4
Diarrhea	2	4	2
Abdominal Pain	2	2	3
Hearing and Vestibular Disorders			
Ear Infection	4	4	5
Platelet, Bleeding, and Clotting Disorders			
Epistaxis	1	4	3
Vision Disorders			
Conjunctivitis	2	4	2
Skin and Appendages Disorders			
Rash	3	4	2

The table above shows all adverse events with an incidence of 3% or more in at least one active treatment group where the incidence was higher with budesonide inhalation suspension than with placebo.

The following adverse events occurred with an incidence of 3% or more in at least one budesonide inhalation suspension group where the incidence was equal to or less than that of the placebo group: fever, sinusitis, pain, pharyngitis, bronchospasm, bronchitis, and headache.

Incidence 1% to ≤3% (by body system)

The information below includes all adverse events with an incidence of 1 to ≤3%, in at least one budesonide inhalation suspension treatment group where the incidence was higher with budesonide inhalation suspension than with placebo, regardless of relationship to treatment.

Body as a whole: allergic reaction, chest pain, fatigue, flu-like disorder
Respiratory system: stridor
Resistance mechanisms: herpes simplex, external ear infection, infection
Central & peripheral nervous system: dysphonia, hyperkinesia
Skin & appendages: eczema, pustular rash, pruritus
Hearing & vestibular: earache
Vision: eye infection
Psychiatric: anorexia, emotional lability
Musculoskeletal system: fracture, myalgia
Application site: contact dermatitis
Platelet, bleeding & clotting: purpura
White cell and resistance: cervical lymphadenopathy

The incidence of reported adverse events was similar between the 447 budesonide inhalation suspension-treated (mean total daily dose 0.5 to 1 mg) and 223 conventional therapy-treated pediatric asthma patients followed for one year in three open-label studies.

Cases of growth suppression have been reported for inhaled corticosteroids including post-marketing reports for budesonide inhalation suspension (see **PRECAUTIONS, Pediatric Use**).

Less frequent adverse events (<1%) reported in the published literature, long-term, open-label clinical trials, or from worldwide marketing experience with any formulation of inhaled budesonide include: immediate and delayed hypersensitivity reactions including rash, contact dermatitis, urticaria, angioedema, and bronchospasm; symptoms of hypocorticism and hypercorticism; glaucoma, cataracts; psychiatric symptoms including depression, aggressive reactions, irritability, anxiety, and psychosis; and bone disorders including avascular necrosis of the femoral head and osteoporosis.

OVERDOSAGE

The potential for acute toxic effects following overdose of budesonide inhalation suspension is low. If inhaled corticosteroids are used at excessive doses for prolonged periods, systemic corticosteroid effects such as hypercorticism or growth suppression may occur (see **PRECAUTIONS**).

In mice the minimal lethal inhalation dose was 100 mg/kg (approximately 410 or 120 times, respectively, the maximum recommended daily inhalation dose in adults or children on a mg/m² basis). In rats there were no deaths at an inhalation dose of 68 mg/kg (approximately 550 or 160 times, respectively, the maximum recommended daily inhalation dose in adults or children on a mg/m² basis). In mice the minimal oral lethal dose was 200 mg/kg (approximately 810 or 240 times, respectively, the maximum recommended daily inhalation dose in adults or children on a mg/m² basis). In rats, the minimal oral lethal dose was less than 100 mg/kg (approximately 810 or 240 times, respectively, the maximum recommended daily inhalation dose in adults or children on a mg/m² basis).

DOSAGE AND ADMINISTRATION

Budesonide inhalation suspension is indicated for use in asthmatic patients 12 months to 8 years of age. Budesonide inhalation suspension should be administered by the inhaled route via jet nebulizer connected to an air compressor. Individual patients will experience a variable onset and degree of symptom relief. Improvement in asthma control following inhaled administration of budesonide inhalation suspension can occur within 2-8 days of initiation of treatment, although maximum benefit may not be achieved for 4-6 weeks. The safety and efficacy of budesonide inhalation suspension when administered in excess of recommended doses have not been established. In all patients, it is desirable to downward-titrate to the lowest effective dose once asthma stability is achieved. The recommended starting dose and highest recommended dose of budesonide inhalation suspension, based on prior asthma therapy, are listed in the following table.

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Bronchodilators alone	0.5 mg total daily dose administered twice daily in divided doses	0.5 mg total daily dose
Inhaled Corticosteroids	0.5 mg total daily dose administered twice daily in divided doses	1 mg total daily dose
Oral Corticosteroids	1 mg total daily dose administered as 0.5 mg twice daily	1 mg total daily dose

Patients Not Receiving Systemic (Oral) Corticosteroids

Patients who require maintenance therapy of their asthma may benefit from treatment with budesonide inhalation suspension at the doses recommended above. Once the desired clinical effect is achieved, consideration should be given to tapering to the lowest effective dose.

Patients Maintained on Chronic Oral Corticosteroids

Initially, budesonide inhalation suspension should be used concurrently with the patient's usual maintenance dose of systemic corticosteroid. After approximately one week, gradual withdrawal of the systemic corticosteroid may be initiated by reducing the daily or alternate daily dose. Further incremental reductions may be made after an interval of one or two weeks, depending on the response of the patient. Generally, these decrements should not exceed 25% of the prednisone dose or its equivalent. A slow rate of withdrawal is strongly recommended. During reduction of oral corticosteroids, patients should be carefully monitored for asthma instability, including objective measures of airway function, and for adrenal insufficiency (see **WARNINGS**). During withdrawal, some patients may experience symptoms of systemic corticosteroid withdrawal, eg, joint and/or muscular pain, lassitude, and depression, despite maintenance or even improvement in pulmonary function. Such patients should be encouraged to continue with budesonide inhalation suspension but should be monitored for objective signs of adrenal insufficiency. If evidence of adrenal insufficiency occurs, the systemic corticosteroid doses should be increased temporarily and thereafter withdrawal should continue more slowly. During periods of stress or a severe asthma attack, transfer patients may require supplementary treatment with systemic corticosteroids.

A Pari-LC-Jet Plus Nebulizer (with face mask or mouthpiece) connected to a Pari Master compressor was used to deliver budesonide inhalation suspension to each patient in 3 U.S. controlled clinical studies. The safety and efficacy of budesonide inhalation suspension delivered by other nebulizers and compressors have not been established.

Budesonide inhalation suspension should be administered via jet nebulizer connected to an air compressor with an adequate air flow, equipped with a mouthpiece or suitable face mask. Ultrasonic nebulizers are not suitable for the adequate administration of budesonide inhalation suspension and, therefore, are NOT recommended.

The effects of mixing budesonide inhalation suspension with other nebulizable medications have not been adequately assessed. Budesonide inhalation suspension should be administered separately in the nebulizer (see **PRECAUTIONS, Information for Patients**).

Directions for Use

Illustrated *Patient's Instructions for Use* accompany each package of Budesonide Inhalation Suspension.

HOW SUPPLIED

Budesonide Inhalation Suspension is supplied in sealed aluminum foil envelopes containing one plastic strip of five single-dose ampules together with patient instructions for use. There are 30 ampules in a carton. Each single-dose ampule contains 2 mL of sterile liquid suspension.

Budesonide Inhalation Suspension is available in two strengths, each containing 2 mL:

NDC 60505-0820-0	0.25 mg/2 mL
NDC 60505-0821-0	0.5 mg/2 mL

Storage

Budesonide Inhalation Suspension should be stored in an upright position at 20-25°C (68-77°F) [see USP Controlled Room Temperature], and protected from light. When an envelope has been opened, the shelf life of the unused ampules is 2 weeks when protected. After opening the aluminum foil envelope, the unused ampules should be returned to the aluminum foil envelope to protect them from light. Any opened ampule must be used promptly. Gently shake the ampule using a circular motion before use. Keep out of reach of children. Do not freeze.

Pulmicort Turbuhaler® is a registered trademark of AstraZeneca.

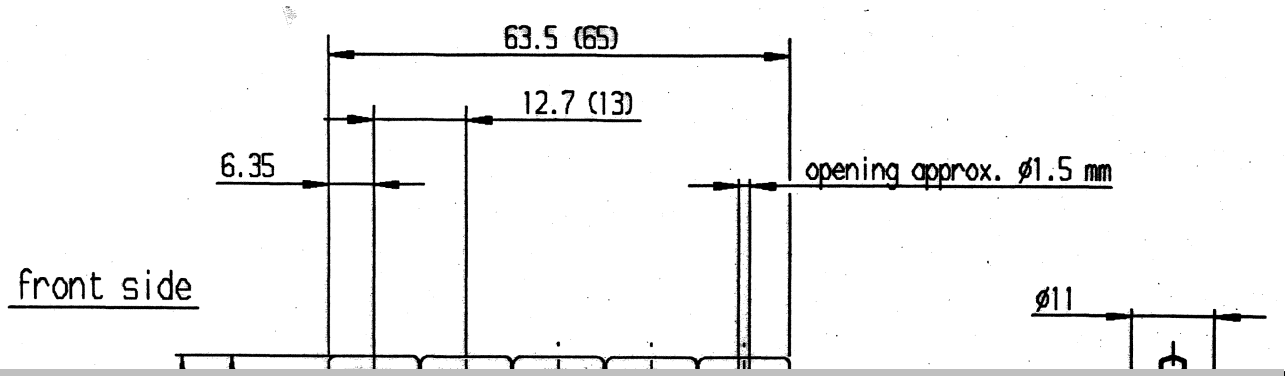
Manufactured by:	Manufactured for:
Apotex Inc.	Apotex Corp.
Toronto, Ontario	Weston, FL
Canada M9L 1T9	33326

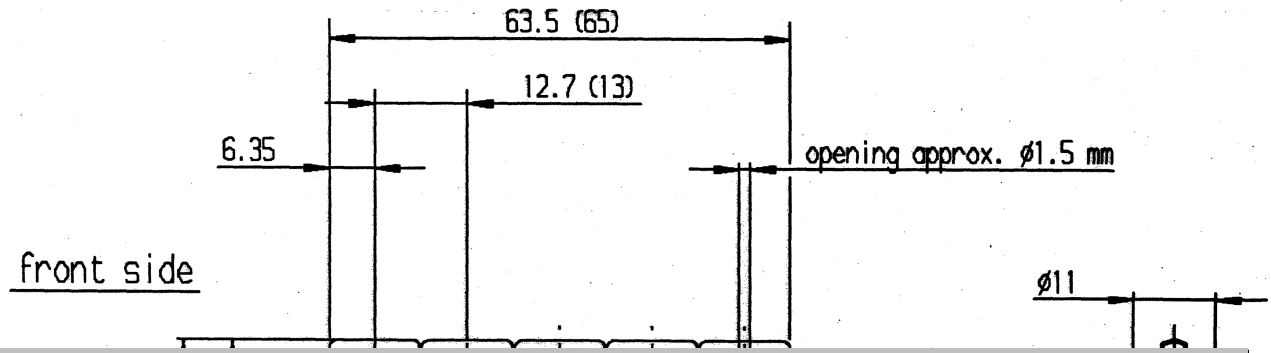
246362 November 2008

PERF.

381 mm

10 mm inside margins


63.5 (65)
12.7 (13)
6.35
opening approx. ø1.5 mm
front side
ø11


63.5 (65)
12.7 (13)
6.35
opening approx. ø1.5 mm
front side
ø11

(b) (4)

AQUEOUS FREE AREA
81.5 mm x 42 mm
FOR PLACEMENT OF LOT & EXP.

246365

NDC 60505-0820-0 30 (6 Pouches x 5)
2 mL Plastic Ampules

Budesonide
Inhalation Suspension

0.25 mg/2 mL

NDC 60505-0820-0 30 (6 Pouches x 5)
2 mL Plastic Ampules

Budesonide
Inhalation Suspension

0.25 mg/2 mL

For Inhalation Only

℞ Only

Sterile Unit Dose Ampules

APOTEX CORP.

Each unit-dose ampule delivers 2 mL of a sterile suspension containing 0.25 mg of micronized budesonide plus inactives citric acid, edetate disodium dihydrate, polysorbate 80, sodium chloride, sodium citrate and Water for Injection.

Once an ampule is opened, use the contents immediately.

For use only in a jet nebulizer. Do NOT use in an ultrasonic nebulizer.

Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Do not freeze. Store unopened ampules in the foil envelope placed upright in the carton. Protect from light.

Once the foil envelope is opened, use the ampules within 2 weeks. Use as directed by a physician.

Follow the Patient Instructions for proper use of Budesonide Inhalation Suspension.

See package insert for full prescribing information.

Keep out of reach of children.

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, FL, 33326

3 60505 08200 1

STORE UPRIGHT

NDC 60505-0820-0 30 (6 Pouches x 5)
2 mL Plastic Ampules

Budesonide
Inhalation Suspension

0.25 mg/2 mL

For Inhalation Only

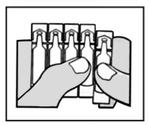
℞ Only

Sterile Unit Dose Ampules

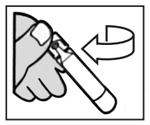
APOTEX CORP.

VARNISH KNOCK OUT
FOR HOTMELT

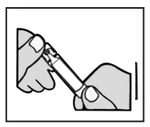
How to use Budesonide Inhalation Suspension



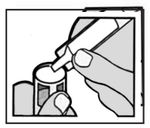
1. Open the sealed aluminum foil envelope and remove one ampule from the plastic strip. Record the date on the foil envelope, in the space provided.



2. Gently shake the ampule using a circular motion.



3. Hold the ampule upright without squeezing and open by twisting off the top.



4. Place the open end of the ampule into the nebulizer cup, and slowly squeeze out all of the contents.

5. Begin nebulizing the medication. Use the nebulizer as directed by manufacturer.

See enclosed Patient Instructions.

NDC 60505-0821-0 30 (6 Pouches x 5)
2 mL Plastic Ampules

Budesonide
Inhalation Suspension
0.5 mg/2 mL

AQUEOUS FREE AREA
81.5 mm x 42 mm
FOR PLACEMENT OF LOT & EXP.

246408

(b) (4)

NDC 60505-0821-0 30 (6 Pouches x 5)
2 mL Plastic Ampules

Budesonide
Inhalation Suspension

0.5 mg/2 mL

For Inhalation Only

℞ Only

Sterile Unit Dose Ampules

APOTEX CORP.

Each unit-dose ampule delivers 2 mL of a sterile suspension containing 0.5 mg of micronized budesonide plus inactives citric acid, edetate disodium dihydrate, polysorbate 80, sodium chloride, sodium citrate and Water for Injection.

Once an ampule is opened, use the contents immediately.

For use only in a jet nebulizer. Do NOT use in an ultrasonic nebulizer.

Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Do not freeze. Store unopened ampules in the foil envelope placed upright in the carton. Protect from light.

Once the foil envelope is opened, use the ampules within 2 weeks. Use as directed by a physician.

Follow the Patient Instructions for proper use of Budesonide Inhalation Suspension.

See package insert for full prescribing information.

Keep out of reach of children.

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, FL, 33326

3 60505 08210 0

STORE UPRIGHT

NDC 60505-0821-0 30 (6 Pouches x 5)
2 mL Plastic Ampules

Budesonide
Inhalation Suspension

0.5 mg/2 mL

For Inhalation Only

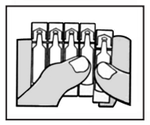
℞ Only

Sterile Unit Dose Ampules

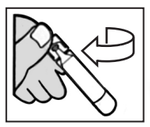
APOTEX CORP.

VARNISH KNOCK OUT
FOR HOTMELT

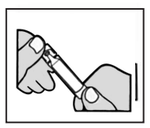
How to use Budesonide Inhalation Suspension



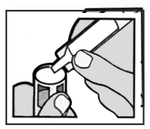
1. Open the sealed aluminum foil envelope and remove one ampule from the plastic strip. Record the date on the foil envelope, in the space provided.



2. Gently shake the ampule using a circular motion.



3. Hold the ampule upright without squeezing and open by twisting off the top.



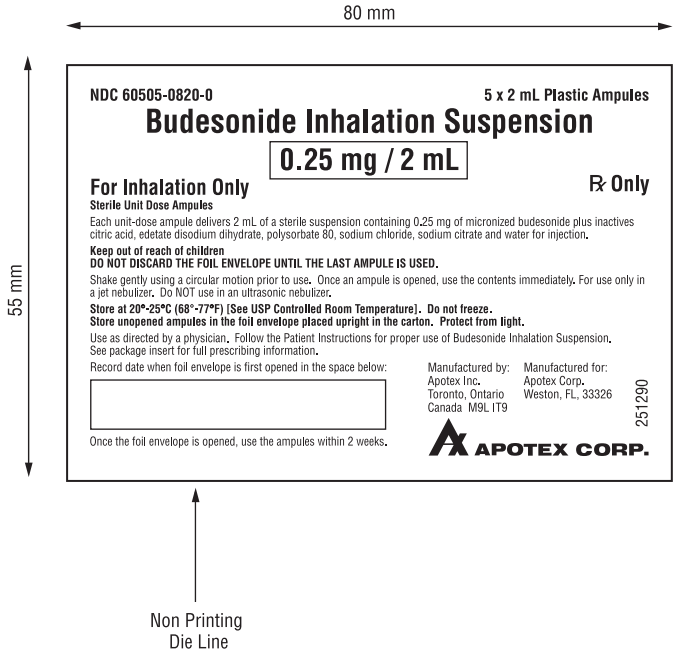
4. Place the open end of the ampule into the nebulizer cup, and slowly squeeze out all of the contents.

5. Begin nebulizing the medication. Use the nebulizer as directed by manufacturer.

See enclosed Patient Instructions.

(b) (4)

[redacted]


80 mm
55 mm
NDC 60505-0820-0
5 x 2 mL Plastic Ampules
Budesonide Inhalation Suspension
0.25 mg / 2 mL
For Inhalation Only
℞ Only
Sterile Unit Dose Ampules
Each unit-dose ampule delivers 2 mL of a sterile suspension containing 0.25 mg of micronized budesonide plus inactives citric acid, edetate disodium dihydrate, polysorbate 80, sodium chloride, sodium citrate and water for injection.
Keep out of reach of children
DO NOT DISCARD THE FOIL ENVELOPE UNTIL THE LAST AMPULE IS USED.
Shake gently using a circular motion prior to use. Once an ampule is opened, use the contents immediately. For use only in a jet nebulizer. Do NOT use in an ultrasonic nebulizer.
Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Do not freeze.
Store unopened ampules in the foil envelope placed upright in the carton. Protect from light.
Use as directed by a physician. Follow the Patient Instructions for proper use of Budesonide Inhalation Suspension.
See package insert for full prescribing information.
Record date when foil envelope is first opened in the space below:
Once the foil envelope is opened, use the ampules within 2 weeks.
Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9
Manufactured for:
Apotex Corp.
Weston, FL, 33326
APOTEX CORP.
251290
Non Printing
Die Line

(b) (4)

[redacted]

80 mm

55 mm

NDC 60505-0821-0

5 x 2 mL Plastic Ampules

Budesonide Inhalation Suspension

0.5 mg / 2 mL

For Inhalation Only

℞ **Only**

Sterile Unit Dose Ampules

Each unit-dose ampule delivers 2 mL of a sterile suspension containing 0.5 mg of micronized budesonide plus inactives citric acid, edetate disodium dihydrate, polysorbate 80, sodium chloride, sodium citrate and water for injection.

Keep out of reach of children

DO NOT DISCARD THE FOIL ENVELOPE UNTIL THE LAST AMPULE IS USED.

Shake gently using a circular motion prior to use. Once an ampule is opened, use the contents immediately. For use only in a jet nebulizer. Do NOT use in an ultrasonic nebulizer.

Store at 20°-25°C (68°-77°F) [See USP Controlled Room Temperature]. Do not freeze.

Store unopened ampules in the foil envelope placed upright in the carton. Protect from light.

Use as directed by a physician. Follow the Patient Instructions for proper use of Budesonide Inhalation Suspension. See package insert for full prescribing information.

Record date when foil envelope is first opened in the space below:

Once the foil envelope is opened, use the ampules within 2 weeks.

Manufactured by:
Apotex Inc.
Toronto, Ontario
Canada M9L 1T9

Manufactured for:
Apotex Corp.
Weston, FL, 33326

APOTEX CORP.

251268

Non Printing
Die Line

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/s/

Angela Payne
12/5/2008 07:40:45 AM
LABELING REVIEWER

John Grace
12/5/2008 09:23:52 AM
LABELING REVIEWER

APPROVAL SUMMARY #1
LABELING REVIEW BRANCH

1. APPLICANT INFORMATION:

ANDA Number	78-202
Date of Submission	07 JUL 2008
Applicant	Apotex
Drug Name	Budesonide Inhalation Suspension
Strength(s)	0.25 mg/2mL and 0.5 mg/2mL unit dose ampule, Sterile

LABELS AND LABELING SUMMARY

Containers- Satisfactory July 7, 2008

\\Cdsesub1\evsprod\ANDA078202\0012\m1\us\114-labeling\final-labeling\final-carton-container-labels\ampule---0-5mg2ml.pdf
\\Cdsesub1\evsprod\ANDA078202\0012\m1\us\114-labeling\final-labeling\final-carton-container-labels\ampule---0-25mg2ml.pdf

Foul Pouches- Satisfactory in FPL as of July 7, 2008

\\Cdsesub1\evsprod\ANDA078202\0012\m1\us\114-labeling\final-labeling\final-carton-container-labels\foil-pouch---0-5mg2ml---251268.pdf

\\Cdsesub1\evsprod\ANDA078202\0012\m1\us\114-labeling\final-labeling\final-carton-container-labels\foil-pouch---0-25mg2ml---251290.pdf

Cartons- Satisfactory in FPL as of July 7, 2008

\\Cdsesub1\evsprod\ANDA078202\0012\m1\us\114-labeling\final-labeling\final-carton-container-labels\carton---0-5mg2ml---246408.pdf

\\Cdsesub1\evsprod\ANDA078202\0012\m1\us\114-labeling\final-labeling\final-carton-container-labels\carton---0-25mg2ml---246365.pdf

Insert- Satisfactory in FPL on July 7, 2008 with Patient leaflet.

\\Cdsesub1\evsprod\ANDA078202\0012\m1\us\114-labeling\final-labeling\final-package-insert-package-inserts\package-insert---246362.pdf

2. NOTE TO CHEMIST: None

3. MODEL LABELING-This review was based on the labeling NDA- see above.

Reference Listed Drug

RLD on the 356(h) form	Pulimcort
NDA Number	20-929
RLD established name	Budesonide Inhalation Suspension (Oral)
Firm	Astrazeneca
Currently approved PI	S-032, (b) (4)
AP Date	6/18/07 - (b) (4)

Note: Several pending supplements. We sought concurrence on the ability to carve out once daily dosing. Consult concurred that once daily dosing can be safely carved out.

4. PATENTS/EXCLUSIVITIES: [Vol. A1.1 pg.] REFERENCE LISTED DRUG:

Patent Data For NDA 20-929

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4787536	FEB 27,2006 peds Aug 27, 2006			PIII	
6598603	DEC 23,2018 peds Jun 23, 2019	u-529	ONCE DAILY TREATMENT OF ASTHMA WITH NEBULIZED BUDESONIDE	MOU	Carved out consulted
6899099	DEC 23,2018 peds Jun 23, 2019	u-529	" "	MOU	Carved out

Exclusivity Data For NDA 20-929

Code/sup	Expiration	Description	*Labeling impact*
None			

5. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM - Manu by APOTEX in Canada for Apotex in Weston FL

6. CONTAINER/CLOSURE and packaging configurations

   RLD: 1s- cartons of 6 pouches x 5 unit-dose vials:ANDA: 30s (6 pouches with 5 unit dose vials

7. Active and INACTIVE INGREDIENTS

   The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. 1.1, pg.] same as the RLD.

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   USP: store in tight containers
   RLD: store at CRT (20-25) (68-77F). See USP. Store Upright and protect from light
   ANDA: Store at 20-25C (68-77F).[See USP CRT]. Store upright protect from light. Do not freeze

9. DISPENSING STATEMENTS COMPARISON

   USP: Not a USP item; RLD: Respules; ANDA (*Insert*): plastic unit dose ampules

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Date of Review: 7/31/08 Date of Submission: 07 JUL 2008

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cc:

ANDA: 78-202
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
v:\firmsam\apotex\lets&rev\78202ap1labdfsreview
Review

8 Pages of Draft Labeling have been Withheld as b4 (CCI/TS) immediately following this page

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

/s/

Angela Payne
7/31/2008 02:18:34 PM
LABELING REVIEWER

John Grace
7/31/2008 03:27:48 PM
LABELING REVIEWER

TENTATIVE APPROVAL SUMMARY #2
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	78-202
Date of Submission	06 NOV 2007
Applicant	Apotex
Drug Name	Budesonide Inhalation Suspension
Strength(s)	0.25 mg/2mL and 0.5 mg/2mL unit dose ampule, Sterile

Labels and Labeling Summary	
Container Labels	\\Cdsesub1\evsprod\ANDA078202\0000\m1\us\114-labeling\draft-labeling\draft-carton-container-labels\draft-ampule-embossing-0-5mg2ml.pdf - \\Cdsesub1\evsprod\ANDA078202\0000\m1\us\114-labeling\draft-labeling\draft-carton-container-labels\draft-ampule-embossing-0-25mg2ml.pdf
Pouches	\\Cdsesub1\evsprod\ANDA078202\0008\m1\us\114-labeling\draft-labeling\draft-carton-container-labels\draft-foil-pouch-0-5mg2ml.pdf
FPL	\\Cdsesub1\evsprod\ANDA078202\0008\m1\us\114-labeling\draft-labeling\draft-carton-container-labels\draft-foil-pouch-0-25mg2ml.pdf
Carton Labels	\\Cdsesub1\evsprod\ANDA078202\0008\m1\us\114-labeling\draft-labeling\draft-carton-container-labels\draft-carton0-5mg2ml.pdf
FPL	\\Cdsesub1\evsprod\ANDA078202\0008\m1\us\114-labeling\draft-labeling\draft-carton-container-labels\draft-carton-0-25mg2ml.pdf
Package Insert	\\Cdsesub1\evsprod\ANDA078202\0008\m1\us\114-labeling\draft-labeling\draft-labeling-text\draft-package-insert-signed.pdf DRAFT
Patient instruction sheet	

REFERENCE LISTED DRUG:

Patent Data For NDA 20-929

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4787536	FEB 27,2006 peds Aug 27, 2006			PIII	
6598603	DEC 23,2018 peds Jun 23, 2019	u-529	ONCE DAILY TREATMENT OF ASTHMA WITH NEBULIZED BUDESONIDE	MOU	Carved out consulted
6899099	DEC 23,2018 peds Jun 23, 2019	u-529	" "	mou	Carved out

Exclusivity Data For NDA 20-929

Code/sup	Expiration	Description	*Labeling impact*
None			

Reference Listed Drug	
RLD on the 356(h) form	Pulimcort
NDA Number	20-929
RLD established name	Budesonide Inhalation Suspension (Oral)
Firm	Astrazeneca
Currently approved PI	S-032, (b) (4)
AP Date	6/18/07 - 6/19/07

hNote: Several pending supplements. We sought concurrence of the ability to carve out once daily dosing. Consult concurred that once daily dosing can be safely carved out.

NOTE TO CHEMIST:

FOR THE RECORD:

1. MODEL LABELING-This review was based on the labeling NDA- see above.

2. PATENTS/EXCLUSIVITIES: See above [Vol. A1.1 pg.]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM - Manu by APOTEX in Canada for Apotex in Weston FL

4. CONTAINER/CLOSURE and packaging configurations

   RLD: 1s- cartons of 6 pouches x 5 unit-dose vials:ANDA: 30s (6 pouches with 5 unit dose vials

5. Active and INACTIVE INGREDIENTS

   The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. 1.1, pg.] same as the RLD.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   USP: store in tight containers
   RLD: store at CRT (20-25) (68-77F). See USP. Store Upright and protect from light
   ANDA: Store at 20-25C (68-77F).[See USP CRT]. Store upright protect from light. Do not freeze

7. DISPENSING STATEMENTS COMPARISON

   USP: Not a USP item; RLD: Respules; ANDA (*Insert*): plastic unit dose ampules

8. BIOAVAILABILITY/BIOEQUIVALENCE:

Date of Review: 12/13/07 Date of Submission: 06 NOV 2007

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cc:

ANDA: 78-202
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
v:\firmsam\apotex\lets&rev\78202tap2labdfsreview
Review

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

/s/

Angela Payne
12/12/2007 07:26:04 AM
LABELING REVIEWER

John Grace
12/12/2007 01:12:45 PM
LABELING REVIEWER

REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **78-202** Dates of Submission: 20 JUN 2006 (original)

Applicant's Name: Apotex Inc.

Established Name: Budesonide Inhalation Suspension 0.25 mg/2mL and 0.5 mg/2 mL, UNIT DOSE ampules

---

Labeling Deficiencies:

1. **CONTAINER**- Satisfactory in draft.

2. **FOIL POUCH -**

   a. The text is difficult to read. Please resubmit with improved readability.
   b. Revise "Each single dose vial to each unit-dose ampule…".
   c. Insert the term "in-actives" just prior to the list of in-actives.
   d. Add "Sterile unit dose ampules" to the label.
   e. Increase the prominence of the strength. Increase the font size.
   f. Differentiate your product strengths by the use of boxing, contrasting colors, or some other means.
   g. Delete "Oral". You can use "Inhalation via use with a jet nebulizer", if you prefer.

3. **CARTON -**

   a. See comments under POUCH.
   b. Identify number of pouches 30s (6 pouches x 5- 2 mL unit dose ampules).
   c. Include the established name and strength on the fop panel.

4. **INSERT-**

   a. GENERAL COMMENT - Please provide a patent certification for patent number. In addition to the changes below please update your labeling to be in accord with the most recent labeling approved for the reference listed drug (NDA 20-929).

   b. CLINICAL PHARMACOLOGY, Pharmacodynamics, 5th paragraph - revise to read "…In the subgroup of children age 6 months to 2 years (n-21) receiving a total daily dose of budesonide inhalation suspension or placebo, the mean change from baseline in ACTH-stimulated cortisol levels show a decline…..statistically significant compare to placebo. Another study was conducted in pediatric patients 6 to 12 months of age with mild to moderate asthma or recurrent/persistent wheezing had an evaluation of serum cortisol levels…value of 500 nmol/L.

      * Note: Retain most of the 5th as seen in the reference listed drug labeling but modify as instructed above.

   c. CLINICAL TRIALS - Revise as follows:

      i.) First paragraph - …and severity. Doses up to the total maximum dose were administered and compared to placebo to provide information. Each of the doses discussed below were ..

      ii.) Second paragraph, First sentence - Results of the three controlled clinical trials for recommended dosages of budesonide inhalation suspension in patients 12 months to 8

years…

iii.) Third paragraph, second sentence - Significant improvements were seen in FEV1 [budesonide inhalation suspension 0.5 mg twice daily] and morning PEF [budesonide inhalation suspension 0.25 mg twice daily; 0.5 mg twice daily] compared to placebo.

d. CLINIICAL TRIALS , Patients Receiving Twice Daily Dosing, Revise second sentence as follows:

i.) Approximately 70% were not previously receiving inhaled corticosteroids. The changes from baseline to weeks 0-12 in night time asthma symptom scores are show in figure 2-. Budesonide inhalation…

ii.) Include the graph in this section. Delete data for once daily dosing.

iii.) Delete last paragraph [redacted] (b) (4)

e. PRECAUTIONS, Delete the text that you have inserted in several sections of this section [redacted] (b) (4) is not necessary.

f. PRECAUTIONS, Pediatric Use subsection- Reinsert the second paragraph of the innovator's labeling. You may modify it as follows: "It has been report a study was conducted in pediatric patients 6 to 12 months of age with mild to moderate asthma or recurrent/persistent wheezing, All patients were randomized to receive either budesonide inhalation suspension or placebo. Adrenal axis function was assessed…respectively.

g. ADVERSE REACTIONS- Delete the text that you have inserted in several sections of this section [redacted] (b) (4) is not necessary. Second paragraph- Delete [redacted] (b) (4) [redacted] (b) (4). In addition, you must also delete the [redacted] (b) (4) mg total dose data in the charts.

h. OVERDOSAGE - Delete the text that you have inserted in several sections of this section [redacted] (b) (4) is not necessary.

i. DOSAGE AND ADMINISTRATION, Patients Not Receiving Systemic (Oral) Corticosteroids, 2nd paragraph, 2nd sentence- Delete [redacted] (b) (4)

j. HOW SUPPLIED- "Add store in an upright position"

k. PATIENT INSTRUCTIONS -

Ensure that the patient instruction sheet is detachable. Provide a separate instruction sheet in each pouch as does the innovator. Each pouch should have a patient instruction sheet. Include the established name with the pronunciation in the title section of the patient instructions sheet. Cite the full established name (Budesonide Inhalation Suspension) in all of the section titles and paragraph rather than using "budesonide".

Revise your labels and labeling, as instructed above, and submit final printed or draft if you prefer electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling and the latest approved labeling for the reference listed drug (or your last submission) with all differences annotated and explained.

SUMMARY
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	78-202
Date of Submission	
Applicant	Apotex
Drug Name	Budesonide Inhalation Suspension
Strength(s)	0.25 mg/2mL and 0.5 mg/2mL unit dose ampule

Labels and Labeling Summary	
Container Labels	**Submitted**
Pouches	
Carton Labels	
Package Insert Labeling	
Patient instruction sheet	

REFERENCE LISTED DRUG:

Patent Data For NDA 20-929

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4787536	FEB 27,2006 peds Aug 27, 2006			PIII	
6598603	DEC 23,2018 peds Jun 23, 2019	u-529	ONCE DAILY TREATMENT OF ASTHMA WITH NEBULIZED BUDESONIDE	MOU	Carved out: need consult
6899099	DEC 23,2018 peds Jun 23, 2019	u-645	For treatment of Asthma	Need to certify	???

Exclusivity Data For NDA 20-929

Code/sup	Expiration	Description	*Labeling impact*
None			

Reference Listed Drug

RLD on the 356(h) form	Pulimcort
NDA Number	20-929
RLD established name	Budesonide Inhalation Suspension (Oral)
Firm	Astrazeneca
Currently approved PI	S-022 - changed to s-029
AP Date	6/30/05 - changed to 11/20/06

Note: Several pending supplements

NOTE TO CHEMIST:

FOR THE RECORD:

1. MODEL LABELING

   This review was based on the labeling NDA- see above.

2. PATENTS/EXCLUSIVITIES: See above [Vol. A1.1 pg.]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM - Manu by APOTEX in Canada for Apotex in Weston FL

4. CONTAINER/CLOSURE and packaging configurations

   RLD: 1s- cartons of 6 pouches x 5 unit-dose vials
   ANDA: 30s (6 pouches with 5 unit dose vials

5. Active and INACTIVE INGREDIENTS

   The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. 1.1, pg.] same as the RLD.

6. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON

   USP: store in tight containers
   RLD: store at CRT (20-25) (68-77F). See USP. Store Upright and protect from light
   ANDA: Store at 20-25C (68-77F).[See USP CRT]. Store upright protect from light. Do not freeze

7. DISPENSING STATEMENTS COMPARISON

   USP: Not a USP item
   RLD: Respules
   ANDA (*Insert*): plastic unit dose ampules

8. BIOAVAILABILITY/BIOEQUIVALENCE:

Date of Review: 2/26/07 Date of Submission: 20 JUN 2006

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cc:

ANDA: 78-202
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
v:\firmsam\apotex\lets&rev\78202na1labdfsreview
Review

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

/s/

Angela Payne
2/28/2007 11:17:54 AM
MEDICAL OFFICER

John Grace
3/2/2007 06:38:29 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-202

MEDICAL REVIEWS

DIVISION OF PULMONARY AND ALLERGY DRUG PRODUCTS
MEDICAL OFFICER CONSULTATION

Date:	March 13, 2007
To:	Angela Payne Office of Generic Drugs
From:	Peter Starke, MD Associate Director for Safety Division of Pulmonary and Allergy Drug Products (DPADP)
Through:	Badrul Chowdhury, MD, PhD Division Director, DPADP
Subject:	Labeling for generic budesonide inhalation suspension products
Materials Reviewed:	Consult for with marked up labeling for ANDAs 77-519 and 78-202

This consult is a response from the Division of Pulmonary and Allergy Products (DPAP) to the Office of Generic Drugs (OGD) for review of the labeling submitted for generic budesonide inhalation suspension products. Specifically, OGD has asked DPAP to review the labeling with regard to removal of efficacy, safety, and Dosage and Administration information that supports once daily dosing, while retaining information that supports BID dosing. We concur that this can be accomplished without losing important information for patients. Our suggested edits to your marked up labeling are attached.

33 Pages of Draft Labeling have been Withheld as b4 (CCI/TS) immediately following this page

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

/s/

Peter Starke
3/13/2007 03:49:59 PM
MEDICAL OFFICER

Badrul Chowdhury
3/13/2007 04:06:03 PM
MEDICAL OFFICER
I concur

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-202

CHEMISTRY REVIEWS

ANDA 78-202

Budesonide Inhalation Suspension
0.25 mg/2mL and 0.5 mg/2mL

Apotex Inc.

Kenneth J. Furnkranz
Division of Chemistry 1
Office of Generic Drugs

Addendum #1
to
Chemistry Review #4

Chemistry Review Data Sheet

1. ANDA 78-202
2. REVIEW #: 4 (Addendum #1)
3. REVIEW DATE: March 18, 2009
4. REVIEWER: Kenneth J. Furnkranz
5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
ANDA Original Submission	3/31/06
ANDA MINOR Amendment	4/16/07
ANDA MINOR Amendment	2/20/08
Telephone Amendment	6/11/08
Telephone Amendment	6/12/08
ANDA MINOR Amendment	8/27/08
Telephone Amendment	11/14/08

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
ANDA Gratuitous Amendment	1/14/09
Telephone Amendment	3/18/09

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Inc.
Address:	380 Elgin Mills Road East Richmond Hills Ontario, Canada L4C 5H2
U.S. Agent	Apotex Corp., U.S. Agent for Apotex Inc. Kiran Krishnan 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326
Telephone:	(954) 384-3986 (Phone) (954) 349-4233 (FAX)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Budesonide

9. LEGAL BASIS FOR SUBMISSION: Pulmocort Respules®; Budesonide Inhalation Suspension (NDA 20-929), Astra Zeneca. NDA was approved on August 8, 2000.

10. PHARMACOL. CATEGORY: Indicated for the maintenance treatment of Asthma and as prophylactic therapy in children 12 months to 8 years of age.

11. DOSAGE FORM: Inhalation Suspension Code: 138

12. STRENGTH/POTENCY: Inhalation Suspension 0.25 mg/2mL and 0.5 mg/2mL.

13. ROUTE OF ADMINISTRATION: Inhalation Code: 018

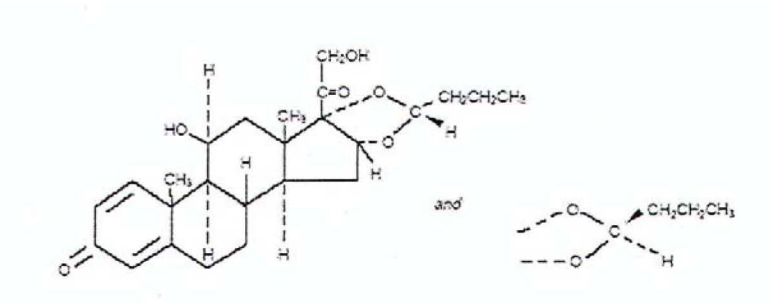
14. Rx/OTC DISPENSED: __X__ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
SPOTS product – Form Completed

X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name:	Budesonide
Chemical name:	(RS)-11β, 16α, 17, 21-tetrahydroxypregna-1,4-diene-3, 20-dione cyclic 16,17-acetal with butyraldehyde. It is provided as a mixture of two epimers (22R and 22S).
Formula:	$C_{25}H_{34}O_6$
Molecular weight:	430.54
CAS registry number(s):	[51333-22-3]



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE1	STATUS2	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	10/29/08	
	III			4			
	III			4			

[1] Action codes for DMF Table:
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)
1 – DMF Reviewed. 2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application 5 – Authority to reference not granted
6 – DMF not available 7 – Other (explain under "Comments")

18.STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	9/4/08	G.Ahrin/N.Sweeney
EES	Acceptable	8/29/08	S. Adams; HFD-322
Methods Validation	Not Necessary	12/13/06	K. Furnkranz
Labeling	Acceptable	12/5/08	A.Payne/J.Grace
Bioequivalence	Acceptable	2/10/09	Ke Ren
EA	Satisfactory	12/13/06	K. Furnkranz
Radiopharmaceutical	N/A	12/13/06	K. Furnkranz

19. ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below: Gratuitous Amendment to a Chemistry Completed Application

STATUS: ANDA is Approvable.

cc: ANDA 78-202
ANDA DUP
DIV FILE
Field Copy

Endorsements:
HFD-625/K.Furnkranz, Review Chemist
HFD-625/R. Randad, Acting Team Leader
HFD-617/E.Chuh, Project Manager

V:\Chemistry Division I\Team 2\TL Folder\ANDA\78202Rev04Addendum1Budesonidekjf.doc

6 Pages have been Withheld as b4 (CCI/TS) immediately following this page

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/s/

Kenneth Furnkranz
3/27/2009 09:53:40 AM
CHEMIST

Esther Chuh
3/30/2009 07:12:42 AM
CHEMIST

Ramnarayan Randad
3/30/2009 09:12:22 AM
CHEMIST

ANDA 78-202

Budesonide Inhalation Suspension
0.25 mg/2mL and 0.5 mg/2mL

Apotex Inc.

Kenneth J. Furnkranz
Division of Chemistry 1
Office of Generic Drugs

Chemistry Review #4

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Chemistry Review Data Sheet

1. ANDA 78-202
2. REVIEW #: 4
3. REVIEW DATE: October 31, 2008
4. REVIEWER: Kenneth J. Furnkranz
5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
ANDA Original Submission	3/31/06
ANDA MINOR Amendment	4/16/07
ANDA MINOR Amendment	2/20/08
Telephone Amendment	6/11/08
Telephone Amendment	6/12/08

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
ANDA MINOR Amendment	8/27/08
Telephone Amendment	11/14/08

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Inc.
Address:	380 Elgin Mills Road East Richmond Hills Ontario, Canada L4C 5H2
U.S. Agent	Apotex Corp., U.S. Agent for Apotex Inc. Kiran Krishnan 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326
Telephone:	(954) 384-3986 (Phone) (954) 349-4233 (FAX)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Budesonide

9. LEGAL BASIS FOR SUBMISSION: Pulmocort Respules®; Budesonide Inhalation Suspension (NDA 20-929), Astra Zeneca. NDA was approved on August 8, 2000.

10. PHARMACOL. CATEGORY: Indicated for the maintenance treatment of Asthma and as prophylactic therapy in children 12 months to 8 years of age.

11. DOSAGE FORM: Inhalation Suspension Code: 138

12. STRENGTH/POTENCY: Inhalation Suspension 0.25 mg/2mL and 0.5 mg/2mL.

13. ROUTE OF ADMINISTRATION: Inhalation Code: 018

14. Rx/OTC DISPENSED: __X__ Rx ___OTC

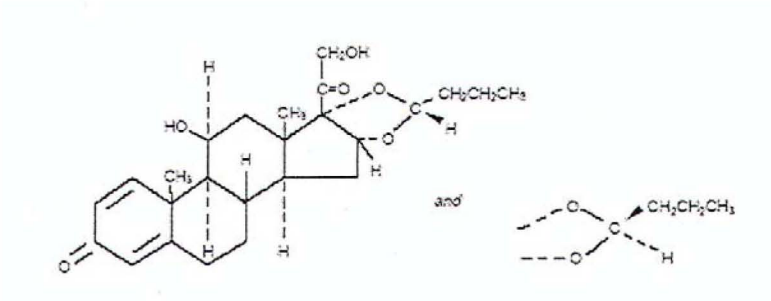
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name: Budesonide
Chemical name: (RS)-11β, 16α, 17, 21-tetrahydroxypregna-1,4-diene-3, 20-dione cyclic 16,17-acetal with butyraldehyde. It is provided as a mixture of two epimers (22R and 22S).
Formula: $C_{25}H_{34}O_6$
Molecular weight: 430.54
CAS registry number(s): [51333-22-3]



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE1	STATUS2	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	10/27/08	
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

18.STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Acceptable	9/4/08	G.Ahrin/N.Sweeney
EES	Acceptable	5/20/08	S. Adams; HFD-322
Methods Validation	Not Necessary	12/13/06	K. Furnkranz
Labeling	Acceptable	7/22/08	A.Payne/J.Grace
Bioequivalence	Pending Review		
EA	Satisfactory	12/13/06	K. Furnkranz
Radiopharmaceutical	N/A	12/13/06	K. Furnkranz

19. ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below: MINOR Amendment

The Chemistry Review for ANDA 78-202

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

CMC is Acceptable. Bioequivalence is Pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable:

- Routine Stability Commitment.
- A commitment that compliance with USP <467> will be re-assessed throughout the product life cycle whenever there are changes to the drug product (e.g., active, pharmaceutical ingredient supplier manufacture, synthesis or USP compendial changes) and will include the implementation of revised controls, if appropriate.
- A commitment to verify the excipient manufacturer's statement concerning (b) (4) in Polysorbate 80 NF ((b) (4) to support USP <467> Compliance. Apotex will submit information supporting verification in a special report within six months of approval.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance: Budesonide is chemically designated as (RS)-11β, 16α, 17, 21-tetrahydroxypregna-1,4-diene-3, 20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is a white or almost white, odorless crystalline solid. Budesonide is practically insoluble in water, (b) (4), sparingly soluble in alcohol. It should be stored in tight containers with protection from humidity and light. Avoid contact with eyes, skin or clothing and avoid breathing dust or mist.

Drug Product: Budesonide Inhalation Suspension 0.25 mg/2mL and 0.5 mg/2mL are indicated for the maintenance treatment of asthma and as a prophylactic therapy in children 12 months to 8 years of age.

B. Description of How the Drug Product is Intended to be Used: Refer to the C.R. #1.

Drug Product: Budesonide Inhalation Suspension is a 2 mL, unit dose vial containing either 0.25 mg or 0.5 mg of Budesonide. The drug product contains sodium chloride ((b) (4)), edetate disodium; EDTA ((b) (4)), Citric Acid (b) (4)

and (b) (4), Polysorbate 80 and Water for Injection, USP.

The drug product is intended to be administered using a nebulizer only under the direction of a physician. The amount distributed to the lungs depends on patient factors, the nebulizer utilized and the compressor performance. Using the PARI LC Jet Plus nebulizer, and the PARI Master® compressor system under in-vitro conditions, the mean delivered dose at the mouthpiece (% nominal dose) was ~17% at a mean flow rate of 5.5 L/min. The mean nebulization time was 5 minutes or less. Budesonide Inhalation Suspension should be administered from Jet Nebulizers at adequate flow rates via face mask or mouthpieces.

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Bronchodilators alone	0.5 mg total daily dose administered twice daily in divided doses	0.5 mg total daily dose
Inhaled Corticosteroids	0.5 mg total daily dose administered twice daily in divided doses	1 mg total daily dose
Oral Corticosteroids	1 mg total daily dose administered as 0.5 mg twice daily	1 mg total daily dose

(b) (4)

C. Basis for Approvability or Not-Approval Recommendation

CMC is Adequate. Bioequivalence Review is Pending.

10 Pages have been Withheld as b4 (CCI/TS) immediately following this page

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/s/

Kenneth Furnkranz
11/17/2008 03:12:45 PM
CHEMIST

Michael Smela
11/17/2008 03:40:36 PM
CHEMIST
The ANDA may be approved when BE is acceptable provided DMF (b) (4) remains adequate, no significant changes are made in USP monographs and no new CMC amendments are submitted.

ANDA 78-202

Budesonide Inhalation Suspension
0.25 mg/2mL and 0.5 mg/2mL

Apotex Inc.

Kenneth J. Furnkranz
Division of Chemistry 1
Office of Generic Drugs

Chemistry Review #3

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B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: 6
II. Summary of Chemistry Assessments 6
A. Description of the Drug Product(s) and Drug Substance(s) 6
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C. Basis for Approvability or Not-Approval Recommendation 7
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Chemistry Assessment 8
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data 8
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 25
R REGIONAL INFORMATION: 25
1.12.14. Environmental Assessment Or Claim Of Categorical Exclusion: 25
1.15.1 Labeling & Package Insert: 25

Chemistry Review Data Sheet

1. ANDA 78-202
2. REVIEW #: 3
3. REVIEW DATE: June 13, 2008
4. REVIEWER: Kenneth J. Furnkranz
5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
ANDA Original Submission	3/31/06
ANDA MINOR Amendment	4/16/07

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
ANDA MINOR Amendment	2/20/08
Telephone Amendment	6/11/08
Telephone Amendment	**6/12/08**

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Inc.
Address:	380 Elgin Mills Road East Richmond Hills Ontario, Canada L4C 5H2
U.S. Agent	Apotex Corp., U.S. Agent for Apotex Inc. Kiran Krishnan 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326
Telephone:	(954) 384-3986 (Phone) (954) 349-4233 (FAX)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Budesonide

9. LEGAL BASIS FOR SUBMISSION: Pulmocort Respules®; Budesonide Inhalation Suspension (NDA 20-929), Astra Zeneca. NDA was approved on August 8, 2000.

10. PHARMACOL. CATEGORY: Indicated for the maintenance treatment of Asthma and as prophylactic therapy in children 12 months to 8 years of age.

11. DOSAGE FORM: Inhalation Suspension Code: 138

12. STRENGTH/POTENCY: Inhalation Suspension 0.25 mg/2mL and 0.5 mg/2mL.

13. ROUTE OF ADMINISTRATION: Inhalation Code: 018

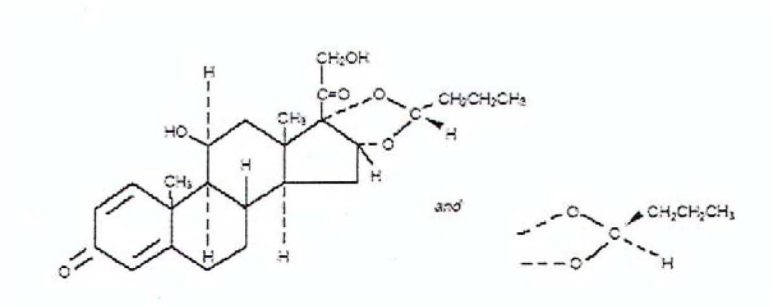
14. Rx/OTC DISPENSED: __X__ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
SPOTS product – Form Completed

X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name:	Budesonide
Chemical name:	(RS)-11β, 16α, 17, 21-tetrahydroxypregna-1,4-diene-3, 20-dione cyclic 16,17-acetal with butyraldehyde. It is provided as a mixture of two epimers (22R and 22S).
Formula:	$C_{25}H_{34}O_6$
Molecular weight:	430.54
CAS registry number(s):	[51333-22-3]



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE1	STATUS2	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II		(b) (4)	1	Adequate	7/15/08	
	III			4			
	III			4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18.STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Acceptable	5/20/08	S. Adams; HFD-322
Methods Validation	Not Necessary	12/13/06	K. Furnkranz
Labeling	Pending		
Bioequivalence	Deficient	7/7/08	B.Li/M.Makary/B.Davit
EA	Satisfactory	12/13/06	K. Furnkranz
Radiopharmaceutical	N/A	12/13/06	K. Furnkranz

19. ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below: MINOR Amendment

The Chemistry Review for ANDA 78-202

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

NA (Minor). Bioequivalence is Deficient. Microbiological and Labeling Review are Pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: None at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance: Budesonide is chemically designated as (RS)-11β, 16α, 17, 21-tetrahydroxypregna-1,4-diene-3, 20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is a white or almost white, odorless crystalline solid. Budesonide is practically insoluble in water, (b) (4), sparingly soluble in alcohol. It should be stored in tight containers with protection from humidity and light. Avoid contact with eyes, skin or clothing and avoid breathing dust or mist.

Drug Product: Budesonide Inhalation Suspension 0.25 mg/2mL and 0.5 mg/2mL are indicated for the maintenance treatment of asthma and as a prophylactic therapy in children 12 months to 8 years of age.

B. Description of How the Drug Product is Intended to be Used: Refer to the C.R. #1.

Drug Product: Budesonide Inhalation Suspension is a 2 mL, unit dose vial containing either 0.25 mg or 0.5 mg of Budesonide. The drug product contains sodium chloride (b) (4) edetate disodium; EDTA (b) (4) Citric Acid (b) (4) and (b) (4), Polysorbate 80 and Water for Injection, USP.

The drug product is intended to be administered using a nebulizer only under the direction of a physician. The amount distributed to the lungs depends on patient factors, the nebulizer utilized and the compressor performance. Using the PARI LC Jet Plus nebulizer, and the PARI Master® compressor system under in-vitro conditions, the mean delivered dose at the mouthpiece (% nominal dose) was ~17% at a mean flow rate of 5.5 L/min. The mean nebulization time was 5 minutes or less. Budesonide Inhalation Suspension should be administered from Jet Nebulizers at adequate flow rates via face mask or mouthpieces.

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Bronchodilators alone	0.5 mg total daily dose administered twice daily in divided doses	0.5 mg total daily dose
Inhaled Corticosteroids	0.5 mg total daily dose administered twice daily in divided doses	1 mg total daily dose
Oral Corticosteroids	1 mg total daily dose administered as 0.5 mg twice daily	1 mg total daily dose

(b) (4)

C. Basis for Approvability or Not-Approval Recommendation

NA (Minor).

cc: ANDA 78-202
ANDA Duplicate
DIV FILE
Field Copy

Endorsement Block:
HFD-625/K.Furnkranz, Review Chemist
HFD-625/M.Smela, Team Leader
HFD-617/E.Chuh, Project Manager
V:\Chemistry Division I\Team 2\ TL Folder\Drafts\78202R03budesonidekjf.doc
F/T by:

TYPE OF LETTER: NA (Minor). Bioequivalence is Deficient. Microbiological Review is Pending.

19 Pages have been Withheld as b4 (CCI/TS) immediately following this page

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

/s/

Eugene Schaefer
7/18/2008 11:18:54 AM
CHEMIST
I am signing this review for Kenneth J. Furnkranz,
who is the author.

Esther Chuh
7/29/2008 07:13:08 AM
CSO

Michael Smela
7/29/2008 09:23:08 AM
CHEMIST

ANDA 78-202

Budesonide Inhalation Suspension
0.25 mg/2mL and 0.5 mg/2mL

Apotex Inc.

Kenneth J. Furnkranz
Division of Chemistry 1
Office of Generic Drugs

Chemistry Review #2

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1.13.14 Environmental Assessment Or Claim Of Categorical Exclusion: 29
1.15.1 Labeling & Package Insert: 29
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Endorsement Block: 35

Chemistry Review Data Sheet

1. ANDA 78-202
2. REVIEW #: 2
3. REVIEW DATE: June 29, 2007
4. REVIEWER: Kenneth J. Furnkranz
5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date
ANDA Original Submission	3/31/06

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
ANDA Gratuitous Amendment (Comparability Protocol for new Filling Line)*	2/21/07
ANDA MINOR Amendment	4/16/07

* - to be reviewed by Microbiological Review Team; See Sect 3.2.P.3.3.

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Inc.
Address:	380 Elgin Mills Road East Richmond Hills Ontario, Canada L4C 5H2
U.S. Agent	Apotex Corp., U.S. Agent for Apotex Inc. Kiran Krishnan 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326
Telephone:	(954) 384-3986 (Phone) (954) 349-4233 (FAX)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Budesonide

9. LEGAL BASIS FOR SUBMISSION: Pulmocort Respules®; Budesonide Inhalation Suspension (NDA 20-929), Astra Zeneca. NDA was approved on August 8, 2000.

10. PHARMACOL. CATEGORY: Indicated for the maintenance treatment of Asthma and as prophylactic therapy in children 12 months to 8 years of age.

11. DOSAGE FORM: Inhalation Suspension Code: 138

12. STRENGTH/POTENCY: Inhalation Suspension 0.25 mg/2mL and 0.5 mg/2mL.

13. ROUTE OF ADMINISTRATION: Inhalation Code: 018

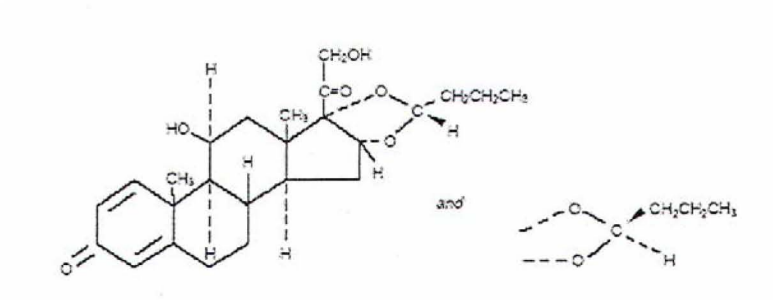
14. Rx/OTC DISPENSED: __X__ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
SPOTS product – Form Completed

X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name:	Budesonide
Chemical name:	(RS)-11β, 16α, 17, 21-tetrahydroxypregna-1,4-diene-3, 20-dione cyclic 16,17-acetal with butyraldehyde. It is provided as a mixture of two epimers (22R and 22S).
Formula:	$C_{25}H_{34}O_6$
Molecular weight:	430.54
CAS registry number(s):	[51333-22-3]



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF # (b) (4)	TYPE	HOLDER	ITEM REFERENCED (b) (4)	CODE[1]	STATUS2	DATE REVIEW COMPLETED	COMMENT
	II			1	**Inadequate**	~6/29/07	
	III			4	Adequate		
	III			4	Adequate		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18.STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Withhold	2/14/07	S. Adams; HFD-322
Methods Validation	Not Necessary	12/13/06	K. Furnkranz
Labeling	Deficient	3/2/07	J.Grace
Bioequivalence (In-Vitro):	Deficient	4/26/07	B.Davit
Bioequivalence (In-Vivo):	Pending		
EA	Satisfactory	12/13/06	K. Furnkranz
Radiopharmaceutical	N/A	12/13/06	K. Furnkranz

19. ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below: MINOR Amendment

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

The Chemistry Review for ANDA 78-202

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

Not Approvable due to minor deficiencies in drug substance, drug product and stability.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: None at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance: Budesonide is chemically designated as (RS)-11β, 16α, 17, 21-tetrahydroxypregna-1,4-diene-3, 20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is a white or almost white, odorless crystalline solid. Budesonide is practically insoluble in water, (b) (4), sparingly soluble in alcohol. It should be stored in tight containers with protection from humidity and light. Avoid contact with eyes, skin or clothing and avoid breathing dust or mist.

Drug Product: Budesonide Inhalation Suspension 0.25 mg/2mL and 0.5 mg/2mL are indicated for the maintenance treatment of asthma and as a prophylactic therapy in children 12 months to 8 years of age.

B. Description of How the Drug Product is Intended to be Used: Refer to the C.R. #1.

Drug Product: Budesonide Inhalation Suspension is a 2 mL, unit dose vial containing either 0.25 mg or 0.5 mg of Budesonide. The drug product contains sodium chloride (b) (4) edetate disodium; EDTA (b) (4) Citric Acid (b) (4) and (b) (4), Polysorbate 80 and Water for Injection, USP.

The drug product is intended to be administered using a nebulizer only under the direction of a physician. The amount distributed to the lungs depends on patient factors, the nebulizer utilized and the compressor performance. Using the PARI LC Jet Plus nebulizer, and the PARI Master® compressor system under in-vitro conditions, the mean delivered dose at the mouthpiece (% nominal dose) was ~17% at a mean flow rate of 5.5 L/min. The mean nebulization time was 5 minutes or less. Budesonide Inhalation Suspension should be administered from Jet Nebulizers at adequate flow rates via face mask or mouthpieces.

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Bronchodilators alone	0.5 mg total daily dose administered twice daily in divided doses	0.5 mg total daily dose
Inhaled Corticosteroids	0.5 mg total daily dose administered twice daily in divided doses	1 mg total daily dose
Oral Corticosteroids	1 mg total daily dose administered as 0.5 mg twice daily	1 mg total daily dose

(b) (4)

C. Basis for Approvability or Not-Approval Recommendation

Not Approvable due to minor deficiencies in drug substance, drug product and stability

cc: ANDA 78-202
ANDA Duplicate
DIV FILE
Field Copy

Endorsement Block:
HFD-625/K.Furnkranz, Review Chemist
HFD-625/M.Smela, Team Leader
HFD-617/S.Eng, Project Manager
V:\Chemistry Division I\Team 2\ TL Folder\Drafts\78202R02budesonidekjf.doc
F/T by:

TYPE OF LETTER: NOT APPROVABLE – MINOR Amendment

27 Pages have been Withheld as b4 (CCI/TS) immediately following this page

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/s/

Kenneth Furnkranz
7/25/2007 05:00:46 PM
CHEMIST

Esther Chuh
7/26/2007 05:05:25 PM
CSO

Michael Smela
7/27/2007 01:36:17 PM
CHEMIST

ANDA 78-202

Budesonide Inhalation Suspension
0.25 mg/2mL and 0.5 mg/2mL

Apotex Inc.

Kenneth J. Furnkranz
Division of Chemistry 1
Office of Generic Drugs

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B. Description of How the Drug Product is Intended to be Used 6
C. Basis for Approvability or Not-Approval Recommendation 7
Chemistry Assessment 8
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data 8
The drug product is manufactured by: 16
II. Review Of Common Technical Document-Quality (Ctd-Q) Module 1 37
1.13.14 Environmental Assessment Or Claim Of Categorical Exclusion: 37
1.15.1 Labeling & Package Insert: 38
R REGIONAL INFORMATION 37
Endorsement Block: 43

Chemistry Review Data Sheet

1. ANDA 78-202
2. REVIEW #: 1
3. REVIEW DATE: December 13, 2006
4. REVIEWER: Kenneth J. Furnkranz
5. PREVIOUS DOCUMENTS: N/A

Previous Documents	Document Date

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
ANDA Original Submission	3/31/06

7. NAME & ADDRESS OF APPLICANT:

Name:	Apotex Inc.
Address:	380 Elgin Mills Road East Richmond Hills Ontario, Canada L4C 5H2
U.S. Agent	Apotex Corp., U.S. Agent for Apotex Inc. John Lay 2400 N. Commerce Parkway, Suite 400 Weston, FL 33326
Telephone:	(954) 349-4200 (Phone) (954) 384-3987 (FAX)

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Budesonide

9. LEGAL BASIS FOR SUBMISSION: Pulmocort Respules®; Budesonide Inhalation Suspension (NDA 20-929), Astra Zeneca. NDA was approved on August 8, 2000.

10. PHARMACOL. CATEGORY: Indicated for the maintenance treatment of Asthma and as prophylactic therapy in children 12 months to 8 years of age.

11. DOSAGE FORM: Inhalation Suspension Code: 138

12. STRENGTH/POTENCY: Inhalation Suspension 0.25 mg/2mL and 0.5 mg/2mL.

13. ROUTE OF ADMINISTRATION: Inhalation Code: 018

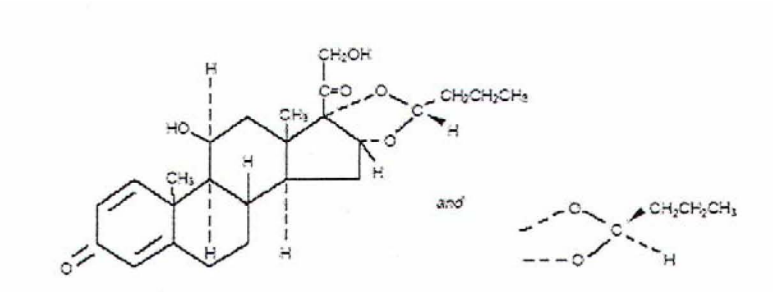
14. Rx/OTC DISPENSED: __X__ Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):
SPOTS product – Form Completed

X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name:	Budesonide
Chemical name:	(RS)-11β, 16α, 17, 21-tetrahydroxypregna-1,4-diene-3, 20-dione cyclic 16,17-acetal with butyraldehyde. It is provided as a mixture of two epimers (22R and 22S).
Formula:	$C_{25}H_{34}O_6$
Molecular weight:	430.54
CAS registry number(s):	[51333-22-3]



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE1	STATUS2	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	**II**		(b) (4)	**1**	**Deficient**	**1/3/07**	
	III			4	Adequate		
	III			4	Adequate		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents: None

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

18.STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	Pending		
EES	Pending		
Methods Validation	Not Necessary		
Labeling	Pending		
Bioequivalence	Pending		
EA	Satisfactory	12/13/06	K. Furnkranz
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW:

The application submission(s) covered by this review was taken in the date order of receipt. __X__ Yes ____ No If no, explain reason(s) below:

The Chemistry Review for ANDA 78-202

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability:

Not Approvable due to minor deficiencies in drug substance, drug product and stability. In addition, the status of the indicated disciplines is as follows:

Labeling: Pending.
Bioequivalence: Pending
EES is Pending
Microbiology is Pending

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable: None at this time.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance: Budesonide is chemically designated as (RS)-11β, 16α, 17, 21-tetrahydroxypregna-1,4-diene-3, 20-dione cyclic 16,17-acetal with butyraldehyde. Budesonide is a white or almost white, odorless crystalline solid. Budesonide is practically insoluble in water, (b) (4), sparingly soluble in alcohol. It should be stored in tight containers with protection from humidity and light. Avoid contact with eyes, skin or clothing and avoid breathing dust or mist.

Drug Product: Budesonide Inhalation Suspension 0.25 mg/2mL and 0.5 mg/2mL are indicated for the maintenance treatment of asthma and as a prophylactic therapy in children 12 months to 8 years of age.

B. Description of How the Drug Product is Intended to be Used

Drug Product: Budesonide Inhalation Suspension is a 2 mL, unit dose vial containing either 0.25 mg or 0.5 mg of Budesonide. The drug product contains sodium chloride (b) (4) edetate disodium; EDTA (b) (4) Citric Acid (b) (4) and (b) (4), Polysorbate 80 and Water for Injection, USP.

The drug product is intended to be administered using a nebulizer only under the direction of a physician. The amount distributed to the lungs depends on patient factors, the nebulizer utilized and the compressor performance. Using the PARI LC Jet

Plus nebulizer, and the PARI Master® compressor system under in-vitro conditions, the mean delivered dose at the mouthpiece (% nominal dose) was ~17% at a mean flow rate of 5.5 L/min. The mean nebulization time was 5 minutes or less. Budesonide Inhalation Suspension should be administered from Jet Nebulizers at adequate flow rates via face mask or mouthpieces.

Previous Therapy	Recommended Starting Dose	Highest Recommended Dose
Bronchodilators alone	0.5 mg total daily dose administered twice daily in divided doses	0.5 mg total daily dose
Inhaled Corticosteroids	0.5 mg total daily dose administered twice daily in divided doses	1 mg total daily dose
Oral Corticosteroids	1 mg total daily dose administered as 0.5 mg twice daily	1 mg total daily dose

(b) (4)

C. Basis for Approvability or Not-Approval Recommendation

Not Approvable due to minor deficiencies in drug substance, drug product and stability

35 Pages have been Withheld as b4 (CCI/TS) immediately following this page

Sincerely yours,

{See appended electronic signature page}

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 78-202
ANDA Duplicate
DIV FILE
Field Copy

Endorsement Block:
HFD-625/K.Furnkranz, Review Chemist
HFD-625/M.Smela, Team Leader
HFD-617/S.Eng, Project Manager
V:\Chemistry Division I\Team 2\ TL Folder\Drafts\78202R01kjf.doc
F/T by:

TYPE OF LETTER: NOT APPROVABLE – MINOR Amendment

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

/s/

Kenneth Furnkranz
1/31/2007 05:54:40 PM
CHEMIST

Simon Eng
2/1/2007 06:41:34 AM
CSO

Michael Smela
2/1/2007 08:53:17 AM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-202

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-202
Drug Product Name	Budesonide Inhalation Suspension
Strength(s)	0.25 mg/2 mL and 0.5 mg/2 mL
Applicant Name	Apotex Inc. 380 Eligin Mills Road East Richmond Hill, Ontario Canada L4C 5H2
Address	Authorized Agent: Apotex Corp. 2400 North Commerce Parkway, Suite 400 Weston, Florida 33326
Applicant's Point of Contact	Kiran Krishnan
Contact's Telephone Number	(954) 384- 3986 or (905) 884-2050
Contact's Fax Number	(954) 349- 4233 or (905) 508-2359
Original Submission Date(s)	March 31, 2006 August 09, 2007 October 01, 2008
Submission Date(s) of Amendment(s) Under Review	January 14, 2009
Reviewer	Ke Ren, Ph.D.
Outcome Decision	**Acceptable**

I. Executive Summary

Apotex Inc. submitted its responses to the deficiency comments made by the Division of Bioequivalence (DBE) in its letter of December 19, 2008. The deficiencies were related to the firm's method validation for the new Cascade Impactor (CI) and the different results observed in the firm's original CI results and the new CI results. The DBE also requested the firm to clarify whether its new batches (Lot # GZ2610 for 0.5 mg/2 mL and Lot # HY9696 for 0.25 mg/2 mL) were manufactured, controlled and released under the same conditions as the previous batches used in the Particle Size Distribution (PSD) in Nebulized Aerosol by Cascade Impaction and Mean Delivery Dose (MDD) at Mouthpiece *in vitro* bioequivalence testing.

In the current amendment, the firm addressed the deficiencies identified by the DBE. The firm submitted method validation report of the new Cascade Impactor (CI). The firm explained the different results obtained from original and new CI were due to the differences in the CI configurations used by different manufacturers and for different models.

The firm also clarified that two new test batches (Batch Nos. GZ2610 for 0.5 mg/2 mL and HY9696 for 0.25 mg/2 mL) were manufactured under the same conditions as the previous batches (Batch Nos. GZ7634, GZ8818, GZ7632 and GZ8410) in terms of formulation, manufacturing process and in-process controls. CMC information for the new test batches

(Batch Nos. GZ2610 and HY9696) is being submitted simultaneously in a CMC amendment to the Division of Chemistry.

Therefore, the Particle Size Distribution (PSD) in Nebulized Aerosol by Cascade Impaction and Mean Delivery Dose (MDD) at Mouthpiece *in vitro* bioequivalence testing are acceptable.

From the DBE point of review, the application is **acceptable** with no deficiencies.

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F. Comments for other OGD Disciplines 9
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III. Background

1. The firm submitted its original application on March 31, 2006. The firm conducted *in vitro* equivalence studies, comparing its test product, Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL, with the RLD product, Pulmicort® Respules, 0.25 mg/2 mL and 0.5 mg/2 mL, respectively, manufactured by AstraZeneca. The firm did not submit its method of the Particle Size Distribution in Nebulized Aerosol test, and the comparative results of the drug polymorph and shape for the low and high strengths of the test and RLD products. In addition, the firm's particle size distribution results measured by two different methods were inconsistent. The *in vitro* studies were found incomplete (DFS 078202 N 000 AC 20-Jun-2006).

2. On August 9, 2007, the firm addressed the deficiencies identified by the DBE. The Particle Size Distribution by Cascade Impaction test was incomplete. In addition, the Mean Delivered Dose (MDD) data for the 0.25 mg/2ml strength product obtained by the firm did not pass the PBE analysis. The deficiency letter was issued to the firm on July 08, 2008 (DFS 078202 N 000 AB 09-Aug-2007). The firm was asked to 1) repeat its Particle Size Distribution by Cascade Impactor test with a sample size of 30 for each test and reference products, and submit the CI data of the individual deposition sites; 2) repeat Mean Delivered Dose test for its 0.25 mg/2 mL strength with a sample size of 30 for each test and reference products.

3. On October 1, 2008, the firm addressed the deficiencies identified by the DBE. The firm repeated Cascade Impaction test and Mean Delivered Dose (MDD) at mouthpiece test with sample size of 30 for each test and reference products. The repeated Particle Size Distribution test was conducted using a new Cascade Impactor. However, the firm did not provide method validation report for new Cascade Impactor and validation data for the two new batches. The deficiency letter was issued to the firm on December 19, 2008 (DFS 078202 N 000 AB 01-Oct-2008). The firm was asked to address the following deficiencies:

   1) *In order to validate the two new test batches (Lot # GZ2610 for 0.5 mg/2 mL, and HY9696 for 0.25 mg/2 mL) used in the Particle Size Distribution (PSD) in Nebulized Aerosol by Cascade Impaction (CI) and Mean Delivery Dose (MDD) at Mouthpiece tests, please submit the following information:*

      - *Statements clarifying whether these batches (Lot # GZ2610 for 0.5 mg/2 mL, and HY9696 for 0.25 mg/2 mL) were manufactured, controlled and released the same way as the previous batches (Lot # GZ7634, GZ8818 for 0.5 mg/2mL, and GZ7632, GZ8410 for 0.25 mg/2mL) used in the earlier in vitro bioequivalence studies, in terms of i) formulation, ii) manufacturing process, and iii) in-process controls.*

      - *Chemistry, Manufacturing and Control (CMC) information for the new batches Lot # GZ2610 and # HY9696. Please contact the Division of Chemistry of the CMC information considered necessary for acceptable validation.*

   2) *The repeated Particle Size Distribution test was conducted using a new Cascade Impactor. Please provide method validation report for this new Cascade Impactor and/or a cross validation study between the original and new Cascade Impactors. Please also explain whether there are any differences between these two Cascade Impactors, whether the test method used with the new Cascade Impactor is the same as the one used with the old Cascade Impactor, and provide comparative setup parameters for both CIs.*

IV. Submission Summary

A. Drug Product Information, PK/PD Information, and Relevant DBE History

See the review of the original submission: DFS 078202 N 000 AC 20-Jun-2006
DFS 078202 N 000 AB 09-Aug-2007
DFS 078202 N 000 AB 01-Oct-2008

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	0
Single-dose fed	No	0
Steady-state	No	0
In vitro dissolution	No	0
Waiver requests	No	0
BCS Waivers	No	0
Vasoconstrictor Studies	No	0
Clinical Endpoints	No	0
Failed Studies	No	0
Amendments	Yes	1

C. Review of Submission

Following are the DBE's previous deficiency comments, the firm's current responses, and the reviewer's current comments:

Deficiency 1: *To validate the two new test batches (Lot # GZ2610 for 0.5 mg/2 mL, and HY9696 for 0.25 mg/2 mL) used in your Particle Size Distribution (PSD) in Nebulized Aerosol by Cascade Impaction (CI) and Mean Delivery Dose (MDD) at Mouthpiece tests, please submit the following information:*

- *Statements clarifying whether these batches (Lot # GZ2610 for 0.5 mg/2 mL, and HY9696 for 0.25 mg/2 mL) were manufactured, controlled and released the same way as the previous batches (Lot # GZ7634, GZ8818 for 0.5 mg/2mL, and GZ7632, GZ8410 for 0.25 mg/2mL) used in the earlier in vitro bioequivalence studies, in terms of i) formulation, ii) manufacturing process, and iii) in-process controls.*

Firm's Response*: Your comment is noted. We confirm that the two new test batches Batch Nos. GZ2610 (0.5 mg/2 mL) and HY9696 (0.25 mg/2 mL) were executed the same way as the previous batches (Batches Nos.GZ7634, GZ8818, GZ7632 and GZ8410) in terms of formulation, manufacturing process and in-process controls.*

A corresponding CMC amendment is being submitted simultaneously with this Bioequivalence amendment to verify the CMC information relating to these two new test batches.

- *Chemistry, Manufacturing and Control (CMC) information for the new batches Lot # GZ2610 and # HY9696. Please contact the Division of Chemistry of the CMC information considered necessary for acceptable validation.*

Firm's Response*: As noted above, the relevant information pertaining to the new batches, Batch Nos. GZ2610 and HY9696, is being submitted simultaneously in a CMC amendment to the Division of Chemistry.*

Reviewer's Comments:

- On October 1, 2008 amendment submission, the firm conducted the Mean Delivered Dose at mouthpiece (MDD) testing on three batches of test and reference products for 0.25 mg/2 mL strength. Both the MDD and Mean Delivered Time at mouthpiece (MDT) for 0.25 mg/2 mL strength product passed the PBE analysis. However, the MDD at mouthpiece test is incomplete due to lack of relevant CMC information of the new batches added in this study. In the current submission, the firm provided the relevant CMC information and clarified that two new test batches were executed under the same conditions as the previous batches in terms of formulation, manufacturing process and in-process controls. Therefore, the MDD at mouthpiece test is acceptable.

- The firm also submitted the CMC information for the new test batches (Batch Nos. GZ2610 and HY9696) in a CMC amendment to the Division of Chemistry.

- From Division of Bioequivalence' point of view; the firm's response to Deficiency #1 is **acceptable.**

Deficiency 2: *Your repeated Particle Size Distribution test was conducted using a new Cascade Impactor. However, you did not provide method validation report for this new Cascade Impactor and/or a cross validation study between the original and new Cascade Impactors. Please submit this information. Please explain whether there are any differences between these two Cascade Impactors, whether the test method used with the new Cascade Impactor is the same as the one used with the old Cascade Impactor, and provide comparative setup parameters for both CIs.*

Firm's Response*: Your comments are noted. Test method PD-102 is used for both the old and new Cascade Impactors and there have been no changes to the set-up parameters. The test method has been updated from issue 3 to issue 4 to include the compressor names in the equipment section, as such, a copy of updated method PD-102 is provided in section 5.3.1.2. Method validation was conducted with the new Cascade Impactor and the report has been provided in section 5.3.1.2. Please see Table 1 below for a description of the two Cascade Impactors:*

Table 1 - Cascade Impactors used for testing Particle Size Distribution

Unit No.	Old Cascade Impactor	New Cascade Impactor
Company	(b) (4) [redacted]	(b) (4) [redacted]
Model		
Date purchased	1994	2007

The number of holes and the diameter of the holes are similar in each company's Cascade Impcator; however the ring pattern dimensions are different. All concentric rings on the old Cascade Impactor stages are smaller than those on the new cascade Impactor. These differences, combined with the age of the instruments, would mean that the results of the old and new Cascade Impactors can not be compared with each other.

As such, Apotex Inc. retested the original test batches using the new Cascade Impactor along with additional batches as requested by the Agency. As the originally tested RLD batches had expired, new RLD batches were tested on the new Cascade Impactor. The use of the new Cascade Impactor for the particle size distribution test provides for an accurate comparison of the results between the test and reference batches.

Reviewer's Comments:

- The firm provided the method PD-102 and method validation documentation for the new Cascade Impactor. The aerodynamic particle size distribution was determined using (b) (4) Cascade Impactor and Pari LC Plus Nebulizer (Method PD-102). HPLC was used for sample analysis. Cascade impaction performed on the product has been done by analyzing the amount of drug deposited on various stages of the impactor.

- Method was validated for repeatability and intermediate precision. The validation results are shown as follows:

Repeatability: The reproducibility of the method was determined by analyzing 6 sample collections (one ampoule per collection) into the new Cascade Impactor using Pari LC Plus Nebulizer. Budesonide Inhalation Suspension (0.125 mg/mL for GZ8410 and 0.25 mg/mL for GZ8818) was used for the test. The range of coefficient of variation for the sum of Material Balance is (b) (4)%.

Table 1 Repeatability

Summary Results of Six Sample Collections_Lot GZ8818 (0.25mg/mL)

Sample Number	MMAD (um)	GSD	% up to (b) (4)	% up to (b) (4)	Material balance (100*C/D)	Respirable Fraction (R/A)	Fine Particle Dose (ug) R/N	Delivered from Mouthpiece (100*A/C)
1	(b) (4)							
2								
3								
4								
5								
6								
Avg (GM)								
RSD,% (GM)	5.55	0.94	3.57	1.03	4.80	2.77	4.73	1.61

Summary Results of Six Sample Collections_Lot GZ8410 (0.125mg/mL)

Sample Number	MMAD (um)	GSD	% up to (b) (4)	% up to (b) (4)	Material balance (100*C/D)	Respirable Fraction (R/A)	Fine Particle Dose (ug) R/N	Delivered from Mouthpiece (100*A/C) (b) (4)
1								
2								
3								
4								
5								
6								
Avg(GM)								
RSD,% (GM)	**5.7**	**3.4**	**4.5**	**2.0**	**0.7**	**4.1**	**2.1**	**3.1**

Intermediate Precision: The MMAD, GSD and material balance for each sample collection were determined. The difference between two-chemist results is less than 10%.

Table 2. Difference Between Two-Chemist Restlts__0.125mg/mL (GZ8410)

Sample Number	Chemist	HPLC#	Cascade#	Column S/N	Nebulizer #	MMAD (um)	GSD	% up to	% up to (b) (4)	Material balance (100*C/D)	Respirable Fraction (R/A)	Fine Particle Dose (ug) R/N	Delivered from Mouthpiece (100*A/C) (b) (4)
1													
2													
3	GM	100	4	T42491R02	7								
4													
5													
6													
Avg(GM)													
RSD,% (GM)						**5.7**	**3.4**	**4.5**	**2.0**	**0.7**	**4.1**	**2.1**	**3.1**
1													(b) (4)
2													
3	JWei	108	5	T43081R09	6								
4													
5													
6													
Avg (JWei)													
RSD,% (JWei)						**6.4**	**1.4**	**4.0**	**1.5**	**1.5**	**3.5**	**1.8**	**1.5**
Difference,% (Two Chemists)						4.5	1.8	3.2	1.4	1.7	2.9	1.7	0.3

Table 3. Difference Between Two-Chemist Restlts__0.25mg/mL (GZ8818)

Sample Number	Chemist	HPLC#	Cascade#	Column S/N	Nebulizer #	MMAD (um)	GSD	% up to	% up to (b) (4)	Material balance (100*C/D)	Respirable Fraction (R/A)	Fine Particle Dose (ug) R/N	Delivered from Mouthpiece (100*A/C) (b) (4)
1													
2													
3	GM	100	4	T42491R02	7								
4													
5													
6													
Avg (GM)													
RSD,% (GM)						5.55	0.94	3.57	1.03	4.80	2.77	4.73	1.61
1													(b) (4)
2													
3	JWei	108	5	T43081R09	6								
4													
5													
6													
Avg (JWei)													
RSD,% (JWei)						3.69	1.23	2.59	0.81	0.77	1.66	1.95	2.57
Difference,%(Two Chemists)						8.0	2.3	5.7	1.9	7.2	6.3	5.4	9.9

- The firm's validation report for the new Cascade Impactor is acceptable.

- Per the firm, the old and new Cascade Impactors were manufactured from different companies, and their configurations are different (e.g., all concentric rings on the old Cascade Impactor stages are smaller than those on the new cascade Impactor). Such differences in configuration could possibly cause different results.

- The test of reference product performance was compared using the same CI (either old or new) and both CIs are validated. In the previous DBE review, the firm's CI results were found acceptable (please refer to DFS 078202 N 000 AB 01-Oct-2008 for extensive discussion of the firm's CI results).

- The firm's response to Deficiency #2 is **acceptable.** The CI testing is acceptable.

D. Deficiency Comments

None.

E. Recommendations

The *in vitro* bioequivalence testing conducted by Apotex Inc. comparing its test product, Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL, with the reference product, Pulmicort® Respules, 0.25 mg/2 mL and 0.5 mg/2 mL, respectively, manufactured by AstraZeneca, is acceptable with no deficiencies.

The Division of Bioequivalence deems the test product, Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL, manufactured by Apotex Inc, to be bioequivalent to the reference listed product, Pulmicort® Respules, 0.25 mg/2 mL and 0.5 mg/2 mL, respectively, manufactured by AstraZeneca.

F. Comments for other OGD Disciplines

Discipline	Comment
	None

BIOEQUIVALENCE COMMENTS TO BE PROVED TO THE APPLICANT

ANDA: 78-202

APPLICANT: Apotex Inc.

DRUG PRODUCT: Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL

The Division of Bioequivalence has completed the review of your application as reported on the cover page and has no further questions at this time.

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

G. Outcome Page

ANDA: 78-202

Reviewer: Ren, Ke

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description: Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL, Apotex Inc.

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
7466	1/14/2009	Other	Study Amendment	1	1
				Bean Total:	1

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

/s/

Ke Ren
2/9/2009 05:44:52 PM
BIOPHARMACEUTICS

Bing Li
2/9/2009 06:06:16 PM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
2/10/2009 05:15:45 PM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of Bioequivalence I

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-202
Drug Product Name	Budesonide Inhalation Suspension
Strength(s)	0.25 mg/2 mL and 0.5 mg/2 mL
Applicant Name	Apotex Inc. 380 Eligin Mills Road East Richmond Hill, Ontario Canada L4C 5H2
Address	Authorized Agent: Apotex Corp. 2400 North Commerce Parkway, Suite 400 Weston, Florida 33326
Applicant's Point of Contact	Kiran Krishnan
Contact's Telephone Number	(954) 384- 3986
Contact's Fax Number	(954) 349- 4233
Original Submission Date(s)	March 31, 2006
Submission Date(s) of Amendment(s) Under Review	October 01, 2008
Reviewer	Ke Ren, Ph.D.
Outcome Decision	**INCOMPLETE**

I. Executive Summary

Apotex Inc. submitted its responses to the deficiency comments made by the Division of Bioequivalence (DBE) in its letter of July 08, 2008. The deficiencies were related its Particle Size Distribution (PSD) by Cascade Impactor (CI) test for both strengths and Mean Delivery Dose test for 0.25 mg/2 mL strength. In the current amendment, the firm has addressed these deficiencies.

The repeated Cascade Impaction test and Mean Delivered Dose (MDD) at mouthpiece test were conducted on three batches of test and reference products for both strengths. The firm added two new batches (Lot # GZ2610 for 0.5 mg/2 mL and Lot # HY9696 for 0.25 mg/2 mL) to increase the sample size to 30 samples for test and reference products each (initially, the firm used two batches of 20 samples of test and reference products each) . To validate these new batches, the firm is requested to submit the Chemistry, Manufacturing and Control information for the new batches, and to assure the DBE that these new batches were manufactured, controlled and released under the same conditions as the batches used in the previous *in vitro* bioequivalence study.

The firm used a new cascade impactor for its repeated CI test, which resulted different results as compared to the results obtained with the old cascade impactor. The firm did not submit method validation report of the new cascade impactor or a cross validation of the old cascade impactor and the new one. The firm is requested to submit this information. The firm is also requested to provide explanation for the different results obtained from

these two cascade impactors. Therefore, the Particle Size Distribution by Cascade Impaction test is **incomplete**.

The application is **incomplete**.

II. Table of Contents

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III. Background

1. The firm submitted its original application on March 31, 2006. The firm conducted *in vitro* equivalence studies, comparing its test product, Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL, with the RLD product, Pulmicort® Respules, 0.25 mg/2 mL and 0.5 mg/2 mL, respectively, manufactured by AstraZeneca. The firm did not submit its method of the Particle Size Distribution in Nebulized Aerosol test, and the comparative results of the drug polymorph and shape between the low strength product and high strength product. In addition, the firm's particle size distribution results measured by two different methods were inconsistent. The *in vitro* studies were found incomplete (DFS 078202 N 000 AC 20-Jun-2006).

2. On August 9, 2007, the firm addressed the deficiencies identified by the DBE. The Particle Size Distribution by Cascade Impaction test was incomplete. In addition, the Mean Delivered Dose (MDD) data for the 0.25 mg/2ml strength product obtained by the firm did not pass the PBE analysis. The deficiency letter was issued to the firm on July 08, 2008 (DFS 078202 N 000 AB 09-Aug-2007). The firm was asked to address the following deficiencies:
   - Repeat its Particle Size Distribution by Cascade Impactor test with a sample size of 30 for each test and reference products, and submit the CI data of the individual deposition sites.
   - Repeat Mean Delivered Dose test for its 0.25 mg/2 mL strength with a sample size of 30 for each test and reference products.

3. In the current amendment, the firm submitted its Particle Size Distribution by Cascade Impactor test and MDD test with a sample size of 30 for each test and reference products.

IV. Submission Summary

A. Drug Product Information, PK/PD Information, and Relevant DBE History

See the review of the original submission: DFS 078202 N 000 AC 20-Jun-2006
DFS 078202 N 000 AB 09-Aug-2007

B. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	0
Single-dose fed	No	0
Steady-state	No	0
In vitro dissolution	No	0
Waiver requests	No	0
BCS Waivers	No	0
Vasoconstrictor Studies	No	0
Clinical Endpoints	No	0
Failed Studies	No	0
Amendments	Yes	1

C. Review of Submission

Following are the DBE's previous deficiency comments, the firm's current responses, and the reviewer's current comments:

Deficiency 1: *Your particle size distribution (PSD) measured by Cascade Impaction (CI) test is incomplete. The DBE currently evaluates the test data using at least 30 samples for both test and reference products (3 batches from each product, 10 samples from each batch). Please repeat this test, and increase the sample size from 20 samples to 30 samples for both test and reference products (3 batches from each product, 10 samples from each batch). The DBE currently also evaluate the data at each individual deposition site. Please submit the CI data for both the original and repeat PSD by CI test results for each individual deposition site (i.e., nebulizer assembly, the induction port and inlet cone, so to filter), and the mass balance data. Please also submit the data in electronic format using similar data template specified by the DBE in the April 27, 2007 letter.*

Firm's Response*: Base on your comments, the particle size distribution (PSD) by Cascade Impaction has been repeated for both the test and reference products using 3 batches from each product (10 samples per batch).*

Reference Batches used for the repeat PSD testing
*Three **new batches** of reference products for each of the two strengths, 0.25 mg/2 ml and 0.5 mg/2 ml strengths, have been utilized for the PSD testing as the original reference product batches used for the PSD testing provided in the original ANDA submission have expired. See Table 1 below for information on reference product used.*

Table 1

Strength	Original Reference Product Lot Number	Expiry Date	Repeat Reference Product Lot Number	Expiry Date
0.5 mg/2mL	LF0054	October 2006	PF0079	April 2010
	LM0080	September 2007	PH0020	May 2010
			PC0126	March 2010
0.25 mg/2mL	LA1801	July 2006	NN0188	November 2009
	LM0022	September 2007	KC156	March 2010
			KC158	March 2010

Test Batches used for the repeat PSD testing
Please refer to Table 2 below for the test batches used for the repeat PSD testing:

Table 2

Strength	Test Product Lot Number	Origin
0.5 mg/2mL	GZ7634	Used for original testing in the ANDA and repeat testing in this amendment
	GZ8818	
	GZ2610	Used as the third batch for repeat testing, as requested in this amendment
0.25 mg/2mL	GZ7632	Used for original testing in the ANDA and repeat testing in this amendment
	GZ8410	
	HY9696	Additional batch manufactured to increase the sample size to 30, as requested in this amendment

* Please note that all the above lots were re-tested/tested and meet the current specification.

The certificates of analysis for the above batches are appended to this cover letter.

PSD Data:
Original and repeat PSD data for each individual deposition site (both 0.25 mg/2 ml and 0.5 mg/2 ml) for both test and reference products are summarized in the new table format specified by the DBE and are included along with their respective SAS files for review in section 5.3.1.2, c-III. The following are the list of files provided:

	Strength	File
Original PSD Data	0.25mg/2mL	*pdf:* Table III-A 0.25mg2mL
		*SAS:*Table III-A 0.25mg2mL
	0.5mg/2mL	*pdf:* Table III-B 0.5mg2mL
		*SAS:*Table III-B 0.5mg2mL
Repeat PSD Data	0.25mg/2mL	*pdf:* Table III-A 0.25mg2mL-repeat
		*SAS:*Table III-A 0.25mg2mL-repeat
	0.5mg/2mL	*pdf:* Table III-B 0.5mg2mL-repeat
		*SAS:*Table III-B 0.5mg2mL-repeat

Please note that the repeat PSD testing has been conducted with a new Cascade Impactor as the original Cascade Impactor has been decommissioned. As a result, it will not be meaningful to compare between results of the original and repeat PSD data. However, since the repeat study is comparative and performed under identical conditions for both the test and reference products, our repeat study data does provide a valid comparison between the three lots of test product and the three lots of reference product studied.

We have further evaluated the repeat PSD data by calculating the ratio of geometric means and the population bioequivalence determinations for the test product versus reference product for each deposition site and additional parameters like Mass Median Aerodynamic Diameter (MMAD), Geometric Standard Deviation (GSD), mass balance, the percentage of particle size up to (b) (4)*, respirable fraction, fine particle and dose delivered from mouthpiece. As per USP, these parameters are considered important to evaluate the PSD data for an inhalation drug product. These results are provided in the appended Tables A and B along with their corresponding figure 1 and 2.*

The results show that the ratio of geometric means for the test and the reference products meet the bioequivalence limit (0.9 to 1.11) for all of the key parameters mentioned above. As well, the results show that population bioequivalence is demonstrated for each of the key parameters above. It is evident from these comparisons that some of the individual deposition sites do not meet bioequivalence criteria. However, when the individual lots of reference batches are compared against each other, they too exhibited significant differences at some stages as indicated by a ratio of Geometric Means outside the 0.9-1.11 interval. Data provided in the following tables demonstrates this point:

Table C: Reference product lot nos. KC156 vs. NN0188

Stage (µg)	KC156 (10 samples) Mean	NN0188 (10 samples) Mean	Ratio of Geometric Means	Within limits	Population BE
S0		(b) (4)	1.023	Yes	Not BE
S1			1.042	Yes	Not BE
S2			1.034	Yes	BE
S3			1.010	Yes	BE
S4			0.950	Yes	Not BE
S5			0.891	No	Not BE
S6			0.914	Yes	BE
S7			0.841	No	Not BE
Filter			0.842	No	Not BE
Nebulizer Cup			0.997	Yes	BE
Induction port			1.243	No	Not BE
Amt_A			0.982	Yes	BE
Amt_B			0.971	Yes	BE
Amt_C			0.990	Yes	BE
Amt_D			0.912	Yes	Not BE
Amt_R			0.956	Yes	BE
MMAD (µm)			1.045	Yes	BE
GSD			0.995	Yes	BE
PCT (%) (b) (4)			0.976	Yes	BE
PCT (%) (b) (4)			0.992	Yes	BE
Mass balance (%)	112.73	101.55	1.085	Yes	Not BE
Respirable fraction	0.76	0.78	0.973	Yes	BE
Fine particle (µg)	78.32	81.82	0.956	Yes	BE
Delivered from Mouthpiece (%)	42.54	42.92	0.991	Yes	BE

Table D: Reference product lot nos. KC156 vs. KC158

Stage (µg)	KC156 (10 samples) Mean	KC158 (10 samples) Mean	Ratio of Geometric Means	Within limits	Population BE
S0		(b) (4)	0.972	Yes	Not BE
S1			0.995	Yes	Not BE
S2			1.029	Yes	BE
S3			0.996	Yes	BE
S4			0.947	Yes	Not BE
S5			0.988	Yes	BE
S6			0.949	Yes	BE
S7			1.031	Yes	BE
Filter			0.959	Yes	BE
Nebulizer Cup			1.002	Yes	BE
Induction port			1.136	No	Not BE
Amt_A			0.986	Yes	BE
Amt_B			0.979	Yes	BE
Amt_C			0.995	Yes	BE
Amt_D			0.922	Yes	Not BE
Amt_R			0.978	Yes	BE
MMAD (µm)		(b) (4)	1.005	Yes	BE
GSD (b) (4)			1.000	Yes	BE
PCT (%) (b) (4)		(b) (4)	0.997	Yes	BE
PCT (%) (b) (4)			0.998	Yes	BE
Mass balance (%)	112.73	102.06	1.080	Yes	Not BE
Respirable fraction	0.76	0.76	0.992	Yes	BE
Fine particle (µg)	78.32	80.0	0.978	Yes	BE
Delivered from Mouthpiece (%)	42.54	42.94	0.991	Yes	BE

Table E: Reference product lot nos. KC158 vs. NN0188

Stage (µg)	KC158 (10 samples) Mean	NN0188 (10 samples) Mean	Ratio of Geometric Means	Within limits	Population BE
S0	(b) (4)		1.053	Yes	Not BE
S1			1.047	Yes	Not BE
S2			1.005	Yes	BE
S3			1.014	Yes	BE
S4			1.003	Yes	BE
S5			0.901	Yes	BE
S6			0.964	Yes	Not BE
S7			0.816	No	Not BE
Filter			0.878	No	Not BE
Nebulizer Cup			0.995	Yes	BE
Induction port			1.094	Yes	Not BE
Amt_A			0.995	Yes	BE
Amt_B			0.991	Yes	BE
Amt_C			0.995	Yes	BE
Amt_D			0.990	Yes	BE
Amt_R			0.978	Yes	BE
MMAD (µm)	(b) (4)		1.040	Yes	BE
GSD			0.995	Yes	BE
PCT (%) (b) (4)		(b) (4)	0.979	Yes	BE
PCT (%) (b) (4)			0.994	Yes	BE
Mass balance (%)	102.06	101.55	1.005	Yes	BE
Respirable fraction	0.76	0.78	0.981	Yes	BE
Fine particle (µg)	80.0	81.82	0.978	Yes	BE
Delivered from Mouthpiece (%)	42.94	42.92	1.000	Yes	BE

Table F: Reference product lot nos. PH0020 vs. PF0079

Stage (µg)	PH0020 (10 samples) Mean	PF0079 (10 samples) Mean	Ratio of Geometric Means	Within limits	Population BE
S0	(b) (4)		0.983	Yes	Not BE
S1			0.998	Yes	Not BE
S2			1.046	Yes	BE
S3			1.179	No	Not BE
S4			1.158	No	Not BE
S5			0.909	Yes	Not BE
S6			0.967	Yes	Not BE
S7			1.113	No	BE
Filter			1.300	No	Not BE
Nebulizer Cup			1.010	Yes	BE
Induction port			1.032	Yes	BE
Amt_A			1.071	Yes	Not BE
Amt_B			1.084	Yes	Not BE
Amt_C			1.041	Yes	BE
Amt_D			0.977	Yes	BE
Amt_R	(b) (4)		1.111	No	Not BE
MMAD (µm)			0.979	Yes	BE
GSD			0.997	Yes	BE
PCT (%) (b) (4)		(b) (4)	1.015	Yes	BE
PCT (%) (b) (4)			1.006	Yes	BE
Mass balance (%)	101.39	95.22	1.065	Yes	BE
Respirable fraction	0.71	0.68	1.041	Yes	BE
Fine particle (µg)	172.80	155.21	1.111	No	Not BE
Delivered from Mouthpiece (%)	49.15	47.69	1.029	Yes	BE

Table G: Reference product lot nos. PC0126 vs. PF0079

Stage (µg)	PC0126 (10 samples) Mean	PF0079 (10 samples) Mean	Ratio of Geometric Means	Within limits	Population BE
S0	(b) (4)		1.004	Yes	Not BE
S1			0.925	Yes	BE
S2			1.057	Yes	BE
S3			1.230	No	Not BE
S4			1.180	No	Not BE
S5			0.985	Yes	BE
S6			0.977	Yes	BE
S7			1.100	Yes	BE
Filter			1.244	No	BE
Nebulizer Cup			0.991	Yes	BE
Induction port			0.976	Yes	BE
Amt_A			1.085	Yes	BE
Amt_B			1.109	Yes	Not BE
Amt_C			1.036	Yes	BE
Amt_D			0.985	Yes	BE
Amt_R			1.147	No	Not BE
MMAD (µm)	(b) (4)		0.973	Yes	BE
GSD			0.987	Yes	BE
PCT (%) (b) (4)		(b) (4)	1.025	Yes	BE
PCT (%) (b) (4)			1.011	Yes	BE
Mass balance (%)	100.14	95.22	1.052	Yes	BE
Respirable fraction	0.72	0.68	1.060	Yes	BE
Fine particle (µg)	178.44	155.21	1.147	No	Not BE
Delivered from Mouthpiece (%)	49.97	47.69	1.047	Yes	BE

The tables are provided as attachment to this cover letter.

Overall, the PSD measured by CI shows comparability of the test and reference products, as bioequivalence criteria for each of the key parameters specified in the USP have been met.

Reviewer's Comments: The firm's response to Deficiency #1 is **incomplete.**

- Six new batches of reference products of 0.25 mg/2 mL and 0.5 mg/2 mL strengths have been used for the Cascade Impaction testing because the original reference product lots have expired.

- The firm repeated the Cascade Impaction test on three batches of test and reference products for both strengths. Two new batches of the test products (Lot # GZ2610 for 0.5 mg/2 mL and Lot # HY9696 for 0.25 mg/2 mL) were used to increase the sample size to 30 samples. The firm submitted the COA for all batches of the test products indicating that all batches met the specifications.

- However, to validate the two new batches of test products (Lot # GZ2610 for 0.5 mg/2 mL and HY9696 for 0.25 mg/2 mL), the firm should submit the Chemistry, Manufacturing and Control information for these two batches. The firm should assure

the DBE that those new batches were manufactured, controlled and release under the same conductions as the original lots used in the previous *in vitro* bioequivalence test. The firm should also submit the batch sizes and manufacturing dates of these two new test products (Lot # GZ2610 and HY9696).

- The repeated PSD test was conducted with a new Cascade Impactor as the original Cascade Impactor has been decommissioned. However, the firm did not provide method validation report for this new Cascade Impactor or a cross-validation study between these two Cascade Impactors. The firm should submit this information. The firm should explain whether there are any differences between these two Cascade Impactors, whether the test method used with the new Cascade Impactor is the same as the one used with the old Cascade Impactor, and the comparative setup parameters of both CIs. The comparison results of MMAD, GSD and MB between original and new Cascade Impactor are summarized in the tables below:

<u>0.25 mg/2 mL:</u>

Products	**Original Cascade Impactor**				**New Cascade Impactor**			
	Batch	**MMAD(um)**	**GSD**	**MB(%)**	**Batch**	**MMAD(um)**	**GSD**	**MB(%)**
Test	GZ7632 GZ8410	(b) (4)			GZ7632 GZ8410 HY9696	(b) (4)		
Reference	LM1801 LM0022	(b) (4)			NN0188 KC156 KC158	(b) (4)		

<u>0.5 mg/2 mL:</u>

Products	**Original Cascade Impactor**				**New Cascade Impactor**			
	Batch	**MMAD(um)**	**GSD**	**MB(%)**	**Batch**	**MMAD(um)**	**GSD**	**MB(%)**
Test	GZ7734 GZ8818	(b) (4)			GZ7634 GZ8818 GZ2610	(b) (4)		
Reference	LF0054 LM0080	(b) (4)			PF0079 PH0020 PC0126	(b) (4)		

It appears that for the key parameters (MMAD, GSD and MB) compared above, there were not significant differences between the data generated from the old and new CIs (except for the MB of one lot reference product (highlighted as bold and yellow, obvious differences were observed).

- The firm also submitted its CI test data on each individual stage and groups the CI results differently. The firm grouped and reported the following parameters:
    - Total Mass of drug delivered from nebulizer (A: C minus Sample Cup);
    - Total Mass of drug found on stages and filter (B: Stage 0 to Filter);

- Total Mass of drug collected (C: Stage 0 to Induction Port + Inlet Cone);
- Total mass of drug found from Stage 2 to Stage 7 and on Filter (R);
- The amount of drug delivered in ug (D)

The comparison between original and new Cascade Impactor for the above grouped parameters are summarized in the tables below:

0.25 mg/2 mL:

Parameters	Products	Original Cascade Impactor	New Cascade Impactor
A (ug)	Test		(b) (4)
	Reference		
B (ug)	Test		
	Reference		
C (ug)	Test		
	Reference		
D (ug)	Test		
	Reference		
R (ug)	Test		
	Reference		

0.5 mg/2 mL:

Parameters	Products	Original Cascade Impactor	New Cascade Impactor
A (ug)	Test		(b) (4)
	Reference		
B (ug)	Test		
	Reference		
C (ug)	Test		
	Reference		
D (ug)	Test		
	Reference		
R (ug)	Test		
	Reference		

For this set of data, significant differences were observed between the data based on the old and new CIs.

- The drug particle and aggregate distribution in nebulized aerosol is the key test to determine whether the *in vivo* BE study could be waived. The firm used (b) (4) Cascade Impactor ((b) (4) to determine the drug particle and aggregate distribution in nebulized aerosol. A typical (b) (4) includes multiple deposition sites (stages 0 through 7, plus filter and other deposition sites), and to date, the FDA has not recommended a statistical method based on **a single metric** for comparison of data obtained at each site.

- The reviewer performed the PBE analysis for each individual deposition site (S0 to filter, the induction port and nebulized cup), mass balance, mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD). Based on the PBE analysis, not all of these parameters pass PBE. The results are summarized in the table below (refer to attachment section for details of PBE analysis).

0.25 mg/2 mL strength: PBE Analysis for each stages of the Cascade Impactor

In Vitro Test	Definition	PBE: Pass or Fail
PSD in nebulized aerosol (Cascade Impactor)	S0	**Fail**
	S1	**Fail**
	S2	**Fail**
	S3	**Pass**
	S4	**Pass**
	S5	**Fail**
	S6	**Fail**
	S7	**Fail**
	Cup	**Pass**
	Port	**Fail**
	Filter	**Fail**
	Mass Balance	**Pass**
	MMAD	**Pass**
	GSD	**Pass**

0.5 mg/2 mL strength: PBE Analysis for each stages of the Cascade Impactor

In Vitro Test	Definition	PBE: Pass or Fail
PSD in nebulized aerosol (Cascade Impactor)	S0	**Pass**
	S1	**Fail**
	S2	**Fail**
	S3	**Pass**
	S4	**Fail**
	S5	**Fail**
	S6	**Fail**
	S7	**Fail**
	Cup	**Pass**
	Port	**Pass**
	Filter	**Fail**
	Mass Balance	**Pass**
	MMAD	**Pass**
	GSD	**Pass**

- The reviewer also performed the PBE analysis for Impactor-Sized Mass (ISM, total drug deposited below the S0 of the cascade impactor) on both strengths, and found that both strengths pass PBE analysis for this parameter.

PBE Analysis for Impactor-sized mass

In Vitro Test	Product strengths	Parameter	PBE: pass or not
PSD in nebulized aerosol (Cascade Impactor	0.25 mg/2 mL	ISM	**Pass**
	0.5 mg/2 mL	ISM	**Pass**

- Furthermore, the reviewer calculated the ratio of the geometric mean of T/R for each individual deposition site (S0 to filter, the induction port and nebulized cup), mass balance, mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD). Based on the ratio of the geometric mean of T/R, not all of these ratio values fall within 90 -111%. The results are summarized in the table below.

0.25 mg/2 mL strength: Geometric mean for each stages of the Cascade Impactor

In Vitro Test	Definition	Ratio of the geometric mean (T/R)	Pass or Fail 90-111%
PSD in nebulized aerosol (Cascade Impactor)	S0	(b) (4)	**Pass**
	S1		**Fail**
	S2		**Fail**
	S3		**Pass**
	S4		**Pass**
	S5		**Fail**
	S6		**Fail**
	S7		**Fail**
	Cup		**Pass**
	Port		**Pass**
	Filter		**Fail**
	Mass Balance		**Pass**
	MMAD		**Pass**
	GSD		**Pass**

0.5 mg/2 mL strength: Geometric mean for each stages of the Cascade Impactor

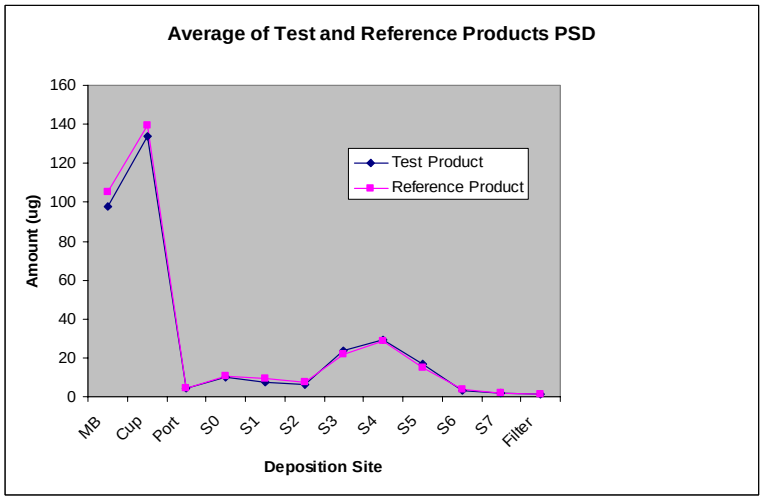
In Vitro Test	Definition	Ratio of the geometric mean (T/R)	Pass or Fail 90-111%
PSD in nebulized	S0	(b) (4)	**Pass**
	S1		**Fail**
	S2		**Fail**
	S3		**Pass**
	S4		**Fail**

aerosol (Cascade Impactor)	S5		(b) (4)		**Fail**
	S6				**Fail**
	S7				**Pass**
	Cup				**Pass**
	Port				**Pass**
	Filter				**Pass**
	Mass Balance				**Pass**
	MMAD				**Pass**
	GSD				**Pass**

- The reviewer composed the following figures which show the comparison of the deposition profile of the test and reference products.

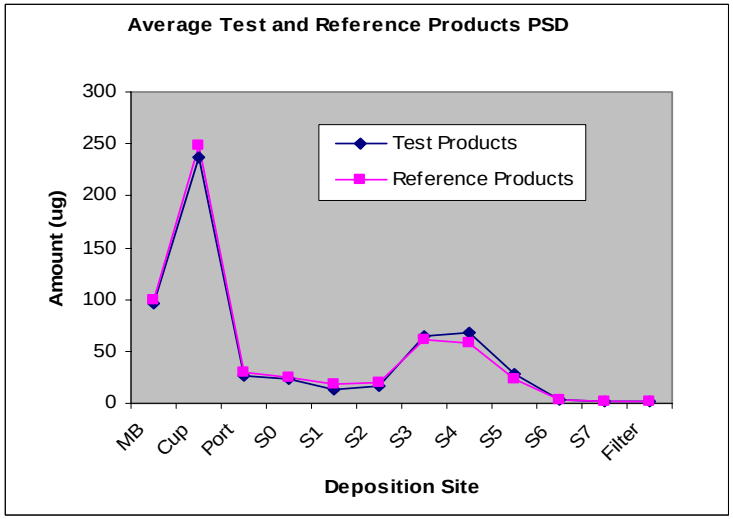
0.25 mg/2 mL strength: Test and Reference Products Deposition Profiles

(b) (4)



0.5 mg/2 mL strength: Test and Reference Products Deposition Profiles

(b) (4)



- Overall, the firm's Cascade Impaction test pass the PBE analysis for all key parameters (e.g., Mass Balance, Impactor-Sized Mass, MMAD and GSD) examined. Although the comparison of the amounts deposited on individual stages did not pass the PBE for certain stages, the firm submitted the justifications indicating that even for two different batches of RLD products, the comparison of the amounts deposited on individual stages fail to pass the PBE for certain stages. At this time, the DBE considered that the PBE analysis and acceptance criteria for the key parameters (e.g., Mass Balance, Impactor-Sized Mass, MMAD and GSD) sufficient for BE evaluation of PSD in Nebulized Aerosol test by Cascade Impaction.

- However, the particle size distribution measured by Cascade Impaction (CI) test is still **incomplete** due to lack of method validation report for the new Cascade Impactor and CMC information for the new batch. The firm's response to Deficiency #1 is **incomplete**.

Deficiency 2: *Your originally submitted Mean Delivered Dose (MDD) at mouthpiece test is incomplete. The MDD test results for the 0.25 mg/2 mL strength product did not meet the population bioequivalence criteria (PBE). For the PBE method and criteria currently used by the Agency to evaluate in vitro testing data, please see the Guidance for Industry: Statistical Information from the June 1999 Draft Guidance and Statistical information for In Vitro Bioequivalence Data (issued April 11, 2003). Please repeat your MDD at mouthpiece test for the 0.25 mg/2 mL strength product, and increase the sample size from 20 samples to 30 samples for both test and reference products (3 batches from each product, 10 samples from each batch). You can measure the MDD test using one of the following two nebulization systems:*

- *Pari-LC-Jet Plus Nebulizer/Pari Master compressor system at the flow rate of 5.5 L/min, as stated in the Control 03-612; or,*
- *Repeat its MDD test using ProNeb Ultra Nebulizer with Pari LC Plus Nebulization at the flow rate of* (b) (4) *L/min, as specified in its method PD-188.*

Please also submit the data for the repeat MDD test in electric format using similar data templates specified by the DBE in the April 27, 2007 letter.

Firm's Response: *As you have requested, the mean delivered dose (MDD) test has been completed using 3 batches (10 samples each) for the 0.25 mg/2 mL strength product. The same test and reference product batches as used for the repeat PSD testing for Point 1) above were used for this MDD test.*

The nebulization system used for the MDD test is the Pari-LC-Jet Plus Nebulizer/PariMaster compressor system with a flow rate of 5.5 L/min as stated on the Control 03-612. In the original test, a flow rate of (b) (4) *L/min was used with the ProNeb Ultra Nebulizer with Pari LC Plus Nebulization. It is noticed that with the higher flow rate nebulizer (5.5 L/min), the nebulization time for both test and reference became shorter.*

The individual sample and summary results of the MDD repeat test (0.25 mg/2 mL) for the both the test and reference products are summarized in the table format specified by DBE. The tablets, in pdf format, are included in section 5.3.1.2, c-II, along with their respective SAS file for review.

The results show that both the delivery dose and the nebulization time of the test product are comparable to those of the reference product when tested under identical conditions.

Reviewer's Comments: The firm's response to Deficiency #2 is **incomplete.**

- The firm used Pari-LC-Jet Plus Nebulizer/Pari Master compressor system at the flow rate of **5.5 L/min** (as stated in the Control 03-612) for its MDD Test on the 0.25 mg/2 mL strength product.

- The firm repeated the MDD testing on three batches of test and reference products for 0.25 mg/2 mL strength.

- The Mean Delivered Dose at mouthpiece for the 0.25 mg/2 mL strength of the test and RLD products ranged 12- 16.36 (% nominal) which is comparable to the 17(% nominal) specified in the RLD product labeling. The Mean Nebulization Time ranged 360- 442 seconds is also considered as comparable to the 300 seconds or less as specified by the RLD labeling.

- The reviewer conducted the PBE analysis for the MDD and Mean Delivery Time (MDT) tests, the results indicated that both the MDD and MDT for 0.25 mg/2 mL strength product passed the PDE analysis.

- However, the Mean Delivered Dose at mouthpiece test is incomplete due to lack of relevant CMC information of the new batches added in this study.

0.25 mg/2 mL strength: PBE Analysis for Mean Delivery Dose

```
In Vitro PBE Analysis - Approximate Confidence Interval
   Using Moment-Based Simplified Parameter Estimates
        For ANDA 78202 Delivered dose: DD

                    I.  Summary

                In Vitro PBE CRITERIA
               MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

                  Linearized Theta P

    Reference-scaled:      Point estimate:   -0.0030
               CI:                -0.0009
                Pass/Fail:          PASS

    Constant-scaled:       Point estimate:   -0.0205
               CI:                -0.0190
                Pass/Fail:          PASS

     Overall Test Outcome:  Pass/Fail:          PASS
```

0.25 mg/2 mL strength: PBE Analysis for Mean Delivery Time

```
In Vitro PBE Analysis - Approximate Confidence Interval
   Using Moment-Based Simplified Parameter Estimates
        For ANDA 78202 Delivered dose: DT

                    I.  Summary

                In Vitro PBE CRITERIA
               MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

                  Linearized Theta P

    Reference-scaled:      Point estimate:   -0.0048
               CI:                 0.0023
                Pass/Fail:          FAIL

    Constant-scaled:       Point estimate:   -0.0165
               CI:                -0.0106
                Pass/Fail:          PASS

      Overall Test Outcome:  Pass/Fail:          PASS
```

D. Deficiency Comments

1. The firm's Cascade Impaction test and the Mean Delivery Dose at mouthpiece test are incomplete due to lack of relevant CMC information of the new test batches, Lot # GZ2610 and HY9696.

   To validate the new batches (Lot # GZ2610 for 0.5 mg/2 mL and HY9696 for 0.25 mg/2 mL), the firm is requested to submit the following information:

   - Statements clarifying whether the batches (Lot # GZ2610 for 0.5 mg/2 mL and HY9696 for 0.25 mg/2 mL) were manufactured, controlled and released the same way as the previous batches (Lot # GZ7634, GZ8818 for 0.5 mg/2mL and GZ7632, GZ8410 for 0.25 mg/2mL) used in the *in vitro* bioequivalence study, in terms of i) manufacturing process, ii) in-process controls.
   - Chemistry, Manufacturing and Control information for the new batches Lot # GZ2610 and # HY9696, as specified by the Division of Chemistry.

2. The firm's repeated PSD test was conducted with a new Cascade Impactor. However, the firm did not provide method validation report for this new Cascade Impactor or a cross-validation study between these two Cascade Impactors. The firm should submit this information. The firm should explain whether there are any differences between these two Cascade Impactors, whether the test method used with the new Cascade Impactor is the same as the one used with the old Cascade Impactor, and provide comparative setup parameters for both CIs.

E. Recommendations

1. The *in vitro* bioequivalence testing conducted by Apotex Inc. comparing its test product, Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL, with the reference product, Pulmicort® Respules, 0.25 mg/2 mL and 0.5 mg/2 mL, respectively, manufactured by AstraZeneca, is **incomplete** due to the reasons cited in the Deficiency Comments above.

2. The application remains **incomplete**.

F. Comments for other OGD Disciplines

Discipline	Comment
Chemistry	The Division of Chemistry should determine if the CMC information for the two NEW test lots, # GZ2610 and # HY9696, is acceptable.

G. Appendix

<u>0.25 mg/2 mL strength Cascade Impaction Test:</u>

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: S0

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0087
	CI:	0.0391
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	0.0160
	CI:	0.0436
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	FAIL

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	9.55	Mean:	10.60	Ratio:	90.04
				90% CI for ratio:		(83.8, 96.7)
(log scale)	Mean:	2.26	Mean:	2.36	Diff:	-0.10
(log scale)	CV:	9.00	CV:	4.92		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.203	SigmaR:	0.116	Ratio:	1.747

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: S1

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.1173
	CI:	0.1854
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	0.1261
	CI:	0.1929
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	FAIL

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	6.92	Mean:	9.29	Ratio:	74.54
				90% CI for ratio:		(67.9, 81.8)
(log scale)	Mean:	1.94	Mean:	2.23	Diff:	-0.29
(log scale)	CV:	14.43	CV:	5.35		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.279	SigmaR:	0.119	Ratio:	2.341

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: S2

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0769
	CI:	0.1032
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	0.0637
	CI:	0.0897
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	FAIL

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	5.97	Mean:	7.76	Ratio:	76.96
				90% CI for ratio:		(73.4, 80.7)
(log scale)	Mean:	1.79	Mean:	2.05	Diff:	-0.26
(log scale)	CV:	8.00	CV:	2.95		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.143	SigmaR:	0.061	Ratio:	2.362

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: S3

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0039
	CI:	0.0028
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0154
	CI:	-0.0102
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	23.84	Mean:	21.70	Ratio:	109.86
				90% CI for ratio:		(107.3,112.5)
(log scale)	Mean:	3.17	Mean:	3.08	Diff:	0.09
(log scale)	CV:	1.15	CV:	2.18		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.036	SigmaR:	0.067	Ratio:	0.544

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: S4

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0189
	CI:	-0.0113
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0251
	CI:	-0.0212
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	29.45	Mean:	28.50	Ratio:	103.34
				90% CI for ratio:		(100.4,106.4)
(log scale)	Mean:	3.38	Mean:	3.35	Diff:	0.03
(log scale)	CV:	1.35	CV:	2.51		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.046	SigmaR:	0.084	Ratio:	0.544

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: S5

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0128
	CI:	0.0271
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	0.0020
	CI:	0.0155
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	FAIL

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	16.81	Mean:	14.75	Ratio:	113.99
				90% CI for ratio:		(109.7,118.5)
(log scale)	Mean:	2.82	Mean:	2.69	Diff:	0.13
(log scale)	CV:	3.73	CV:	2.58		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.105	SigmaR:	0.069	Ratio:	1.515

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: S6

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0012
	CI:	0.0131
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0045
	CI:	0.0053
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	FAIL

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	3.25	Mean:	3.70	Ratio:	87.95
				90% CI for ratio:		(84.7, 91.3)
(log scale)	Mean:	1.18	Mean:	1.31	Diff:	-0.13
(log scale)	CV:	7.44	CV:	6.53		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.088	SigmaR:	0.085	Ratio:	1.027

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: S7

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0255
	CI:	0.0077
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	0.0023
	CI:	0.0273
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	FAIL

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	1.69	Mean:	1.93	Ratio:	88.02
				90% CI for ratio:		(81.9, 94.6)
(log scale)	Mean:	0.53	Mean:	0.66	Diff:	-0.13
(log scale)	CV:	33.96	CV:	23.30		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.179	SigmaR:	0.153	Ratio:	1.174

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: port

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0303
	CI:	0.0204
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	0.0108
	CI:	0.0531
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	FAIL

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	4.47	Mean:	4.41	Ratio: 101.36
				90% CI for ratio:	(92.3,111.3)
(log scale)	Mean:	1.50	Mean:	1.48	Diff: 0.01
(log scale)	CV:	16.92	CV:	11.60	
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio: -
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio: -
(log scale)	SigmaT:	0.253	SigmaR:	0.172	Ratio: 1.472

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: cup

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0011
	CI:	0.0020
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0190
	CI:	-0.0182
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	134.09	Mean:	139.64	Ratio: 96.03
				90% CI for ratio:	(95.1, 97.0)
(log scale)	Mean:	4.90	Mean:	4.94	Diff: -0.04
(log scale)	CV:	0.52	CV:	0.39	
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio: -
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio: -
(log scale)	SigmaT:	0.026	SigmaR:	0.019	Ratio: 1.330

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: filter

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0179
	CI:	0.0253
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	0.0186
	CI:	0.0533
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	FAIL

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	1.26	Mean:	1.47	Ratio:	85.47
				90% CI for ratio:		(78.7, 92.8)
(log scale)	Mean:	0.23	Mean:	0.39	Diff:	-0.16
(log scale)	CV:	92.36	CV:	42.94		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.212	SigmaR:	0.166	Ratio:	1.276

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: MB

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0407
	CI:	-0.0256
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0309
	CI:	-0.0248
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	97.58	Mean:	104.53	Ratio:	93.36
				90% CI for ratio:		(89.9, 97.0)
(log scale)	Mean:	4.58	Mean:	4.65	Diff:	-0.07
(log scale)	CV:	0.45	CV:	2.60		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.020	SigmaR:	0.121	Ratio:	0.168

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: MMAD

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0003
	CI:	0.0034
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0172
	CI:	-0.0145
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	3.04	Mean:	3.18	Ratio:	95.54
					90% CI for ratio:	(93.5, 97.6)
(log scale)	Mean:	1.11	Mean:	1.16	Diff:	-0.05
(log scale)	CV:	5.30	CV:	3.50		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.059	SigmaR:	0.040	Ratio:	1.455

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: GSD

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0001
	CI:	0.0014
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0191
	CI:	-0.0181
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	2.23	Mean:	2.33	Ratio:	95.65
				90% CI for ratio:		(94.5, 96.8)
(log scale)	Mean:	0.80	Mean:	0.85	Diff:	-0.04
(log scale)	CV:	3.20	CV:	3.37		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.026	SigmaR:	0.029	Ratio:	0.899

Class Levels (total number bottles/product = 60; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 CI New Test: MMAD
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	30	31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60
	lot	3	KC156 KC158 NN0188
TEST	product	1	TEST
	container	30	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
	lot	3	GZ7632 GZ8410 HY9696

Listing, Raw & Log Data for ANDA 78202 CI New Test: MMAD

Obs	product	lot	container	S0	S1	S2	S3	S4	S5	S6
1	REF	KC156	31	[redacted]						
2	REF	KC156	32							
3	REF	KC156	33							
4	REF	KC156	34							
5	REF	KC156	35							
6	REF	KC156	36							
7	REF	KC156	37							
8	REF	KC156	38							
9	REF	KC156	39							
10	REF	KC156	40							

(b) (4)

Obs	S7	filter	cup	port	MB	MMAD	GSD	lnS0	lnS1	lnS2
1	[redacted]									
2										
3										
4										
5										
6										
7										
8										
9										
10										

(b) (4)

Obs	lnS3	lnS4	lnS5	lnS6	lnS7	lnfilter	lncup
1	[redacted]						
2							
3							
4							
5							
6							
7							
8							
9							
10							

(b) (4)

Obs	lnport	lnMB	lnMMAD	lnGSD	sect	vbl	vbl_
1	[redacted]						
2							
3							
4							
5							

(b) (4)

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0.5 mg/2 mL strength Cascade Impaction Test:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: S0

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0539
	CI:	-0.0182
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0145
	CI:	0.0087
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	22.43	Mean:	23.78	Ratio:	94.30
				90% CI for ratio: (87.4,101.8)		
(log scale)	Mean:	3.11	Mean:	3.17	Diff:	-0.06
(log scale)	CV:	5.92	CV:	5.36		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.184	SigmaR:	0.170	Ratio:	1.084

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: S1

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0227
	CI:	0.0817
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	0.0676
	CI:	0.1186
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	FAIL

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	13.13	Mean:	17.20	Ratio:	76.33
				90% CI for ratio:		(70.0, 83.3)
(log scale)	Mean:	2.57	Mean:	2.84	Diff:	-0.27
(log scale)	CV:	8.66	CV:	6.24		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.223	SigmaR:	0.177	Ratio:	1.257

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: S2

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0273
	CI:	0.0408
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	0.0151
	CI:	0.0280
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	FAIL

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	17.07	Mean:	20.35	Ratio:	83.88
				90% CI for ratio:		(80.9, 86.9)
(log scale)	Mean:	2.84	Mean:	3.01	Diff:	-0.18
(log scale)	CV:	3.47	CV:	2.13		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.098	SigmaR:	0.064	Ratio:	1.530

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: S3

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0588
	CI:	-0.0314
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0294
	CI:	-0.0140
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	64.32	Mean:	60.73	Ratio:	105.92
				90% CI for ratio: (99.8,112.4)		
(log scale)	Mean:	4.16	Mean:	4.11	Diff:	0.06
(log scale)	CV:	2.79	CV:	3.78		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.116	SigmaR:	0.155	Ratio:	0.749

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: S4

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0250
	CI:	0.0055
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0022
	CI:	0.0212
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	FAIL

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	67.56	Mean:	56.62	Ratio:	119.31
				90% CI for ratio:		(113.1,125.8)
(log scale)	Mean:	4.21	Mean:	4.04	Diff:	0.18
(log scale)	CV:	2.30	CV:	3.58		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.097	SigmaR:	0.145	Ratio:	0.670

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: S5

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0195
	CI:	0.0373
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	0.0143
	CI:	0.0307
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	FAIL

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	28.31	Mean:	23.45	Ratio:	120.75
				90% CI for ratio:		(116.3,125.4)
(log scale)	Mean:	3.34	Mean:	3.15	Diff:	0.19
(log scale)	CV:	2.61	CV:	2.75		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.087	SigmaR:	0.087	Ratio:	1.007

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: S6

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0186
	CI:	0.0419
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	0.0162
	CI:	0.0380
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	FAIL

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	3.05	Mean:	3.50	Ratio:	87.11
				90% CI for ratio:		(82.1, 92.4)
(log scale)	Mean:	1.11	Mean:	1.25	Diff:	-0.14
(log scale)	CV:	15.06	CV:	7.52		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.168	SigmaR:	0.094	Ratio:	1.782

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: S7

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0436
	CI:	0.0085
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	0.0098
	CI:	0.0498
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	FAIL

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	1.38	Mean:	1.52	Ratio:	90.78
				90% CI for ratio:		(82.6, 99.8)
(log scale)	Mean:	0.32	Mean:	0.42	Diff:	-0.10
(log scale)	CV:	75.76	CV:	44.86		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.245	SigmaR:	0.189	Ratio:	1.300

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: cup

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0031
	CI:	0.0053
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0166
	CI:	-0.0145
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	237.08	Mean:	249.30	Ratio: 95.10
				90% CI for ratio:	(93.5, 96.7)
(log scale)	Mean:	5.47	Mean:	5.52	Diff: -0.05
(log scale)	CV:	0.90	CV:	0.43	
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio: -
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio: -
(log scale)	SigmaT:	0.049	SigmaR:	0.024	Ratio: 2.087

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: filter

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0939
	CI:	0.0356
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	0.0545
	CI:	0.1593
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	FAIL

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	1.11	Mean:	1.15	Ratio: 96.47
				90% CI for ratio:	(82.9,112.2)
(log scale)	Mean:	0.10	Mean:	0.14	Diff: -0.04
(log scale)	CV:	386.26	CV:	202.56	
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio: -
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio: -
(log scale)	SigmaT:	0.404	SigmaR:	0.285	Ratio: 1.419

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: GSD

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0001
	CI:	0.0006
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0200
	CI:	-0.0194
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	2.05	Mean:	2.13	Ratio:	96.60
				90% CI for ratio:		(95.8, 97.4)
(log scale)	Mean:	0.72	Mean:	0.75	Diff:	-0.03
(log scale)	CV:	2.11	CV:	2.91		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.015	SigmaR:	0.022	Ratio:	0.691

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: MB

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0027
	CI:	-0.0006
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0200
	CI:	-0.0186
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	95.28	Mean:	98.84	Ratio:	96.40
				90% CI for ratio:		(94.8, 98.0)
(log scale)	Mean:	4.56	Mean:	4.59	Diff:	-0.04
(log scale)	CV:	0.81	CV:	0.90		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.037	SigmaR:	0.041	Ratio:	0.891

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: MMAD

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0016
	CI:	0.0033
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0161
	CI:	-0.0121
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	3.41	Mean:	3.61	Ratio:	94.38
				90% CI for ratio:		(91.9, 97.0)
(log scale)	Mean:	1.23	Mean:	1.28	Diff:	-0.06
(log scale)	CV:	5.67	CV:	4.32		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.069	SigmaR:	0.055	Ratio:	1.252

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 CI New Test: port

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.1545
	CI:	-0.0703
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0230
	CI:	0.0261
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	25.95	Mean:	28.16	Ratio:	92.16
				90% CI for ratio: (		82.2,103.4)
(log scale)	Mean:	3.26	Mean:	3.34	Diff:	-0.08
(log scale)	CV:	8.06	CV:	8.09		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.262	SigmaR:	0.270	Ratio:	0.972

Class Levels (total number bottles/product = 60; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 CI New Test: port
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	30	31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60
	lot	3	PC0126 PF0079 PH0020
TEST	product	1	TEST
	container	30	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
	lot	3	GZ2610 GZ7634 GZ8818

Listing, Raw & Log Data for ANDA 78202 CI New Test: port

Obs	product	lot	container	S0	S1	S2	S3	S4	S5	S6
1	REF	PC0126	31	(b) (4)						
2	REF	PC0126	32							
3	REF	PC0126	33							
4	REF	PC0126	34							
5	REF	PC0126	35							
6	REF	PC0126	36							
7	REF	PC0126	37							
8	REF	PC0126	38							
9	REF	PC0126	39							
10	REF	PC0126	40							

Obs	S7	filter	cup	port	MB	MMAD	GSD	lnS0	lnS1	lnS2
1	(b) (4)									
2										
3										
4										
5										
6										
7										
8										
9										
10										

Obs	lnS3	lnS4	lnS5	lnS6	lnS7	lnfilter	lncup
1	(b) (4)						
2							
3							
4							
5							
6							
7							
8							
9							
10							

Obs	lnport	lnMB	lnMMAD	lnGSD	sect	vbl	vbl_
1	(b) (4)						
2							
3							

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0.25 mg/2 mL MDD at Mouthpiece Test:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 Delivered dose: Delivery Time

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0030
	CI:	-0.0009
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0205
	CI:	-0.0190
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	6.55	Mean:	6.56	Ratio:	99.76
				90% CI for ratio:		(97.9,101.7)
(log scale)	Mean:	1.88	Mean:	1.88	Diff:	-0.00
(log scale)	CV:	2.48	CV:	2.16		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.047	SigmaR:	0.041	Ratio:	1.148

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
For ANDA 78202 Delivered dose: Delivery Dose

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0048
	CI:	0.0023
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0165
	CI:	-0.0106
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	PASS

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	37.17	Mean:	34.88	Ratio:	106.55
				90% CI for ratio:		(103.4,109.8)
(log scale)	Mean:	3.62	Mean:	3.55	Diff:	0.06
(log scale)	CV:	1.98	CV:	1.87		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.072	SigmaR:	0.067	Ratio:	1.077

Class Levels (total number bottles/product = 60; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 Delivered dose: DT
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	30	31 32 33 34 35 36 37 38 39 40 41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60
	lot	3	KC156 KC158 NN0188
TEST	product	1	TEST
	container	30	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30
	lot	3	GZ7632 GZ8410 HY9696

Listing, Raw & Log Data for ANDA 78202 Delivered dose: DD

Obs	product	lot	container	DD	DT	lnDD	lnDT	sect
								(b) (4)
1	REF	KC156	31					
2	REF	KC156	32					
3	REF	KC156	33					
4	REF	KC156	34					
5	REF	KC156	35					
6	REF	KC156	36					
7	REF	KC156	37					
8	REF	KC156	38					
9	REF	KC156	39					
10	REF	KC156	40					
11	REF	KC158	41					
12	REF	KC158	42					
13	REF	KC158	43					
14	REF	KC158	44					
15	REF	KC158	45					
16	REF	KC158	46					
17	REF	KC158	47					
18	REF	KC158	48					
19	REF	KC158	49					
20	REF	KC158	50					
21	REF	NN0188	51					
22	REF	NN0188	52					
23	REF	NN0188	53					
24	REF	NN0188	54					
25	REF	NN0188	55					
26	REF	NN0188	56					
27	REF	NN0188	57					
28	REF	NN0188	58					
29	REF	NN0188	59					
30	REF	NN0188	60					
31	TEST	GZ7632	1					
32	TEST	GZ7632	2					
33	TEST	GZ7632	3					

(b) (4)

34	TEST	GZ7632	4
35	TEST	GZ7632	5
36	TEST	GZ7632	6
37	TEST	GZ7632	7
38	TEST	GZ7632	8
39	TEST	GZ7632	9
40	TEST	GZ7632	10
41	TEST	GZ8410	11
42	TEST	GZ8410	12
43	TEST	GZ8410	13
44	TEST	GZ8410	14
45	TEST	GZ8410	15
46	TEST	GZ8410	16
47	TEST	GZ8410	17
48	TEST	GZ8410	18
49	TEST	GZ8410	19
50	TEST	GZ8410	20
51	TEST	HY9696	21
52	TEST	HY9696	22

Listing, Raw & Log Data for ANDA 78202 Delivered dose: DD

(b) (4)

Obs	product	lot	container	DD	DT	lnDD	lnDT	sect
53	TEST	HY9696	23					
54	TEST	HY9696	24					
55	TEST	HY9696	25					
56	TEST	HY9696	26					
57	TEST	HY9696	27					
58	TEST	HY9696	28					
59	TEST	HY9696	29					
60	TEST	HY9696	30					

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-202

APPLICANT: Apotex Inc.

DRUG PRODUCT: Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL

The Division of Bioequivalence has completed the review of your submission acknowledged on the cover page. The following deficiencies have been identified:

1. To validate the two new test batches (Lot # GZ2610 for 0.5 mg/2 mL, and HY9696 for 0.25 mg/2 mL) used in your Particle Size Distribution (PSD) in Nebulized Aerosol by Cascade Impaction (CI) and Mean Delivery Dose (MDD) at Mouthpiece tests, please submit the following information:

- Statements clarifying whether these batches (Lot # GZ2610 for 0.5 mg/2 mL, and HY9696 for 0.25 mg/2 mL) were manufactured, controlled and released the same way as the previous batches (Lot # GZ7634, GZ8818 for 0.5 mg/2mL, and GZ7632, GZ8410 for 0.25 mg/2mL) used in the earlier *in vitro* bioequivalence studies, in terms of i) formulation, ii) manufacturing process, and iii) in-process controls.

- Chemistry, Manufacturing and Control (CMC) information for the new batches Lot # GZ2610 and # HY9696. Please contact the Division of Chemistry of the CMC information considered necessary for acceptable validation.

2. Your repeated Particle Size Distribution test was conducted using a new Cascade Impactor. However, you did not provide method validation report for this new Cascade Impactor and/or a cross validation study between the original and new Cascade Impactors. Please submit this information. Please explain whether there are any differences between these two Cascade Impactors, whether the test method used with the new Cascade Impactor is the same as the one used with the old Cascade Impactor, and provide comparative setup parameters for both CIs.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

H. Outcome Page

ANDA: 78-202

Reviewer: Ren, Ke

Date Completed:

Verifier:

Date Verified:

Division: Division of Bioequivalence

Description: Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL, Apotex Inc.

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
6721	10/1/2008	Other	Study Amendment	1	1
				Bean Total:	1

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

/s/

Ke Ren
12/16/2008 03:41:20 PM
BIOPHARMACEUTICS

Bing Li
12/16/2008 03:45:02 PM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
12/17/2008 09:55:02 PM
BIOPHARMACEUTICS
For Dale P. Conner, Pharm. D., Director, Division of Bioequivalence I

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-202
Drug Product Name	Budesonide Inhalation Suspension
Strength(s)	0.25mg/2mL and 0.5mg/2mL
Applicant Name	Apotex Inc. 380 Elgin Mills Road East Richmond Hill, Ontario Canada L4C 5H2
Address	Authorized Agent: Apotex Corp. 2400 North Commerce Parkway, Suite 400 Weston, Florida 33326
Applicant's Point of Contact	Paul Bonnici, B.Sc.
Contact's Telephone Number	Tel: (905) 508-2396
Contact's Fax Number	Fax: (905) 508-2359
Original Submission Date(s)	March 31, 2006
Submission Date(s) of Amendment(s) Under Review	August 09, 2007
Reviewer	Bing V. Li, Ph. D.
Outcome Decision	**Incomplete**

I. Executive Summary

Apotex submitted its responses to the deficiency comments made by the Division of Bioequivalence (DBE) in its letter of April 27, 2007. In the original application, the firm did not submit its method of the particle size distribution in nebulized aerosol test, as well as the comparative results of the drug polymorph and shape between the low strength product and high strength product. In addition, the firm's particle size distribution results measured by two different methods were inconsistent.

In the current amendment, the firm addressed the deficiencies identified by the DBE. The firm also submitted its SAS transformed data for all of its in vitro tests. The firm's test for particle size distribution (PSD) measured by Cascade Impactor (CI) is incomplete. The firm did not submit the PSD results on each individual deposition site; rather, the firm grouped the PSD results differently. Certain parameters of the firm's PSD results did not pass Population Bioequivalence (PBE) analysis. The firm should repeat its CI test using a larger sample size (30 samples for each test and reference products), and submit the CI data for each individual deposition site. In addition, the firm's test results for Mean Delivered Dose at Mouthpiece (MDD) for its 0.25 mg/2 ml strength did not pass the PBE analysis. The firm is asked to repeat its MDD for its 0.25 mg/2 ml strength product, using a larger sample size (30 samples for each test and reference products).

The application is **incomplete.**

Background

On March 31, 2006, the firm submitted the results of *in vitro* bioequivalence testing comparing its Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL, with Astra Zeneca's Pulmicort® Respules, 0.25 mg/2 mL and 0.5 mg/2 mL, respectively. The firm did not submit its method of the particle size distribution in nebulized aerosol test (measured by Cascade Impactor), as well as the comparative results of the drug polymorph and shape between the low strength product and high strength product. In addition, the firm's particle size distribution results measured by two different methods were inconsistent (DFS 078202 N 000 20-Jun-2006).

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III. Submission Summary

A. Drug Product Information, PK/PD Information, and Relevant DBE History

1. OGD recommendations for this drug product at different levels of BE assessment are summarized in the table below: (For detailed recommendations, please refer Control Document No. 03-612, To Apotex, letter date 09/16/2005):

Levels of BE Assessment	BE Assessment
Drug Substance and Drug Product	• Sameness of polymorphic form based on X-ray diffraction • Sameness of shape (crystalline habit) • Particle Size Distribution (PSD) of the active pharmaceutical ingredient (API) in the product, and comparative PSD in the suspension (in the ampoule)
Nebulization Process	• Mean nebulization time

	• Mean delivered dose at the mouthpiece
Nebulized Aerosol	• Sameness of aqueous droplet size of the nebulized aerosol by a laser diffraction • Sameness of particle size of drug and agglomerates in the nebulized aerosol
In Vivo	If the Sameness of particle size of drug and agglomerates in the nebulized aerosol could not be measured: • A clinical endpoint bioequivalence study for local delivery, with demonstration of acceptable dose-response for test and reference products to assure study sensitivity. • A systemic exposure (pharmacokinetic) bioequivalence study.

2. In the past, the OGD has reviewed one ANDA (First Generic) for this product. The methods used for the in vitro tests are summarized as follows:

	77-519 (Ivax, First Generic)	**78-202 (Apotex, Current application)**	**NDA 20-929 (RLD)**
PSD in the suspension	Laser Diffraction	Laser Diffraction	Coulter Counter
Droplet size of the nebulized aerosol	Laser Diffraction	Laser Diffraction	NA
Particle size of drug and agglomerates in the nebulized aerosol	Samples were collected in a New Generation Cascade Impaction, then samples were combined to run through a Coulter Counter	(b) (4) Cascade Impactor	NA

B. Contents of Submission

Study Types	**Yes/No?**	**How many?**
Single-dose fasting	No	
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	No	
Waiver requests	No	
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	1

C. Review of Submission

Reviewer's Notes:

The firm conducted all of its in vitro tests using 20 samples (2 batches, each 10 samples) of test and reference products, rather than 30 samples (3 batches, each 10 samples) stated in

FDA's Guidance for Industry: Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action (April 2003) as follows:

"*In vitro BE studies for nasal aerosols and sprays would generally be performed on samples from each of* ***three or more batches*** *of the test product and three or more batches of the reference listed drug. Test product samples would be from the primary stability batches used to establish the expiration dating period. When three batches are studied, we recommend the test product be manufactured, preferably from three different batches of the drug substance, different batches of critical excipients, and different batches of container and closure components. However, the container (canister or bottle) can be from the same batch. For nasal sprays formulated as solutions, in vitro BE tests can alternatively be performed on three sublots of product prepared from one batch of the solution*".

However, since the Control document to the firm (No. 03-612 (Apotex, letter date 09/16/2005) did not specify the sample size to be tested, the reviewer considered the sample size as submitted acceptable for the in vitro results that met the BE acceptance criteria at this sample size. However, the reviewer has recommended the firm to increase the sample size to 30 samples for the incomplete tests which are to be repeated. In addition, for the future submission of such product, the DBE recommends the in vitro tests be conducted in 3 batches (30 samples), and the selection of these 3 batches (30 samples) should follow the Nasal Aerosols and Nasal Sprays BA/BE guidance.

Deficiency 1: *You did not submit the method of particle size distribution in the nebulized aerosol using cascade impactor (method PD 102). Instead, you submitted two copies of the method validation report. Please submit the method describing the procedures of how the measurement was conducted and how data were collected and analyzed for this test. In addition, please provide the rational of using this method for the measurement of particle size of drug and agglomerates in the nebulized aerosol.*

Firm's Response: *Method PD-102 (Determination of Aerodynamic Particle Size Distribution in Budesonide Inhalation Suspension using* (b) (4) *Cascade Impactor) was inadvertently missed in our initial submission. The document has now been placed in section 5. 3.1.2 and is available for your review.*

This method was used for the measurement of particle size distribution of the drug since the Cascade Impactor is a USP <601> recommended apparatus for testing particle size distribution in spray discharge from metered-dose inhalers. This method determines the aerodynamic size distribution of the drug aerosol leaving the inhaler, which in turn defines the manner in which an aerosol deposits during inhalation. Agglomeration, if present in the nebulized aerosol, will affect the deposition pattern of the drug particles on the cascade stages. When the Cascade Impaction system is set up under the controlled conditions indicated in method PD-102, the material balance, fine particle dose, respirable fraction and the amount of drug delivered from the nebulizer mouthpiece can be calculated in addition to the particle size (Mass Median Aerodynamic Diameter (MMAD) and Geometric Standard Deviation (GSD)) and distribution (% accumulated up to (b) (4) *um and* (b) (4) *um).*

Please also note that the Apotex and the Reference Listed Drug (RLD) products show similar drug deposition profiles throughout the cascade stages, therefore they have similar agglomeration, if any. Please refer to section 5.3.1.2 for the particle size distribution results for both products.

Reviewer's Comments: The firm's response to Deficiency #1 is **not** acceptable.

1. The drug particle and aggregate distribution in nebulized aerosol is the key test to determine whether in vivo BE testing could be waived. Currently, the DBE does not recommend a specific method for this test. In an earlier submission (ANDA 77-519, first Generic by Ivax), Ivax described its method as followings: "*The nebulized aerosol was collected by nebulizing one ampoule and collecting the nebulized droplets by impacting/impinging the droplets in placebo solution located in the cups (4 cups) of a Next Generation Impactor/HEPA filtered compressed air supply (at flow rate of 5.5 L/min). The captured suspension was combined and transferred to a volumetric flask and made up to the mark. The particle size distribution of the captured nebulized aerosol was measured using a* [redacted] (b) (4) *Coulter Counter*". Ivax has provided it's rational in selecting this method (DBE Review for 77-519, DFS N077519 N 000 30-Dec-2004) and it was found acceptable by DBE.

2. In this application, the firm used [redacted] (b) (4) Cascade Impactor ([redacted] (b) (4) to determine the drug particle and aggregate distribution in nebulized aerosol. Per Dr. Wallace Adams, an OGD expert for nasal and orally inhaled products, this method is considered as acceptable in determining the aerodynamic particle size distribution (APSD) in nebulized aerosol. However, a typical [redacted] (b) (4) includes multiple deposition sites (stages 0 through 7, plus filter and other deposition sites), and to date, the FDA has not found a statistical method based on **a single metric** that incorporated differences on all sites. In 1997, the FDA formed a Product Quality Research Institute (PQRI) working group that intended to find a robust method for assessing the APSD equivalence. The working group investigated the Chi-square ratio method, and combination of Chi-square ratio method and population bioequivalence test for impactor-sized mass (ISM, sum of the mass from below S0 to the filter), using real case scenarios as case study. However, in the end, the working group did **not** recommend a statistical test for APSD profile equivalence.[1,2,3]

---

[1] Product Quality Research Institute evaluation of cascade impactor profiles of pharmaceutical aerosols, part 1: background for a statistical method. Adams WP, Christopher D, Lee DS, Morgan B, Pan Z, Singh GJ, Tsong Y, Lyapustina S. AAPS PharmSciTech. 2007 Jan 19;8(1):4.

[2] Product Quality Research Institute evaluation of cascade impactor profiles of pharmaceutical aerosols: part 2--evaluation of a method for determining equivalence, Christopher D, Adams WP, Lee DS, Morgan B, Pan Z, Singh GJ, Tsong Y, Lyapustina S. AAPS PharmSciTech. 2007 Jan 19;8(1):5.

3 Product Quality Research Institute evaluation of cascade impactor profiles of pharmaceutical aerosols. Part 3. Final report on a statistical procedure for determining equivalence, Christopher D, Adams W, Amann A, Bertha C, Byron PR, Doub W, Dunbar C, Hauck W, Lyapustina S, Mitchell J, Morgan B, Nichols S, Pan Z, Singh GJ, Tougas T, Tsong Y, Wolff R, Wyka B., AAPS PharmSciTech. 2007 Nov 2;8(4):E90.

3. The firm collected the samples for each stages of the CI listed in the following table:

Collection No.	Corresponding Stages	Particle Size (ECD)μm (Effective Cutoff Diameter)
1	Nebulizer Assembly	N/A
2	Induction Port, Inlet Cone	(b) (4)
3	Stage 0	
4	Stage 1	
5	Stage 2	
6	Stage 3	
7	Stage 4	
8	Stage 5	
9	Stage 6	
10	Stage 7	
11	Filter	

4. However, the firm did not submit its CI test data on each individual stage; rather, the firm grouped the CI results differently. The firm grouped and reported the following parameters as the outcome of its CI test (Please refer to Appendix Section for the detailed definition and calculations of these parameters):
    - Total Mass of drug delivered from nebulizer (A, C minus Sample Cup);
    - Total Mass of drug found on stages and filter (B: Stage 0 to Filter);
    - Total Mass of drug collected (C: Stage 0 to Induction Port + Inlet Cone);
    - Total mass of drug found from Stage 2 to Stage 7 and on Filter (R);
    - The amount of drug delivered in ug (D);
    - Mass Median Aerodynamic Diameter (MMAD);
    - Geometric Standard Deviation (GSD);
    - Cumulative % Mass up to (b) um;
    - Cumulative % Mass up to (b) (4) um;
    - Material Balance (C/D);
    - Fine Particle Dose (R/N);
    - Respirable Fraction (R/A);

5. The reviewer performed the PBE analysis for some firm-determined group parameters listed above. Based on the PBE analysis, not all of these parameters pass PBE. The results are summarized in the table below (refer to attachment section for details of PBE analysis):

In vitro Test	Product Strengths	Parameters	Definition	PBE: pass or not
	0.5 mg	Amount B	S0-filter	**No**
	0.25 mg			**No**
PSD in nebulized aerosol (Cascade Impactor	0.5 mg	Amount R	S2-filter	**No**
	0.25 mg			**No**
	0.5 mg	Amount A	Total Mass of drug delivered from nebulizer (C minus Sample Cup)	**No**
	0.25 mg			**No**
	0.5 mg	Amount C	S0 to Induction Port + Inlet Cone	Yes
	0.25 mg			Yes
	0.5 mg	Amount D	The amount of drug delivered in ug	Yes
	0.25 mg			Yes
	0.5 mg	Mass Balance		Yes
	0.25 mg			Yes

6. The firm's particle size distribution (PSD) measured by CI test is not acceptable. The firm needs to repeat its PSD by CI test, and increase its sample size from 20 samples to 30 samples for both test and reference products (3 batches, 10 samples from each batch). The firm needs to submit the CI data for the individual deposition site (i.e., S0 to filter, the induction port and inlet cone, and nebulizer assembly), and the mass balance data, using the data format DBE recommended in the April 27, 2007 letter.

Deficiency 2: *You did not submit the X-ray Diffraction results and the Particle Size Distribution Determination by Light microscopic Image Analysis results for the 0.25 mg/2 ml product. Please submit information to prove that "the budesonide (bulk drug) used in the lower strength is the same as that used in the higher strength product, i.e., same particle size, PSD, polymorphic form, and shape". Alternatively, you submit the comparison between the high strength product and low strength product.*

Firm's Response: *The bulk drug batches used to manufacture both strengths of Budesonide Inhalation Suspension used in the bioequivalence study are presented in the following table. As shown in the table,* ***the same bulk drug*** *Lot No. 2110M10020430 was used to manufacture one of the 0.5 mg/2 mL finished product batches and both of the 0.25 mg/2 mL finished product batches.*

Strength	Raw Material SAP No.	Apotex Finished Product Lot No.	Apotex Bulk Drug Batch No.	Manufacturer Bulk Drug Lot No.
0.25 mg/2 mL	(b) (4)	GZ7632	GW4027	(b) (4)
		GZ8410	GZ4058	
0.5 mg/2 mL		GZ8818	GW4027	
		GZ7634	GX5473	

The original ANDA included bioequivalence study results for polymorphic form and shape for the 0.5 mg/2 mL finished product in section 5.3.1.2. These results are also applicable to the 0.25 mg/2 mL finished product since both strengths were manufactured using the same bulk drug source.

Particle size is monitored on the drug substance specification. The Certificates of Analysis for bulk drug Batch Nos. GZ4058 and GW4027 were included in the original ANDA in section 3.2.S.4.4. At this time we have also included the Certificate of Analysis for Bulk Drug Batch No. GX5473 in the same section. For ease of review we have provided a table below that summarizes the data for the particle size distribution. The results indicate that all of the bulk drug batches have similar particle size distribution.

Strength	Bulk Drug Manufacturer Lot No.	Apotex Bulk Drug Lot No.	10% D(v,0.1)	50% D(v,0.5)	90% D(v,0.9)
0.25 mg/2 mL	(b) (4)	GZ4058	(b) (4)		
0.25 mg/2 mL		GW4027			
0.5 mg/2 mL		GW4027			
0.5 mg/2 mL		GX5473			

Based on the data provided it can be concluded that the bulk drug used in the lower strength (0.25 mg/2 mL) finished product is the same as that used in the higher strength (0.5 mg/2 mL) finished product, (i.e. it has the same particle size, PSD, polymorphic form and shape).

Reviewer's Comments: Per the firm, the bulk drug budesonide used in the lower strength is **the same lot** as that used in the higher strength product, therefore, the physical properties such as particle size, PSD, polymorphic form, and shape, are the same. The firm's response to deficiency #2 is acceptable.

Deficiency 3: *Your Mean Delivered Dose values obtained for the test and reference listed drug (RLD) products ranged* (b) (4) *(% nominal), compared with 17(% nominal) specified in the RLD product labeling. Please provide explanation for the difference between your test results and the Mean Delivered Dose specified in the labeling.*

Firm's Response: *The RLD package insert states that the amount of drug delivered to the lungs will depend on patient factors, type of jet nebulizer and compressor performance. The jet nebulizer/compressor system used by Apotex to obtain the Mean Delivered Dose values as per method PD-188 is the ProNeb Ultra Nebulizer with Pari LC Plus Nebulization that delivers* (b) (4) ***L/min**, rather than **5.5 L/min** specified by the RLD insert. During testing, the flow rate of the compressor was regulated to ensure that both the Apotex and the RLD products were tested under controlled flow rate conditions. In*

addition, the Nebulization cup was agitated to ensure complete Nebulization of the product. ***The difference in flow rate as well as the agitation during the Nebulization process will affect the Nebulization time and the delivered dose results****. Also, a higher flow rate will allow the aqueous phase to evaporate faster during Nebulization, leaving a higher percentage of non-nebulised active in the cup as residue. Method PO-188 is adapted from the USP <601> thiel tube method. It is designed to ensure that the nebulised drug is not lost to the atmosphere; furthermore, the sample collecting tube is capable of quantitatively collecting the delivered dose. Thus, higher assay values are expected from a system with such attributes.*

Please note that the Apotex and the RLD products were tested under the same conditions (method PD-188) and the results are comparable. We are confident that if both of these products were subjected to a different testing procedure, the results would also be comparable.

Reviewer's Comments: The firm's response to Deficiency #3 is **not** acceptable.

1. The RLD label has made the following statements regarding the nebulizer and compressor used for RLD:

- *For PULMICORT® RESPULES, like all other nebulized treatments, the amount delivered to the lungs will depend on patient factors, the jet nebulizer utilized, and compressor performance.*
- *PULMICORT RESPULES should be administered with a jet nebulizer connected to a compressor with an adequate air flow, equipped with a mouthpiece or suitable face mask.*
- *Ultrasonic nebulizers are not suitable for the adequate administration of PULMICORT® RESPULES and, therefore, are not recommended.*
- *Using the Pari-LC-Jet Plus Nebulizer/Pari Master compressor system, under* in vitro *conditions, the mean delivered dose at the mouthpiece (% nominal dose) was approximately 17% at a mean flow rate of 5.5 L/min. The mean nebulization time was 5 minutes or less.*

2. Control Document No. 03-612 (Apotex, letter date 09/16/2005) stated that "*In-vitro bioequivalence studies should be conducted using the Pari-LC-Jet Plus Nebulizer/Pari Master compressor system as necessary*". The control document also stated that the Mean nebulization time and mean delivered dose at the mouthpiece (% nominal dose) should be tested "*at the labeled flow rate of 5.5 L/min*".

3. In the current application, Apotex claims that the Mean Delivered Dose data was obtained using "*the ProNeb Ultra Nebulizer with Pari LC Plus Nebulization that delivers* (b) (4) *L/min, rather than 5.5 L/min specified by the RLD insert*". Apotex also stated that "*In addition, the Nebulization cup was agitated to ensure complete Nebulization of the product*". Apotex claims that "*the difference in flow rate as well as the agitation during the Nebulization process will affect the Nebulization time and the delivered dose results*".

4. The firm used a different compressor (ProNeb Ultra Nebulizer compressor) than stated in the RLD labeling (Pari Master compressor). Based on the literature data, the choice of compressor affects the aerosol parameters and the delivery of drug.[4]

5. The reviewer found the following information about the ProNeb Ultra Nebulizer Compressor from an internet website: (http://www.specialtymedicalsupply.com/medical-supply-products/PRONEB-ULTRA-LC-PLUS-Nebulizer-Compressor.html): *The PRONEB® ULTRA is a* ***high output compressor that can shorten the treatment time*** *while delivering more medication to the patient's lungs. When combined with the PARI LC PLUS® or PARI LC STAR® Reusable Nebulizer, the particle sizes of medications are optimized for inhalation and retention into the lungs.*

6. In Apotex's MDD study, the test product was "administered with a jet nebulizer connected to a compressor with an adequate air flow", and the ProNeb Ultra Nebulizer Compressor is NOT an "Ultrasonic nebulizer", which fulfills the requirements the RLD labeling stated for the administration of the product. It is, therefore, **acceptable** to the DBE that the firm used the "ProNeb Ultra Nebulizer Compressor" as the compressor to replace the "Pari Master compressor" recommended in the Control document.

7. However, the PBE analysis for the MDD test indicated that the MDD for 0.5mg/2 ml passed PBE but the 0.25 mg/ml strength did NOT pass PBE (summary results shown below, please refer to Attachment section for more details):

0.5 mg/2ml strength: PBE Analysis for Mean Delivered Dose:

```
In Vitro PBE Analysis - Approximate Confidence Interval
   Using Moment-Based Simplified Parameter Estimates
                          for
             ANDA 78202 MEAN DELIVERED DOSE:

I.  Summary
```

[4] The Choice of Compressor Effects the Aerosol Parameters and the Delivery of Tobramycin from a Single Model Nebulizer, T.A. STANDAERT, Ph.D., D. VANDEVANTER, Ph.D., B.W. RAMSEY, M.D., M. VASILJEV-K, B.A., P. NARDELLA, B.S., D. GMUR, B.S., C. BREDL, B.S., A. MURPHY, Ph.D., and A.B. MONTGOMERY, M.D., JOURNAL OF AEROSOL MEDICINE Volume 13, Number 2, 2000 Mary Ann Liebert, Inc. Pp. 147–153.

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0076
	CI:	0.0139
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0099
	CI:	-0.0039
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	**PASS**

0.25 mg/2ml strength: PBE Analysis for Mean Delivered Dose:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 78202 MEAN DELIVERED DOSE:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0296
	CI:	0.0419
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	0.0130
	CI:	0.0251
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	**FAIL**

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	41.32	Mean:	34.55	Ratio:	119.59
				90% CI for ratio:		**(116.1,123.2)**
(log scale)	Mean:	3.72	Mean:	3.54	Diff:	0.18
(log scale)	CV:	1.74	CV:	1.28		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.065	SigmaR:	0.045	Ratio:	1.435

Class Levels (total number samples/product = 40; number of sectors = 1)

8. Since the firm's 0.25 mg/ml product did not pass the PBE analysis for its MDD test, the firm needs to repeat its MDD test for **the 0.25 mg/2ml strength product,** and increase the sample size from 20 samples to 30 samples for both test and reference products (3 batches, 10 samples from each batch). The firm can measure its MDD test using one of the following two nebulization systems:

- Pari-LC-Jet Plus Nebulizer/Pari Master compressor system at the flow rate of 5.5 L/min, as stated in the Control 03-612; or,

- Repeat its MDD test using ProNeb Ultra Nebulizer with Pari LC Plus Nebulization at the flow rate of (b) (4) L/min, as specified in its method PD-188;

9. It is also noted that a similar question was brought up in the first generic application for Budisonide Inhalation Suspension (ANDA 77-519, Ivax). Ivax provided a different explanation as follows:

> *"The Mean Delivered Dose (MDD) procedure incorporates a flow of air through the mouthpiece of the nebulizer to simulate inhalation of the patient. This airflow may be either constant or sinusoidal (simulated breathing pattern). The values obtained for the Test and RLD by Ivax have collected with a flow rate of 5.5 L/min, as requested in correspondence with FDA, OGD# 01- 344. The Ivax procedure utilizes a (b) (4) to achieve a constant flow of 5.5 L/min through the mouthpiece of the PARI LC Plus nebulizer during testing of both the Test and RLD. By this method the results compared favorably to the RLD.*
>
> *When using a simulated breathing pattern the inhalation/exhalation cycle reduces the amount of budesonide delivered through the nebulizer, as the patient only receives the dose during inhalation. Thus the Mean Delivered Dose obtained using a breath simulator is expected to be approximately half that obtained using a constant airflow. The results appearing in the labeling by the RLD (17% nominal) are approximately half the test results obtained by Ivax using a constant flow ((b) (4)% nominal).*
>
> *It would seem a reasonable conclusion then, that the value for MDD in the brand labeling was generated using sinusoidal airflow."*

Deficiency 4: *Your mean nebulization time obtained for the test and RLD was ten (10) minutes, compared with 5 minutes or less specified in the RLD product labeling. Please provide explanation for the difference between your test results and the mean nebulization time specified in the labeling.*

Firm's Response: *The jet Nebulizer/compressor system used by Apotex to obtain the Mean Nebulization Time values, as per method PD-188, is the* ***ProNeb Ultra Nebulizer*** *with Pari LC Plus Nebulization. This system delivers (b) (4)****L/min****, rather than* ***5.5 L/min*** *specified by the RLD insert. During Nebulization Time testing, the flow rate of the compressor was regulated to make sure that both the Apotex and the RLD products were tested under*

controlled flow rate conditions. In addition, the Nebulization cup was agitated to ensure complete Nebulization of the product. The difference in flow rate as well as the agitation during the Nebulization process will affect the nebulization time results.

Please note that under the Apotex test conditions the total Nebulization time is approximately 10 minutes for both the Apotex and the RLD products, which is in line with the 5-10 minutes time range specified in the Pulmicort Patient Instructions.

Reviewer's Comments: The firm's response to Deficiency #4 is acceptable.

1. As discussed above, it is acceptable to the DBE for the firm to use ProNeb Ultra Nebulizer with Pari LC Plus Nebulization for its Mean Delivery Time (MDT) test.

2. The Reviewer ran the PBE analysis for the MDT test, the results indicated that the MDT for both strength products passed the PBE analysis.

<u>0.5 mg/2ml strength: PBE Analysis for Mean Delivery Time:</u>

```
In Vitro PBE Analysis - Approximate Confidence Interval
            Using Moment-Based Simplified Parameter Estimates
                                for
         ANDA 78202 MEAN DELIVERY TIME:


      I.  Summary

                      In Vitro PBE CRITERIA
                      MIXED SCALING APPROACH
      Point Estimate and Upper Bound of 95% Confidence Interval

                       Linearized Theta P

      Reference-scaled:      Point estimate:   -0.0028
                             CI:               -0.0009
                             Pass/Fail:          PASS

      Constant-scaled:       Point estimate:   -0.0208
                             CI:               -0.0197
                             Pass/Fail:          PASS

      Overall Test Outcome:  Pass/Fail:          PASS
```

<u>0.25 mg/2ml strength: PBE Analysis for Mean Delivery Time:</u>

```
In Vitro PBE Analysis - Approximate Confidence Interval
            Using Moment-Based Simplified Parameter Estimates
                                for
         ANDA 78202 MEAN DELIVERY TIME:


      I.  Summary
```

```
                 In Vitro PBE CRITERIA
                 MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

                  Linearized Theta P

Reference-scaled:      Point estimate:   -0.0040
                       CI:               -0.0012
                       Pass/Fail:          PASS

Constant-scaled:       Point estimate:   -0.0210
                       CI:               -0.0191
                       Pass/Fail:          PASS

Overall Test Outcome:  Pass/Fail:          PASS
```

Deficiency 5: *The results of your particle size distribution (PSD) in suspension measured by two different methods are inconsistent. The PSD measured by Laser Diffraction is significantly greater than that measured by light microscopy. Please investigate your method of PSD measurement by laser diffraction. You may use other alternative particle size measurement method, such as Coulter Multisizer, to confirm the study results.*

Firm's Response: *The principles of Laser Diffraction and Light Microscopy are quite different. Laser Diffraction measures the scattering of light of particles as they are drawn through the path of a laser beam in a 3-Dimensional form. The scattered dates are subsequently collected to build up an image through an algorithm. The PSD is reported based on the equivalent sphere volume of a given size. Light microscopy, on the other hand, measures the particles on a microscopic slide in a 1-Dimensional form. The diameter is determined as the maximum particle length. The PSD is reported on a number-based counting technique. Therefore, the PSD values obtained by the two methods are not necessarily correlated. As shown in Fig. 4 (below), in the article by Paul Kippax, the number distribution tends to be shifted to smaller sizes compared to the volume distribution.*

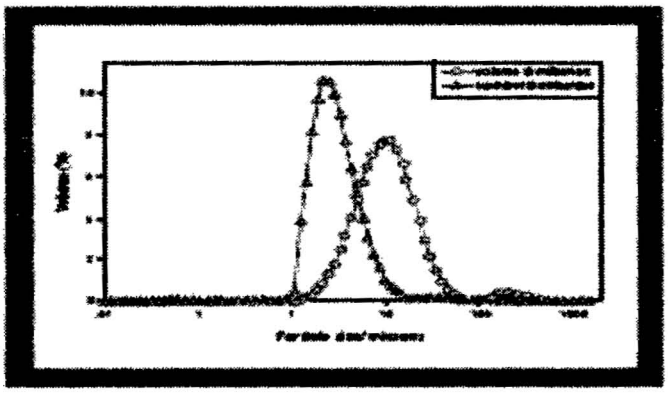

Figure 4: Volume and number distributions reported for the same product. As is shown, the number distribution is shifted to smaller sizes compared with the volume distribution. The agglomerates reported in the volume distribution also are insignificant in number terms.

As Dr. Alan Rawle described it, "different measurement techniques" yield "different answers". He also stated that "the answers become meaningless if two different measuring procedures are used to compare values at different points in the processing chain, or if different departments use different measurement methods. Each answer will be correct, giving a true result for the property being measurement. It follows therefore, that the only sensible comparison of measurements is by using the same technique.

Furthermore, as Dr. F. M. Etzler and R. Daeanne of Boehringer Ingelheim Pharmaceuticals pointed out, "considerable variations exist between the results obtained on laser diffraction instruments manufactured by different companies". Therefore, if variations exist within the same technique by different manufacturers, the variations in results obtained with different techniques are magnified, regardless if Coulter Multisizer, Laser Diffraction or Image Analysis are used.

The basis of our study is to compare the test product with the reference product. In this respect, the results obtained by laser diffraction for the two products are found to be equivalent. Using Image Analysis, the Test Product is also found to be equivalent to the Reference product. Due to the different nature of the two measurement techniques, and the way that results are obtained (number-based vs. volume-based), the two sets of data are not correlated.

Reviewer's Comments: The firm's response to Deficiency #5 is acceptable.

Deficiency 6: *Please re-submit raw data for the in vitro tests (Unit Dose Content of Drug in the Ampoules, Mean Nebulization Time and Mean Delivered Dose at the Mouthpiece, Particle Size Distribution of the Active Ingredient in the Suspension, Droplet Size Distribution of the Nebulized Aerosol) of the test and reference products, in electronic SAS Transport files, in the format of recommended tables provided.*

Firm's Response: *As requested, the raw data for the in vitro tests (Unit Dose Content of Drug in the Ampoules, Mean Nebulization Time, Mean Delivered Dose at the Mouthpiece, Particle Size Distribution of the Active Ingredient in the Suspension and Droplet Size Distribution of the Nebulized Aerosol) of the test and reference products in electronic SAS transport files having the required format have been placed in section 5.3.1,2 for your review.*

Reviewer's Comments: The firm's response to Deficiency #6 is acceptable.

Deficiency 7: *Please submit the batch sizes and manufacturing dates of the test product.*

Firm's Response: *As per your request, the following table presents the sizes and the manufacturing dates for the submitted batches of the Finished Product:*

Batch	Batch Size	Manufacturing Date
GZ8410	(b) (4)	12/20/2005
GZ8818		12/16/2005

Reviewer's Comments: All Apotex' in vitro test were conducted on two batches, 10 samples of each batches (20 samples) as opposed to 3 batches and 10 samples of each test (30 samples) recommended for the nasal spray product. However, since FDA did not specify the number of samples used for this product, it is acceptable for the firm to use two batches of 20 samples for this time.

Deficiency 8: *Please submit the study site information for each in vitro test.*

Firm's Response: *As per your request, the following table presents the study site information for each of the in vitro testing:*

Site of Testing	Test
Apotex Inc. 380 Elgin Mills Road East Richmond Hill, Ontario Canada L4C 5H2	Assay, Identification and Content Uniformity
	Delivered Dose at Mouthpiece and Nebulization Time
	Determination of Aerodynamic Particle Size Distribution by Cascade Impactor
	Particle Size Distribution Determination by Light Microscopic Image Analysis
	Determination of Droplet Size Distribution Using the Malvern Spray Tec RT Sizer
[redacted] (b) (4)	
Apotex Inc. Analytical Services Lab. 400 Ormont Drive Toronto, Ontario M9L 1N9 Canada	Particle Size by Laser Diffraction

Reviewer's Comments: The firm's response to Deficiency #8 is acceptable.

D. Reviewer's Overall Comments on the Firm's In vitro Testing:

The reviewer run a number of PBE analysis for the critical parameters of the in-vitro testing and the results are summarized in the following table:

In vitro Test	Product Strengths	Parameters	PBE: pass or not	Comments
Unit dose content of drug in the ampules	0.5 mg	% label	Yes	Test acceptable
	0.25 mg	% label	Yes	
Mean nebulization time	0.5 mg	Time	Yes	Test acceptable
	0.25 mg	Time	Yes	
Mean delivered dose	0.5 mg	% label	Yes	Test acceptable
	0.25 mg	% label	**No**	Deficient
PSD in the suspension (in the ampoule)	0.5 mg	D50	Yes	Test acceptable
		Span	Yes	
	0.25 mg	D50	Yes	
		Span	Yes	
Droplet SD in nebulized aerosol	0.5 mg	D50	Yes	Test acceptable
		Span	Yes	
		D50	Not required per	

	0.25 mg		Control 03-612	
		Span	Not required per Control 03-612	
PSD in nebulized aerosol (Cascade Impactor	0.5 mg	Amount B	**No**	Deficient
	0.25 mg		**No**	
	0.5 mg	Amount R	**No**	
	0.25 mg		**No**	
	0.5 mg	Amount A	**No**	
	0.25 mg		**No**	
	0.5 mg	Amount C	Yes	
	0.25 mg		Yes	
	0.5 mg	Amount D	Yes	
	0.25 mg		Yes	
	0.5 mg	Mass Balance	Yes	
	0.25 mg		Yes	

E. Waiver Request(s)

None.

F. Deficiency Comments

1. The firm's particle size distribution (PSD) measured by CI test is **incomplete**. The firm is asked to repeat its PSD by CI test, and increase the sample size from 20 samples to 30 samples for both test and reference products (3 batches from each product, 10 samples from each batch). The firm should submit the CI data of both the original and repeat PSD by CI tests for the individual deposition site (i.e., S0 to filter, the induction port and inlet cone, and nebulizer assembly), and the mass balance data, using the data format DBE specified in the April 27, 2007 letter.

2. The firm's Mean Delivered Dose (MDD) at mouthpiece for its 0.25 mg/2 ml strength product is **incomplete**. The firm is asked to repeat its MDD test for **the 0.25 mg/2 ml strength product,** and increase the sample size from 20 samples to 30 samples for both test and reference products (3 batches from each product, 10 samples from each batch). The firm can measure its MDD test using one of the following two nebulization systems:

- Pari-LC-Jet Plus Nebulizer/Pari Master compressor system at the flow rate of 5.5 L/min, as stated in the Control 03-612; or,

- Repeat its MDD test using ProNeb Ultra Nebulizer with Pari LC Plus Nebulization at the flow rate of (b) (4) L/min, as specified in its method PD-188;

G. Recommendations

The *in vitro* bioequivalence testing conducted by Apotex Inc. comparing its test product, Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL, with the reference product, Pulmicort Respules, 0.25 mg/2 mL and 0.5 mg/2 mL, respectively, manufactured by Astra Zeneca, is **incomplete** for the reasons cited in the Deficiency Comments above.

IV. Appendix:

A. Analysis for the In Vitro Studies

1. Unit Dose Content of Drug in the Ampoules

Dose Content Uniformity Amount								
				Variability (%CV)			TEST/REF	
Sector	Product	Mean		Within-Lot		Total	Arith Mean	Geo Mean
		Arith	Geo	Min	Max			
		(N=20)	(N=20)	(N=10)	(N=10)	(N=20)	(N=20)	(N=20)
0.5 mg/2ml	Test	0.54	0.54	1.08	1.17	2.30	1.07	1.07
	Ref	0.51	0.51	1.34	1.36	1.82		
0.25 mg/2ml	Test	0.27	0.27	1.15	2.16	1.71	1.04	1.04
	Ref	0.26	0.26	1.12	2.12	1.65		

Dose Content Uniformity %LC								
				Variability (%CV)			TEST/REF	
Sector	Product	Mean		Within-Lot		Total	Arith Mean	Geo Mean
		Arith	Geo	Min	Max			
		(N=20)	(N=20)	(N=10)	(N=10)	(N=20)	(N=20)	(N=20)
0.5 mg/2ml	Test	108.96	108.93	1.09	1.20	2.33	1.07	1.07
	Ref	101.70	101.68	1.33	1.36	1.80		
0.25 mg/2ml	Test	106.85	106.84	1.12	2.17	1.70	1.04	1.04
	Ref	102.78	102.77	1.08	2.19	1.68		

Comparison of the High Strength and Low Strength Product		
	High/Low ratio	High/Low ratio
	Arith mean	Geo mean
Test	2.04	2.04
Ref	1.98	1.98

<u>0.5 mg/2ml strength: PBE Analysis for DCU (Label%):</u>

```
In Vitro PBE Analysis - Approximate Confidence Interval
          Using Moment-Based Simplified Parameter Estimates
```

for
ANDA 78202 DOSE CONTENT UNIFORMITY:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0042
	CI:	0.0060
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0160
	CI:	-0.0143
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	**PASS**

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	108.93	Mean: 101.68	Ratio:	107.12
			90% CI for ratio:		(105.9,108.3)
(log scale)	Mean:	4.69	Mean: 4.62	Diff:	0.07
(log scale)	CV:	0.50	CV: 0.39		
(log scale)	SigmaBT:	-	SigmaBR: -	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR: -	Ratio:	-
(log scale)	SigmaT:	0.023	SigmaR: 0.018	Ratio:	1.292

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 DOSE CONTENT UNIFORMITY:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	181 182 183 184 185 186 187 188 189 190

```
                                   191 192 193 194 195 196 197 198 199 200
            lot              2  LF0054 LM0080

   TEST     product          1  TEST
            container       20  161 162 163 164 165 166 167 168 169 170
                                171 172 173 174 175 176 177 178 179 180
            lot              2  GZ7634 GZ8818
```

Listing, Raw & Log Data for ANDA 78202 DOSE CONTENT UNIFORMITY:

Obs	product	sect	container	lot	amount	pctlabel	lnDCU
1	REF		181	LF0054			
2	REF		182	LF0054			
3	REF		183	LF0054			
4	REF		184	LF0054			
5	REF		185	LF0054			
6	REF		186	LF0054			
7	REF		187	LF0054			
8	REF		188	LF0054			
9	REF		189	LF0054			
10	REF		190	LF0054			
11	REF		191	LM0080			
12	REF		192	LM0080			
13	REF		193	LM0080			
14	REF		194	LM0080			
15	REF		195	LM0080			
16	REF		196	LM0080			
17	REF		197	LM0080			
18	REF		198	LM0080			
19	REF		199	LM0080			
20	REF		200	LM0080			
21	TEST		161	GZ7634			
22	TEST		162	GZ7634			
23	TEST		163	GZ7634			
24	TEST		164	GZ7634			
25	TEST		165	GZ7634			
26	TEST		166	GZ7634			
27	TEST		167	GZ7634			
28	TEST		168	GZ7634			
29	TEST		169	GZ7634			
30	TEST		170	GZ7634			
31	TEST		171	GZ8818			
32	TEST		172	GZ8818			
33	TEST		173	GZ8818			
34	TEST		174	GZ8818			
35	TEST		175	GZ8818			
36	TEST		176	GZ8818			
37	TEST		177	GZ8818			
38	TEST		178	GZ8818			
39	TEST		179	GZ8818			
40	TEST		180	GZ8818			

(b) (4)

0.25 mg/2ml strength: PBE Analysis for DCU (Label%):

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 78202 DOSE CONTENT UNIFORMITY:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0009
	CI:	0.0018
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0194
	CI:	-0.0186
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	**PASS**

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	106.84	Mean:	102.77	Ratio:	103.96
				90% CI for ratio:		(103.0,104.9)
(log scale)	Mean:	4.67	Mean:	4.63	Diff:	0.04
(log scale)	CV:	0.36	CV:	0.36		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.017	SigmaR:	0.017	Ratio:	1.013

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 DOSE CONTENT UNIFORMITY:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	101 102 103 104 105 106 107 108 109 110 111 112 113 114 115 116 117 118 119 120
	lot	2	LA1801 LM0022

```
TEST      product         1  TEST
          container      20  81 82 83 84 85 86 87 88 89 90 91 92 93
                             94 95 96 97 98 99 100
          lot             2  GZ7632 GZ8410
```

Listing, Raw & Log Data for ANDA 78202 DOSE CONTENT UNIFORMITY:

Obs	product	sect	container	lot	amount	pctlabel	lnDCU
							(b) (4)
1	REF		101	LA1801			
2	REF		102	LA1801			
3	REF		103	LA1801			
4	REF		104	LA1801			
5	REF		105	LA1801			
6	REF		106	LA1801			
7	REF		107	LA1801			
8	REF		108	LA1801			
9	REF		109	LA1801			
10	REF		110	LA1801			
11	REF		111	LM0022			
12	REF		112	LM0022			
13	REF		113	LM0022			
14	REF		114	LM0022			
15	REF		115	LM0022			
16	REF		116	LM0022			
17	REF		117	LM0022			
18	REF		118	LM0022			
19	REF		119	LM0022			
20	REF		120	LM0022			
21	TEST		81	GZ7632			
22	TEST		82	GZ7632			
23	TEST		83	GZ7632			
24	TEST		84	GZ7632			
25	TEST		85	GZ7632			
26	TEST		86	GZ7632			
27	TEST		87	GZ7632			
28	TEST		88	GZ7632			
29	TEST		89	GZ7632			
30	TEST		90	GZ7632			
31	TEST		91	GZ8410			
32	TEST		92	GZ8410			
33	TEST		93	GZ8410			
34	TEST		94	GZ8410			
35	TEST		95	GZ8410			
36	TEST		96	GZ8410			
37	TEST		97	GZ8410			
38	TEST		98	GZ8410			
39	TEST		99	GZ8410			
40	TEST		100	GZ8410			

2. Mean Nebulization Time and Mean Delivered Dose at the Mouthpiece

Mean Delivered Dose (%)						
			Variability (%CV)		TEST/REF	
Sector	Product	Mean	Within-Lot	Total	Arith	Geo

		Arith	Geo	Min	Max		Mean	Mean
		(N=20)	(N=20)	(N=10)	(N=10)	(N=20)	(N=20)	(N=20)
0.5 mg/2ml	Test	39.82	39.77	4.97	5.00	5.14	1.11	1.11
	Ref	35.98	35.95	3.29	3.93	3.95		
0.25 mg/2ml	Test	41.41	41.32	4.97	7.28	6.62	1.20	1.20
	Ref	34.59	34.55	4.58	4.72	4.56		

Mean Delivered Time (min)								
				Variability (%CV)			TEST/REF	
Sector	Product	Mean		Within-Lot		Total	Arith Mean	Geo Mean
		Arith	Geo	Min	Max			
		(N=20)	(N=20)	(N=10)	(N=10)	(N=20)	(N=20)	(N=20)
0.5 mg/2ml	Test	10.24	10.23	2.14	3.28	2.76	0.97	0.97
	Ref	10.54	10.53	2.38	4.90	3.79		
0.25 mg/2ml	Test	10.42	10.41	4.24	4.81	4.52	1.00	1.00
	Ref	10.41	10.40	2.91	5.22	4.27		

Comparison of the high strength and low strength product			
	High/Low ratio	High/Low ratio	
	Arith mean	Geo mean	
Test	0.96	0.96	
Ref	1.04	1.04	

0.5 mg/2ml strength: PBE Analysis for Mean Delivered Dose:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 78202 MEAN DELIVERED DOSE:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0076
	CI:	0.0139
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0099
	CI:	-0.0039
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	**PASS**

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	39.77	Mean:	35.95	Ratio:	110.60
				90% CI for ratio:		(107.9,113.4)
(log scale)	Mean:	3.68	Mean:	3.58	Diff:	0.10
(log scale)	CV:	1.39	CV:	1.12		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.051	SigmaR:	0.040	Ratio:	1.282

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 MEAN DELIVERED DOSE:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	141 142 143 144 145 146 147 148 149 150 151 152 153 154 155 156 157 158 159 160
	lot	2	LF0054 LM0080
TEST	product	1	TEST
	container	20	121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137 138 139 140
	lot	2	GZ7634 GZ8818

Listing, Raw & Log Data for ANDA 78202 MEAN DELIVERED DOSE:

Obs	product	sect	container	lot	Mean DT	Mean DD	lnMDD
1	REF		141	LF0054			
2	REF		142	LF0054			
3	REF		143	LF0054			
4	REF		144	LF0054			
5	REF		145	LF0054			
6	REF		146	LF0054			
7	REF		147	LF0054			
8	REF		148	LF0054			
9	REF		149	LF0054			
10	REF		150	LF0054			
11	REF		151	LM0080			
12	REF		152	LM0080			
13	REF		153	LM0080			
14	REF		154	LM0080			
15	REF		155	LM0080			
16	REF		156	LM0080			
17	REF		157	LM0080			
18	REF		158	LM0080			
19	REF		159	LM0080			
20	REF		160	LM0080			
21	TEST		121	GZ7634			
22	TEST		122	GZ7634			
23	TEST		123	GZ7634			
24	TEST		124	GZ7634			
25	TEST		125	GZ7634			
26	TEST		126	GZ7634			
27	TEST		127	GZ7634			
28	TEST		128	GZ7634			
29	TEST		129	GZ7634			
30	TEST		130	GZ7634			
31	TEST		131	GZ8818			
32	TEST		132	GZ8818			
33	TEST		133	GZ8818			
34	TEST		134	GZ8818			
35	TEST		135	GZ8818			
36	TEST		136	GZ8818			
37	TEST		137	GZ8818			
38	TEST		138	GZ8818			
39	TEST		139	GZ8818			
40	TEST		140	GZ8818			

(b) (4)

0.25 mg/2ml strength: PBE Analysis for Mean Delivered Dose:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 78202 MEAN DELIVERED DOSE:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0296
	CI:	0.0419
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	0.0130
	CI:	0.0251
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	**FAIL**

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	41.32	Mean:	34.55	Ratio:	119.59
				90% CI for ratio:		(116.1,123.2)
(log scale)	Mean:	3.72	Mean:	3.54	Diff:	0.18
(log scale)	CV:	1.74	CV:	1.28		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.065	SigmaR:	0.045	Ratio:	1.435

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 MEAN DELIVERED DOSE:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80
	lot	2	LA1801 LM0022
TEST	product	1	TEST
	container	20	41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60
	lot	2	GZ7632 GZ8410

Listing, Raw & Log Data for ANDA 78202 MEAN DELIVERED DOSE:

Obs	product	sect	container	lot	Mean DT	Mean DD	lnMDD
							(b) (4)
1	REF		61	LA1801			
2	REF		62	LA1801			
3	REF		63	LA1801			
4	REF		64	LA1801			
5	REF		65	LA1801			
6	REF		66	LA1801			
7	REF		67	LA1801			
8	REF		68	LA1801			
9	REF		69	LA1801			
10	REF		70	LA1801			
11	REF		71	LM0022			
12	REF		72	LM0022			
13	REF		73	LM0022			
14	REF		74	LM0022			
15	REF		75	LM0022			
16	REF		76	LM0022			
17	REF		77	LM0022			
18	REF		78	LM0022			
19	REF		79	LM0022			
20	REF		80	LM0022			
21	TEST		41	GZ7632			
22	TEST		42	GZ7632			
23	TEST		43	GZ7632			
24	TEST		44	GZ7632			
25	TEST		45	GZ7632			
26	TEST		46	GZ7632			
27	TEST		47	GZ7632			
28	TEST		48	GZ7632			
29	TEST		49	GZ7632			
30	TEST		50	GZ7632			
31	TEST		51	GZ8410			
32	TEST		52	GZ8410			
33	TEST		53	GZ8410			
34	TEST		54	GZ8410			
35	TEST		55	GZ8410			
36	TEST		56	GZ8410			
37	TEST		57	GZ8410			
38	TEST		58	GZ8410			
39	TEST		59	GZ8410			
40	TEST		60	GZ8410			

0.5 mg/2ml strength: PBE Analysis for Mean Delivery Time:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 78202 MEAN DELIVERY TIME:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0028
	CI:	-0.0009
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0208
	CI:	-0.0197
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	**PASS**

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	10.23	Mean:	10.53	Ratio:	97.20
				90% CI for ratio:		(95.5, 98.9)
(log scale)	Mean:	2.33	Mean:	2.35	Diff:	-0.03
(log scale)	CV:	1.20	CV:	1.58		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.028	SigmaR:	0.037	Ratio:	0.752

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 MEAN DELIVERY TIME:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	141 142 143 144 145 146 147 148 149 150 151 152 153 154 155 156 157 158 159 160
	lot	2	LF0054 LM0080
TEST	product	1	TEST
	container	20	121 122 123 124 125 126 127 128 129 130 131 132 133 134 135 136 137 138 139 140
	lot	2	GZ7634 GZ8818

Listing, Raw & Log Data for ANDA 78202 MEAN DELIVERY TIME:

Obs	product	sect	container	lot	Mean dd	Mean dt	lnMDT
					(b) (4)		
1	REF		141	LF0054			
2	REF		142	LF0054			
3	REF		143	LF0054			
4	REF		144	LF0054			
5	REF		145	LF0054			
6	REF		146	LF0054			
7	REF		147	LF0054			
8	REF		148	LF0054			
9	REF		149	LF0054			
10	REF		150	LF0054			
11	REF		151	LM0080			
12	REF		152	LM0080			
13	REF		153	LM0080			
14	REF		154	LM0080			
15	REF		155	LM0080			
16	REF		156	LM0080			
17	REF		157	LM0080			
18	REF		158	LM0080			
19	REF		159	LM0080			
20	REF		160	LM0080			
21	TEST		121	GZ7634			
22	TEST		122	GZ7634			
23	TEST		123	GZ7634			
24	TEST		124	GZ7634			
25	TEST		125	GZ7634			
26	TEST		126	GZ7634			
27	TEST		127	GZ7634			
28	TEST		128	GZ7634			
29	TEST		129	GZ7634			
30	TEST		130	GZ7634			
31	TEST		131	GZ8818			
32	TEST		132	GZ8818			
33	TEST		133	GZ8818			
34	TEST		134	GZ8818			
35	TEST		135	GZ8818			
36	TEST		136	GZ8818			
37	TEST		137	GZ8818			
38	TEST		138	GZ8818			
39	TEST		139	GZ8818			
40	TEST		140	GZ8818			

0.25 mg/2ml strength: PBE Analysis for Mean Delivery Time:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 78202 MEAN DELIVERY TIME:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0040
	CI:	-0.0012
	Pass/Fail:	PASS
Constant-scaled:	Point estimate:	-0.0210
	CI:	-0.0191
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	**PASS**

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	10.41	Mean:	10.40	Ratio:	100.18
				90% CI for ratio:		(97.9,102.5)
(log scale)	Mean:	2.34	Mean:	2.34	Diff:	0.00
(log scale)	CV:	1.90	CV:	1.85		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.045	SigmaR:	0.043	Ratio:	1.030

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 MEAN DELIVERY TIME:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80
	lot	2	LA1801 LM0022
TEST	product	1	TEST
	container	20	41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60
	lot	2	GZ7632 GZ8410

Listing, Raw & Log Data for ANDA 78202 MEAN DELIVERY TIME:

Obs	product	sect	container	lot	Mean dd	Mean dt	lnMDT
							(b) (4)
1	REF		61	LA1801			
2	REF		62	LA1801			
3	REF		63	LA1801			
4	REF		64	LA1801			
5	REF		65	LA1801			
6	REF		66	LA1801			
7	REF		67	LA1801			
8	REF		68	LA1801			
9	REF		69	LA1801			
10	REF		70	LA1801			
11	REF		71	LM0022			
12	REF		72	LM0022			
13	REF		73	LM0022			
14	REF		74	LM0022			
15	REF		75	LM0022			
16	REF		76	LM0022			
17	REF		77	LM0022			
18	REF		78	LM0022			
19	REF		79	LM0022			
20	REF		80	LM0022			
21	TEST		41	GZ7632			
22	TEST		42	GZ7632			
23	TEST		43	GZ7632			
24	TEST		44	GZ7632			
25	TEST		45	GZ7632			
26	TEST		46	GZ7632			
27	TEST		47	GZ7632			
28	TEST		48	GZ7632			
29	TEST		49	GZ7632			
30	TEST		50	GZ7632			
31	TEST		51	GZ8410			
32	TEST		52	GZ8410			
33	TEST		53	GZ8410			
34	TEST		54	GZ8410			
35	TEST		55	GZ8410			
36	TEST		56	GZ8410			
37	TEST		57	GZ8410			
38	TEST		58	GZ8410			
39	TEST		59	GZ8410			
40	TEST		60	GZ8410			

3. Particle Size of Budesonide Inhalation Suspension by Laser Diffraction (API in suspension/ampoule)

0.5 mg/2ml strength: PBE Analysis for Particle Size Distribution D50:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 78202 PARTICLE SIZE IN SOLUTION:

I. Summary

In Vitro PBE CRITERIA

MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0001
	CI:	0.0087
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0133
	CI:	-0.0056
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	**PASS**

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	9.38	Mean:	8.59	Ratio:	109.16
				90% CI for ratio:		(105.7,112.8)
(log scale)	Mean:	2.24	Mean:	2.15	Diff:	0.09
(log scale)	CV:	2.79	CV:	2.79		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.062	SigmaR:	0.060	Ratio:	1.042

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 PARTICLE SIZE IN SOLUTION:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	221 222 223 224 225 226 227 228 229 230 231 232 233 234 235 236 237 238 239 240
	lot	2	LF0054 LM0080
TEST	product	1	TEST

```
container      20  201 202 203 204 205 206 207 208 209 210
                   211 212 213 214 215 216 217 218 219 220
lot             2  GZ7634 GZ8818
```

Listing, Raw & Log Data for ANDA 78202 PARTICLE SIZE IN SOLUTION:

Obs	product	sect	container	lot	SPAN	D50	lnD50
							(b) (4)
1	REF	B	221	LF0054			
2	REF	B	222	LF0054			
3	REF	B	223	LF0054			
4	REF	B	224	LF0054			
5	REF	B	225	LF0054			
6	REF	B	226	LF0054			
7	REF	B	227	LF0054			
8	REF	B	228	LF0054			
9	REF	B	229	LF0054			
10	REF	B	230	LF0054			
11	REF	B	231	LM0080			
12	REF	B	232	LM0080			
13	REF	B	233	LM0080			
14	REF	B	234	LM0080			
15	REF	B	235	LM0080			
16	REF	B	236	LM0080			
17	REF	B	237	LM0080			
18	REF	B	238	LM0080			
19	REF	B	239	LM0080			
20	REF	B	240	LM0080			
21	TEST	B	201	GZ7634			
22	TEST	B	202	GZ7634			
23	TEST	B	203	GZ7634			
24	TEST	B	204	GZ7634			
25	TEST	B	205	GZ7634			
26	TEST	B	206	GZ7634			
27	TEST	B	207	GZ7634			
28	TEST	B	208	GZ7634			
29	TEST	B	209	GZ7634			
30	TEST	B	210	GZ7634			
31	TEST	B	211	GZ8818			
32	TEST	B	212	GZ8818			
33	TEST	B	213	GZ8818			
34	TEST	B	214	GZ8818			
35	TEST	B	215	GZ8818			
36	TEST	B	216	GZ8818			
37	TEST	B	217	GZ8818			
38	TEST	B	218	GZ8818			
39	TEST	B	219	GZ8818			
40	TEST	B	220	GZ8818			

0.25 mg/2ml strength: PBE Analysis for Particle Size Distribution D50:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 78202 PARTICLE SIZE IN SOLUTION:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0042
	CI:	0.0023
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0184
	CI:	-0.0129
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	**PASS**

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	8.14	Mean:	8.09	Ratio:	100.64
				90% CI for ratio:		(97.0,104.4)
(log scale)	Mean:	2.10	Mean:	2.09	Diff:	0.01
(log scale)	CV:	3.71	CV:	2.70		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.078	SigmaR:	0.056	Ratio:	1.381

Listing, Raw & Log Data for ANDA 78202 PARTICLE SIZE IN SOLUTION:

Obs	product	sect	container	lot	SPAN	D50	lnD50
1	REF	B	.	141	(b) (4)		
2	REF	B	.	142			
3	REF	B	.	143			
4	REF	B	.	144			
5	REF	B	.	145			
6	REF	B	.	146			
7	REF	B	.	147			
8	REF	B	.	148			
9	REF	B	.	149			
10	REF	B	.	150			
11	REF	B	.	151			
12	REF	B	.	152			

(b) (4)

13	REF	B	.	153
14	REF	B	.	154
15	REF	B	.	155
16	REF	B	.	156
17	REF	B	.	157
18	REF	B	.	158
19	REF	B	.	159
20	REF	B	.	160
21	TEST	B	.	121
22	TEST	B	.	122
23	TEST	B	.	123
24	TEST	B	.	124
25	TEST	B	.	125
26	TEST	B	.	126
27	TEST	B	.	127
28	TEST	B	.	128
29	TEST	B	.	129
30	TEST	B	.	130
31	TEST	B	.	131
32	TEST	B	.	132
33	TEST	B	.	133
34	TEST	B	.	134
35	TEST	B	.	135
36	TEST	B	.	136
37	TEST	B	.	137
38	TEST	B	.	138
39	TEST	B	.	139
40	TEST	B	.	140

0.5 mg/2ml strength: PBE Analysis for Particle Size Distribution Span:

```
In Vitro PBE Analysis - Approximate Confidence Interval
                     Using Moment-Based Simplified Parameter Estimates
                                          for
                 ANDA 78202 PARTICLE SIZE IN SOLUTION:


    I.  Summary

                                In Vitro PBE CRITERIA
                                MIXED SCALING APPROACH
             Point Estimate and Upper Bound of 95% Confidence Interval

                                 Linearized Theta P

             Reference-scaled:      Point estimate:    0.0009
                                    CI:                0.0022
                                    Pass/Fail:          FAIL

             Constant-scaled:       Point estimate:   -0.0190
                                    CI:               -0.0178
                                    Pass/Fail:          PASS

             Overall Test Outcome:  Pass/Fail:          PASS


    Notes:  Constant-scaled tests are based on SigmaT0 = 0.10 and
        Epsilon = 0.01.  Linearized tests are based on regulatory limit
        (Theta P) of 2.0891.  For linearized theta P, if the upper bound of
        the confidence interval is < 0, PASS.  For linearized theta P, if the
```

upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	1.37	Mean:	1.43	Ratio:	96.13
				90% CI for ratio:		(94.8, 97.5)
(log scale)	Mean:	0.32	Mean:	0.36	Diff:	-0.04
(log scale)	CV:	9.26	CV:	6.05		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.029	SigmaR:	0.022	Ratio:	1.361

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 PARTICLE SIZE IN SOLUTION:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	221 222 223 224 225 226 227 228 229 230 231 232 233 234 235 236 237 238 239 240
	lot	2	LF0054 LM0080
TEST	product	1	TEST
	container	20	201 202 203 204 205 206 207 208 209 210 211 212 213 214 215 216 217 218 219 220
	lot	2	GZ7634 GZ8818

Listing, Raw & Log Data for ANDA 78202 PARTICLE SIZE IN SOLUTION:

Obs	product	sect	container	lot	D50	SPAN	lnSPAN
1	REF	B	221	LF0054	[redacted]		
2	REF	B	222	LF0054			
3	REF	B	223	LF0054			
4	REF	B	224	LF0054			
5	REF	B	225	LF0054			
6	REF	B	226	LF0054			
7	REF	B	227	LF0054			
8	REF	B	228	LF0054			
9	REF	B	229	LF0054			
10	REF	B	230	LF0054			
11	REF	B	231	LM0080			
12	REF	B	232	LM0080			

(b) (4)

13	REF	B	233	LM0080	(b) (4)
14	REF	B	234	LM0080	
15	REF	B	235	LM0080	
16	REF	B	236	LM0080	
17	REF	B	237	LM0080	
18	REF	B	238	LM0080	
19	REF	B	239	LM0080	
20	REF	B	240	LM0080	
21	TEST	B	201	GZ7634	
22	TEST	B	202	GZ7634	
23	TEST	B	203	GZ7634	
24	TEST	B	204	GZ7634	
25	TEST	B	205	GZ7634	
26	TEST	B	206	GZ7634	
27	TEST	B	207	GZ7634	
28	TEST	B	208	GZ7634	
29	TEST	B	209	GZ7634	
30	TEST	B	210	GZ7634	
31	TEST	B	211	GZ8818	
32	TEST	B	212	GZ8818	
33	TEST	B	213	GZ8818	
34	TEST	B	214	GZ8818	
35	TEST	B	215	GZ8818	
36	TEST	B	216	GZ8818	
37	TEST	B	217	GZ8818	
38	TEST	B	218	GZ8818	
39	TEST	B	219	GZ8818	
40	TEST	B	220	GZ8818	

0.25 mg/2ml strength: PBE Analysis for Particle Size Distribution Span:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 78202 PARTICLE SIZE IN SOLUTION:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0085
	CI:	0.0142
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0074
	CI:	-0.0023
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	**PASS**

c

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the

upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	1.37	Mean:	1.55	Ratio:	88.50
				90% CI for ratio:		(86.5, 90.5)
(log scale)	Mean:	0.31	Mean:	0.44	Diff:	-0.12
(log scale)	CV:	10.55	CV:	11.18		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.033	SigmaR:	0.049	Ratio:	0.680

Listing, Raw & Log Data for ANDA 78202 PARTICLE SIZE IN SOLUTION:

Obs	product	sect	container	lot	D50	SPAN	lnSPAN
							(b) (4)
1	REF	B	.	141			
2	REF	B	.	142			
3	REF	B	.	143			
4	REF	B	.	144			
5	REF	B	.	145			
6	REF	B	.	146			
7	REF	B	.	147			
8	REF	B	.	148			
9	REF	B	.	149			
10	REF	B	.	150			
11	REF	B	.	151			
12	REF	B	.	152			
13	REF	B	.	153			
14	REF	B	.	154			
15	REF	B	.	155			
16	REF	B	.	156			
17	REF	B	.	157			
18	REF	B	.	158			
19	REF	B	.	159			
20	REF	B	.	160			
21	TEST	B	.	121			
22	TEST	B	.	122			
23	TEST	B	.	123			
24	TEST	B	.	124			
25	TEST	B	.	125			
26	TEST	B	.	126			
27	TEST	B	.	127			
28	TEST	B	.	128			
29	TEST	B	.	129			
30	TEST	B	.	130			
31	TEST	B	.	131			
32	TEST	B	.	132			
33	TEST	B	.	133			

34	TEST	B	.	134	(b) (4)
35	TEST	B	.	135	
36	TEST	B	.	136	
37	TEST	B	.	137	
38	TEST	B	.	138	
39	TEST	B	.	139	
40	TEST	B	.	140	

4. Droplet Size Distribution of the Nebulized Aerosol by Laser Diffraction

0.5 mg/2ml strength: PBE Analysis for Droplet Size Distribution D50:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 78202 DROPLET SIZE IN AEROSOL:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0016
	CI:	0.0011
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0197
	CI:	-0.0174
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	**PASS**

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST		REFERENCE		T/R Ratio
(orig scale) Mean:	3.06	Mean:	2.97	Ratio:	103.25

				90% CI for ratio:	(101.2,105.4)	
(log scale)	Mean:	1.12	Mean:	1.09	Diff:	0.03
(log scale)	CV:	3.62	CV:	3.35		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.041	SigmaR:	0.036	Ratio:	1.112

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 DROPLET SIZE IN AEROSOL:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	101 102 103 104 105 106 107 108 109 110 111 112 113 114 115 116 117 118 119 120
	lot	2	LF0054 LM0080
TEST	product	1	TEST
	container	20	81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100
	lot	2	GZ7634 GZ8818

Listing, Raw & Log Data for ANDA 78202 DROPLET SIZE IN AEROSOL:

Obs	product	sect	container	lot	D50	SPAN	lnSPAN
							(b) (4)
1	REF	B	101	LF0054			
2	REF	B	102	LF0054			
3	REF	B	103	LF0054			
4	REF	B	104	LF0054			
5	REF	B	105	LF0054			
6	REF	B	106	LF0054			
7	REF	B	107	LF0054			
8	REF	B	108	LF0054			
9	REF	B	109	LF0054			
10	REF	B	110	LF0054			
11	REF	B	111	LM0080			
12	REF	B	112	LM0080			
13	REF	B	113	LM0080			
14	REF	B	114	LM0080			
15	REF	B	115	LM0080			
16	REF	B	116	LM0080			
17	REF	B	117	LM0080			
18	REF	B	118	LM0080			
19	REF	B	119	LM0080			
20	REF	B	120	LM0080			
21	TEST	B	81	GZ7634			
22	TEST	B	82	GZ7634			
23	TEST	B	83	GZ7634			
24	TEST	B	84	GZ7634			
25	TEST	B	85	GZ7634			
26	TEST	B	86	GZ7634			
27	TEST	B	87	GZ7634			

28	TEST	B	88	GZ7634	(b) (4)
29	TEST	B	89	GZ7634	
30	TEST	B	90	GZ7634	
31	TEST	B	91	GZ8818	
32	TEST	B	92	GZ8818	
33	TEST	B	93	GZ8818	
34	TEST	B	94	GZ8818	
35	TEST	B	95	GZ8818	
36	TEST	B	96	GZ8818	
37	TEST	B	97	GZ8818	
38	TEST	B	98	GZ8818	
39	TEST	B	99	GZ8818	
40	TEST	B	100	GZ8818	

0.25 mg/2ml strength: PBE Analysis for Droplet Size Distribution D50:

This data is not needed per OGD Control # 03-612.

0.5 mg/2ml strength: PBE Analysis for Droplet Size Distribution Span:

```
In Vitro PBE Analysis - Approximate Confidence Interval
          Using Moment-Based Simplified Parameter Estimates
                                for
       ANDA 78202 DROPLET SIZE IN AEROSOL:


I.  Summary

                        In Vitro PBE CRITERIA
                        MIXED SCALING APPROACH
     Point Estimate and Upper Bound of 95% Confidence Interval

                         Linearized Theta P

     Reference-scaled:      Point estimate:   -0.0098
                            CI:               -0.0049
                            Pass/Fail:          PASS

     Constant-scaled:       Point estimate:   -0.0226
                            CI:               -0.0201
                            Pass/Fail:          PASS

     Overall Test Outcome:  Pass/Fail:          PASS


Notes:  Constant-scaled tests are based on SigmaT0 = 0.10 and
    Epsilon = 0.01.  Linearized tests are based on regulatory limit
    (Theta P) of 2.0891.  For linearized theta P, if the upper bound of
    the confidence interval is < 0, PASS.  For linearized theta P, if the
    upper bound of the confidence interval is > 0, FAIL.  If the estimate
    of sigmaR > sigmaT0, use reference scaling.  If sigmaR < sigmaT0,
    use constant scaling.  If sigmaR = 0.10, sponsors should use either
    reference scaling or constant scaling at either side of the changeover
    point (0.10).



II.  Statistical Details
```

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	3.16	Mean:	3.18	Ratio:	99.39
				90% CI for ratio:		(96.5,102.4)
(log scale)	Mean:	1.15	Mean:	1.16	Diff:	-0.01
(log scale)	CV:	4.23	CV:	5.36		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.049	SigmaR:	0.062	Ratio:	0.785

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 DROPLET SIZE IN AEROSOL:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	101 102 103 104 105 106 107 108 109 110 111 112 113 114 115 116 117 118 119 120
	lot	2	LF0054 LM0080
TEST	product	1	TEST
	container	20	81 82 83 84 85 86 87 88 89 90 91 92 93 94 95 96 97 98 99 100
	lot	2	GZ7634 GZ8818

Listing, Raw & Log Data for ANDA 78202 DROPLET SIZE IN AEROSOL:

Obs	product	sect	container	lot	SPAN	D50	lnD50
							(b) (4)
1	REF	B	101	LF0054			
2	REF	B	102	LF0054			
3	REF	B	103	LF0054			
4	REF	B	104	LF0054			
5	REF	B	105	LF0054			
6	REF	B	106	LF0054			
7	REF	B	107	LF0054			
8	REF	B	108	LF0054			
9	REF	B	109	LF0054			
10	REF	B	110	LF0054			
11	REF	B	111	LM0080			
12	REF	B	112	LM0080			
13	REF	B	113	LM0080			
14	REF	B	114	LM0080			
15	REF	B	115	LM0080			
16	REF	B	116	LM0080			
17	REF	B	117	LM0080			
18	REF	B	118	LM0080			
19	REF	B	119	LM0080			
20	REF	B	120	LM0080			

21	TEST	B	81	GZ7634	(b) (4)
22	TEST	B	82	GZ7634	
23	TEST	B	83	GZ7634	
24	TEST	B	84	GZ7634	
25	TEST	B	85	GZ7634	
26	TEST	B	86	GZ7634	
27	TEST	B	87	GZ7634	
28	TEST	B	88	GZ7634	
29	TEST	B	89	GZ7634	
30	TEST	B	90	GZ7634	
31	TEST	B	91	GZ8818	
32	TEST	B	92	GZ8818	
33	TEST	B	93	GZ8818	
34	TEST	B	94	GZ8818	
35	TEST	B	95	GZ8818	
36	TEST	B	96	GZ8818	
37	TEST	B	97	GZ8818	
38	TEST	B	98	GZ8818	
39	TEST	B	99	GZ8818	
40	TEST	B	100	GZ8818	

0.25 mg/2ml strength: PBE Analysis for Droplet Size Distribution Span:

This data is not needed per OGD Control # 03-612.

5. Particle (and Aggregates) Size Distribution of the Nebulized Aerosol by Cascade Impactor

0.5 mg/2ml strength: PBE Analysis for Amount A:

```
In Vitro PBE Analysis - Approximate Confidence Interval
                     Using Moment-Based Simplified Parameter Estimates
                                          for
                  ANDA 78202 Cascade Impactor Amount A:


    I.  Summary

                                In Vitro PBE CRITERIA
                                MIXED SCALING APPROACH
             Point Estimate and Upper Bound of 95% Confidence Interval

                                 Linearized Theta P

             Reference-scaled:      Point estimate:    0.0130
                                    CI:                0.0219
                                    Pass/Fail:          FAIL

             Constant-scaled:       Point estimate:   -0.0058
                                    CI:                0.0030
                                    Pass/Fail:          FAIL

             Overall Test Outcome:  Pass/Fail:          FAIL


    Notes:  Constant-scaled tests are based on SigmaT0 = 0.10 and
        Epsilon = 0.01.  Linearized tests are based on regulatory limit
        (Theta P) of 2.0891.  For linearized theta P, if the upper bound of
```

the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	199.28	Mean:	179.69	Ratio:	110.90
				90% CI for ratio:		(107.5,114.4)
(log scale)	Mean:	5.29	Mean:	5.19	Diff:	0.10
(log scale)	CV:	1.43	CV:	0.61		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.076	SigmaR:	0.032	Ratio:	2.381

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 Cascade Impactor Amount A:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80
	lot	2	LF0054 LM0080
TEST	product	1	TEST
	container	20	41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60
	lot	2	GZ7634 GZ8818

Listing, Raw & Log Data for ANDA 78202 Cascade Impactor Amount A:

Obs	product	sect	container	lot	amount B	amount A	lnA
1	REF	B	61	LF0054	(b) (4)		
2	REF	B	62	LF0054			
3	REF	B	63	LF0054			
4	REF	B	64	LF0054			
5	REF	B	65	LF0054			
6	REF	B	66	LF0054			
7	REF	B	67	LF0054			
8	REF	B	68	LF0054			
9	REF	B	69	LF0054			
10	REF	B	70	LF0054			
11	REF	B	71	LM0080			

12	REF	B	72	LM0080	(b) (4)
13	REF	B	73	LM0080	
14	REF	B	74	LM0080	
15	REF	B	75	LM0080	
16	REF	B	76	LM0080	
17	REF	B	77	LM0080	
18	REF	B	78	LM0080	
19	REF	B	79	LM0080	
20	REF	B	80	LM0080	
21	TEST	B	41	GZ7634	
22	TEST	B	42	GZ7634	
23	TEST	B	43	GZ7634	
24	TEST	B	44	GZ7634	
25	TEST	B	45	GZ7634	
26	TEST	B	46	GZ7634	
27	TEST	B	47	GZ7634	
28	TEST	B	48	GZ7634	
29	TEST	B	49	GZ7634	
30	TEST	B	50	GZ7634	
31	TEST	B	51	GZ8818	
32	TEST	B	52	GZ8818	
33	TEST	B	53	GZ8818	
34	TEST	B	54	GZ8818	
35	TEST	B	55	GZ8818	
36	TEST	B	56	GZ8818	
37	TEST	B	57	GZ8818	
38	TEST	B	58	GZ8818	
39	TEST	B	59	GZ8818	
40	TEST	B	60	GZ8818	

0.25 mg/2ml strength: PBE Analysis for Amount A:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 78202 Cascade Impactor Amount A:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0171
	CI:	0.0247
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0003
	CI:	0.0071
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	**FAIL**

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of

the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

	TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	101.42	Mean:	87.97	Ratio: 115.30
				90% CI for ratio:	(112.7,118.0)
(log scale)	Mean:	4.62	Mean:	4.48	Diff: 0.14
(log scale)	CV:	1.00	CV:	0.90	
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio: -
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio: -
(log scale)	SigmaT:	0.046	SigmaR:	0.040	Ratio: 1.144

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 Cascade Impactor Amount A:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40
	lot	2	LA1801 LM0022
TEST	product	1	TEST
	container	20	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
	lot	2	GZ7632 GZ8410

Listing, Raw & Log Data for ANDA 78202 Cascade Impactor Amount A:

Obs	product	sect	container	lot	amount B	amount A	lnA
1	REF	B	21	LA1801	[redacted]		
2	REF	B	22	LA1801			
3	REF	B	23	LA1801			
4	REF	B	24	LA1801			
5	REF	B	25	LA1801			
6	REF	B	26	LA1801			
7	REF	B	27	LA1801			
8	REF	B	28	LA1801			
9	REF	B	29	LA1801			
10	REF	B	30	LA1801			
11	REF	B	31	LM0022			
12	REF	B	32	LM0022			

(b) (4)

					(b) (4)
13	REF	B	33	LM0022	
14	REF	B	34	LM0022	
15	REF	B	35	LM0022	
16	REF	B	36	LM0022	
17	REF	B	37	LM0022	
18	REF	B	38	LM0022	
19	REF	B	39	LM0022	
20	REF	B	40	LM0022	
21	TEST	B	1	GZ7632	
22	TEST	B	2	GZ7632	
23	TEST	B	3	GZ7632	
24	TEST	B	4	GZ7632	
25	TEST	B	5	GZ7632	
26	TEST	B	6	GZ7632	
27	TEST	B	7	GZ7632	
28	TEST	B	8	GZ7632	
29	TEST	B	9	GZ7632	
30	TEST	B	10	GZ7632	
31	TEST	B	11	GZ8410	
32	TEST	B	12	GZ8410	
33	TEST	B	13	GZ8410	
34	TEST	B	14	GZ8410	
35	TEST	B	15	GZ8410	
36	TEST	B	16	GZ8410	
37	TEST	B	17	GZ8410	
38	TEST	B	18	GZ8410	
39	TEST	B	19	GZ8410	
40	TEST	B	20	GZ8410	

0.5 mg/2ml strength: PBE Analysis for Amount B:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 78202 Cascade Impactor **Amount B**:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0075
	CI:	0.0195
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0058
	CI:	0.0055
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	**FAIL**

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate

of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	179.25	Mean:	160.07	Ratio:	111.98
				90% CI for ratio:		(107.8,116.3)
(log scale)	Mean:	5.19	Mean:	5.08	Diff:	0.11
(log scale)	CV:	1.54	CV:	1.19		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.080	SigmaR:	0.060	Ratio:	1.324

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 Cascade Impactor Amount B:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80
	lot	2	LF0054 LM0080
TEST	product	1	TEST
	container	20	41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60
	lot	2	GZ7634 GZ8818

Listing, Raw & Log Data for ANDA 78202 Cascade Impactor Amount B:

Obs	product	sect	container	lot	Amount A	Amount B	lnB
1	REF	B	61	LF0054	[redacted]		
2	REF	B	62	LF0054			
3	REF	B	63	LF0054			
4	REF	B	64	LF0054			
5	REF	B	65	LF0054			
6	REF	B	66	LF0054			
7	REF	B	67	LF0054			
8	REF	B	68	LF0054			
9	REF	B	69	LF0054			
10	REF	B	70	LF0054			
11	REF	B	71	LM0080			
12	REF	B	72	LM0080			
13	REF	B	73	LM0080			
14	REF	B	74	LM0080			
15	REF	B	75	LM0080			
16	REF	B	76	LM0080			

(b) (4)

17	REF	B	77	LM0080	(b) (4)
18	REF	B	78	LM0080	
19	REF	B	79	LM0080	
20	REF	B	80	LM0080	
21	TEST	B	41	GZ7634	
22	TEST	B	42	GZ7634	
23	TEST	B	43	GZ7634	
24	TEST	B	44	GZ7634	
25	TEST	B	45	GZ7634	
26	TEST	B	46	GZ7634	
27	TEST	B	47	GZ7634	
28	TEST	B	48	GZ7634	
29	TEST	B	49	GZ7634	
30	TEST	B	50	GZ7634	
31	TEST	B	51	GZ8818	
32	TEST	B	52	GZ8818	
33	TEST	B	53	GZ8818	
34	TEST	B	54	GZ8818	
35	TEST	B	55	GZ8818	
36	TEST	B	56	GZ8818	
37	TEST	B	57	GZ8818	
38	TEST	B	58	GZ8818	
39	TEST	B	59	GZ8818	
40	TEST	B	60	GZ8818	

0.25 mg/2ml strength: PBE Analysis for Amount B:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 78202 Cascade Impactor Amount B:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0153
	CI:	0.0233
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0015
	CI:	0.0063
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	**FAIL**

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover

point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	89.52	Mean:	77.91	Ratio:	**114.90**
				90% CI for ratio:		**(112.1,117.8)**
(log scale)	Mean:	4.49	Mean:	4.36	Diff:	0.14
(log scale)	CV:	1.07	CV:	1.02		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.048	SigmaR:	0.045	Ratio:	1.081

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 Cascade Impactor Amount B:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40
	lot	2	LA1801 LM0022
TEST	product	1	TEST
	container	20	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
	lot	2	GZ7632 GZ8410

Listing, Raw & Log Data for ANDA 78202 Cascade Impactor Amount B:

Obs	product	sect	container	lot	amount A	amount B	lnB
1	REF	B	21	LA1801	[redacted]		
2	REF	B	22	LA1801			
3	REF	B	23	LA1801			
4	REF	B	24	LA1801			
5	REF	B	25	LA1801			
6	REF	B	26	LA1801			
7	REF	B	27	LA1801			
8	REF	B	28	LA1801			
9	REF	B	29	LA1801			
10	REF	B	30	LA1801			
11	REF	B	31	LM0022			
12	REF	B	32	LM0022			
13	REF	B	33	LM0022			
14	REF	B	34	LM0022			
15	REF	B	35	LM0022			
16	REF	B	36	LM0022			
17	REF	B	37	LM0022			

(b) (4)

(b) (4)

18	REF	B	38	LM0022
19	REF	B	39	LM0022
20	REF	B	40	LM0022
21	TEST	B	1	GZ7632
22	TEST	B	2	GZ7632
23	TEST	B	3	GZ7632
24	TEST	B	4	GZ7632
25	TEST	B	5	GZ7632
26	TEST	B	6	GZ7632
27	TEST	B	7	GZ7632
28	TEST	B	8	GZ7632
29	TEST	B	9	GZ7632
30	TEST	B	10	GZ7632
31	TEST	B	11	GZ8410
32	TEST	B	12	GZ8410
33	TEST	B	13	GZ8410
34	TEST	B	14	GZ8410
35	TEST	B	15	GZ8410
36	TEST	B	16	GZ8410
37	TEST	B	17	GZ8410
38	TEST	B	18	GZ8410
39	TEST	B	19	GZ8410
40	TEST	B	20	GZ8410

0.5 mg/2ml strength: PBE Analysis for Amount R:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 78202 Cascade Impactor Amount R:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0131
	CI:	0.0345
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	0.0051
	CI:	0.0254
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	**FAIL**

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	136.85	Mean:	118.44	Ratio:	115.54
				90% CI for ratio:		(109.8,121.6)
(log scale)	Mean:	4.92	Mean:	4.77	Diff:	0.14
(log scale)	CV:	2.25	CV:	1.65		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.111	SigmaR:	0.079	Ratio:	1.405

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 Cascade Impactor Amount R:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80
	lot	2	LF0054 LM0080
TEST	product	1	TEST
	container	20	41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60
	lot	2	GZ7634 GZ8818

Listing, Raw & Log Data for ANDA 78202 Cascade Impactor Amount R:

Obs	product	sect	container	lot	amount A	amount R	lnR
							(b) (4)
1	REF	B	61	LF0054			
2	REF	B	62	LF0054			
3	REF	B	63	LF0054			
4	REF	B	64	LF0054			
5	REF	B	65	LF0054			
6	REF	B	66	LF0054			
7	REF	B	67	LF0054			
8	REF	B	68	LF0054			
9	REF	B	69	LF0054			
10	REF	B	70	LF0054			
11	REF	B	71	LM0080			
12	REF	B	72	LM0080			
13	REF	B	73	LM0080			
14	REF	B	74	LM0080			
15	REF	B	75	LM0080			
16	REF	B	76	LM0080			
17	REF	B	77	LM0080			
18	REF	B	78	LM0080			
19	REF	B	79	LM0080			

20	REF	B	80	LM0080	(b) (4)
21	TEST	B	41	GZ7634	
22	TEST	B	42	GZ7634	
23	TEST	B	43	GZ7634	
24	TEST	B	44	GZ7634	
25	TEST	B	45	GZ7634	
26	TEST	B	46	GZ7634	
27	TEST	B	47	GZ7634	
28	TEST	B	48	GZ7634	
29	TEST	B	49	GZ7634	
30	TEST	B	50	GZ7634	
31	TEST	B	51	GZ8818	
32	TEST	B	52	GZ8818	
33	TEST	B	53	GZ8818	
34	TEST	B	54	GZ8818	
35	TEST	B	55	GZ8818	
36	TEST	B	56	GZ8818	
37	TEST	B	57	GZ8818	
38	TEST	B	58	GZ8818	
39	TEST	B	59	GZ8818	
40	TEST	B	60	GZ8818	

0.25 mg/2ml strength: PBE Analysis for Amount R:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 78202 Cascade Impactor Amount R:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0401
	CI:	0.0568
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	0.0265
	CI:	0.0427
	Pass/Fail:	FAIL
Overall Test Outcome:	Pass/Fail:	**FAIL**

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	74.38	Mean:	59.93	**Ratio:**	**124.11**
				90% CI for ratio:		**(120.0,128.4)**
(log scale)	Mean:	4.31	Mean:	4.09	Diff:	0.22
(log scale)	CV:	1.56	CV:	1.44		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.067	SigmaR:	0.059	Ratio:	1.146

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 Cascade Impactor Amount R:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40
	lot	2	LA1801 LM0022
TEST	product	1	TEST
	container	20	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
	lot	2	GZ7632 GZ8410

Listing, Raw & Log Data for ANDA 78202 Cascade Impactor Amount R:

Obs	product	sect	container	lot	amount A	amount R	lnR
1	REF	B	21	LA1801			
2	REF	B	22	LA1801			
3	REF	B	23	LA1801			
4	REF	B	24	LA1801			
5	REF	B	25	LA1801			
6	REF	B	26	LA1801			
7	REF	B	27	LA1801			
8	REF	B	28	LA1801			
9	REF	B	29	LA1801			
10	REF	B	30	LA1801			
11	REF	B	31	LM0022			
12	REF	B	32	LM0022			
13	REF	B	33	LM0022			
14	REF	B	34	LM0022			
15	REF	B	35	LM0022			
16	REF	B	36	LM0022			
17	REF	B	37	LM0022			
18	REF	B	38	LM0022			
19	REF	B	39	LM0022			
20	REF	B	40	LM0022			
21	TEST	B	1	GZ7632			

(b) (4)

(b) (4)

22	TEST	B	2	GZ7632
23	TEST	B	3	GZ7632
24	TEST	B	4	GZ7632
25	TEST	B	5	GZ7632
26	TEST	B	6	GZ7632
27	TEST	B	7	GZ7632
28	TEST	B	8	GZ7632
29	TEST	B	9	GZ7632
30	TEST	B	10	GZ7632
31	TEST	B	11	GZ8410
32	TEST	B	12	GZ8410
33	TEST	B	13	GZ8410
34	TEST	B	14	GZ8410
35	TEST	B	15	GZ8410
36	TEST	B	16	GZ8410
37	TEST	B	17	GZ8410
38	TEST	B	18	GZ8410
39	TEST	B	19	GZ8410
40	TEST	B	20	GZ8410

0.5 mg/2ml strength: PBE Analysis for Amount C:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 78202 Cascade Impactor Amount C:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0003
	CI:	0.0008
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0203
	CI:	-0.0193
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	**PASS**

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	472.35	Mean:	469.11	**Ratio:**	**100.69**
				90% CI for ratio:		**(99.2,102.2)**
(log scale)	Mean:	6.16	Mean:	6.15	Diff:	0.01
(log scale)	CV:	0.54	CV:	0.34		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.033	SigmaR:	0.021	Ratio:	1.570

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 Cascade Impactor Amount C:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80
	lot	2	LF0054 LM0080
TEST	product	1	TEST
	container	20	41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60
	lot	2	GZ7634 GZ8818

Listing, Raw & Log Data for ANDA 78202 Cascade Impactor Amount C:

Obs	product	sect	container	lot	amount A	amount C	lnC
							(b) (4)
1	REF	B	61	LF0054			
2	REF	B	62	LF0054			
3	REF	B	63	LF0054			
4	REF	B	64	LF0054			
5	REF	B	65	LF0054			
6	REF	B	66	LF0054			
7	REF	B	67	LF0054			
8	REF	B	68	LF0054			
9	REF	B	69	LF0054			
10	REF	B	70	LF0054			
11	REF	B	71	LM0080			
12	REF	B	72	LM0080			
13	REF	B	73	LM0080			
14	REF	B	74	LM0080			
15	REF	B	75	LM0080			
16	REF	B	76	LM0080			
17	REF	B	77	LM0080			
18	REF	B	78	LM0080			
19	REF	B	79	LM0080			
20	REF	B	80	LM0080			
21	TEST	B	41	GZ7634			
22	TEST	B	42	GZ7634			
23	TEST	B	43	GZ7634			

(b) (4)

24	TEST	B	44	GZ7634
25	TEST	B	45	GZ7634
26	TEST	B	46	GZ7634
27	TEST	B	47	GZ7634
28	TEST	B	48	GZ7634
29	TEST	B	49	GZ7634
30	TEST	B	50	GZ7634
31	TEST	B	51	GZ8818
32	TEST	B	52	GZ8818
33	TEST	B	53	GZ8818
34	TEST	B	54	GZ8818
35	TEST	B	55	GZ8818
36	TEST	B	56	GZ8818
37	TEST	B	57	GZ8818
38	TEST	B	58	GZ8818
39	TEST	B	59	GZ8818
40	TEST	B	60	GZ8818

0.25 mg/2ml strength: PBE Analysis for Amount C:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 78202 Cascade Impactor Amount C:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	-0.0015
	CI:	0.0004
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0203
	CI:	-0.0187
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	**PASS**

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	237.04	Mean:	233.80	Ratio:	101.39
				90% CI for ratio:		(99.5,103.3)
(log scale)	Mean:	5.47	Mean:	5.45	Diff:	0.01
(log scale)	CV:	0.71	CV:	0.58		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.039	SigmaR:	0.032	Ratio:	1.234

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 Cascade Impactor Amount C:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40
	lot	2	LA1801 LM0022
TEST	product	1	TEST
	container	20	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
	lot	2	GZ7632 GZ8410

Listing, Raw & Log Data for ANDA 78202 Cascade Impactor Amount C:

Obs	product	sect	container	lot	amount A	amount C	lnC
							(b) (4)
1	REF	B	21	LA1801			
2	REF	B	22	LA1801			
3	REF	B	23	LA1801			
4	REF	B	24	LA1801			
5	REF	B	25	LA1801			
6	REF	B	26	LA1801			
7	REF	B	27	LA1801			
8	REF	B	28	LA1801			
9	REF	B	29	LA1801			
10	REF	B	30	LA1801			
11	REF	B	31	LM0022			
12	REF	B	32	LM0022			
13	REF	B	33	LM0022			
14	REF	B	34	LM0022			
15	REF	B	35	LM0022			
16	REF	B	36	LM0022			
17	REF	B	37	LM0022			
18	REF	B	38	LM0022			
19	REF	B	39	LM0022			
20	REF	B	40	LM0022			
21	TEST	B	1	GZ7632			
22	TEST	B	2	GZ7632			
23	TEST	B	3	GZ7632			
24	TEST	B	4	GZ7632			

(b) (4)

25	TEST	B	5	GZ7632
26	TEST	B	6	GZ7632
27	TEST	B	7	GZ7632
28	TEST	B	8	GZ7632
29	TEST	B	9	GZ7632
30	TEST	B	10	GZ7632
31	TEST	B	11	GZ8410
32	TEST	B	12	GZ8410
33	TEST	B	13	GZ8410
34	TEST	B	14	GZ8410
35	TEST	B	15	GZ8410
36	TEST	B	16	GZ8410
37	TEST	B	17	GZ8410
38	TEST	B	18	GZ8410
39	TEST	B	19	GZ8410
40	TEST	B	20	GZ8410

0.5 mg/2ml strength: PBE Analysis for Amount D:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 78202 Cascade Impactor Amount D:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0014
	CI:	0.0034
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0188
	CI:	-0.0169
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	**PASS**

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	492.61	Mean:	480.25	Ratio:	102.57
				90% CI for ratio:		(100.8,104.4)
(log scale)	Mean:	6.20	Mean:	6.17	Diff:	0.03
(log scale)	CV:	0.68	CV:	0.28		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.042	SigmaR:	0.017	Ratio:	2.476

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 Cascade Impactor Amount D:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80
	lot	2	LF0054 LM0080
TEST	product	1	TEST
	container	20	41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60
	lot	2	GZ7634 GZ8818

Listing, Raw & Log Data for ANDA 78202 Cascade Impactor Amount D:

Obs	product	sect	container	lot	amount A	amount D	lnD
							(b) (4)
1	REF	B	61	LF0054			
2	REF	B	62	LF0054			
3	REF	B	63	LF0054			
4	REF	B	64	LF0054			
5	REF	B	65	LF0054			
6	REF	B	66	LF0054			
7	REF	B	67	LF0054			
8	REF	B	68	LF0054			
9	REF	B	69	LF0054			
10	REF	B	70	LF0054			
11	REF	B	71	LM0080			
12	REF	B	72	LM0080			
13	REF	B	73	LM0080			
14	REF	B	74	LM0080			
15	REF	B	75	LM0080			
16	REF	B	76	LM0080			
17	REF	B	77	LM0080			
18	REF	B	78	LM0080			
19	REF	B	79	LM0080			
20	REF	B	80	LM0080			
21	TEST	B	41	GZ7634			
22	TEST	B	42	GZ7634			
23	TEST	B	43	GZ7634			

24	TEST	B	44	GZ7634	(b) (4) [redacted]
25	TEST	B	45	GZ7634	
26	TEST	B	46	GZ7634	
27	TEST	B	47	GZ7634	
28	TEST	B	48	GZ7634	
29	TEST	B	49	GZ7634	
30	TEST	B	50	GZ7634	
31	TEST	B	51	GZ8818	
32	TEST	B	52	GZ8818	
33	TEST	B	53	GZ8818	
34	TEST	B	54	GZ8818	
35	TEST	B	55	GZ8818	
36	TEST	B	56	GZ8818	
37	TEST	B	57	GZ8818	
38	TEST	B	58	GZ8818	
39	TEST	B	59	GZ8818	
40	TEST	B	60	GZ8818	

0.25 mg/2ml strength: PBE Analysis for Amount D:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 78202 Cascade Impactor Amount D:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0001
	CI:	0.0007
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0203
	CI:	-0.0198
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	**PASS**

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	241.50	Mean:	236.12	Ratio:	102.28
				90% CI for ratio:		(101.4,103.1)
(log scale)	Mean:	5.49	Mean:	5.46	Diff:	0.02
(log scale)	CV:	0.31	CV:	0.27		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.017	SigmaR:	0.015	Ratio:	1.153

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 Cascade Impactor Amount D:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40
	lot	2	LA1801 LM0022
TEST	product	1	TEST
	container	20	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
	lot	2	GZ7632 GZ8410

Listing, Raw & Log Data for ANDA 78202 Cascade Impactor Amount D:

Obs	product	sect	container	lot	amount A	Amount D	lnD
1	REF	B	21	LA1801	[redacted]		
2	REF	B	22	LA1801			
3	REF	B	23	LA1801			
4	REF	B	24	LA1801			
5	REF	B	25	LA1801			
6	REF	B	26	LA1801			
7	REF	B	27	LA1801			
8	REF	B	28	LA1801			
9	REF	B	29	LA1801			
10	REF	B	30	LA1801			
11	REF	B	31	LM0022			
12	REF	B	32	LM0022			
13	REF	B	33	LM0022			
14	REF	B	34	LM0022			
15	REF	B	35	LM0022			
16	REF	B	36	LM0022			
17	REF	B	37	LM0022			
18	REF	B	38	LM0022			
19	REF	B	39	LM0022			
20	REF	B	40	LM0022			
21	TEST	B	1	GZ7632			

(b) (4)

22	TEST	B	2	GZ7632	(b) (4) [redacted]
23	TEST	B	3	GZ7632	
24	TEST	B	4	GZ7632	
25	TEST	B	5	GZ7632	
26	TEST	B	6	GZ7632	
27	TEST	B	7	GZ7632	
28	TEST	B	8	GZ7632	
29	TEST	B	9	GZ7632	
30	TEST	B	10	GZ7632	
31	TEST	B	11	GZ8410	
32	TEST	B	12	GZ8410	
33	TEST	B	13	GZ8410	
34	TEST	B	14	GZ8410	
35	TEST	B	15	GZ8410	
36	TEST	B	16	GZ8410	
37	TEST	B	17	GZ8410	
38	TEST	B	18	GZ8410	
39	TEST	B	19	GZ8410	
40	TEST	B	20	GZ8410	

0.5 mg/2ml strength: PBE Analysis for Mass Balance:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 78202 Cascade Impactor Mass Balance:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0007
	CI:	0.0013
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0200
	CI:	-0.0193
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	**PASS**

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	95.89	Mean:	97.68	Ratio:	98.16
				90% CI for ratio:		(97.1, 99.2)
(log scale)	Mean:	4.56	Mean:	4.58	Diff:	-0.02
(log scale)	CV:	0.58	CV:	0.22		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.026	SigmaR:	0.010	Ratio:	2.608

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 Cascade Impactor Mass Balance:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	61 62 63 64 65 66 67 68 69 70 71 72 73 74 75 76 77 78 79 80
	lot	2	LF0054 LM0080
TEST	product	1	TEST
	container	20	41 42 43 44 45 46 47 48 49 50 51 52 53 54 55 56 57 58 59 60
	lot	2	GZ7634 GZ8818

Listing, Raw & Log Data for ANDA 78202 Cascade Impactor Mass Balance:

Obs	product	sect	container	lot	amount A	MB	lnMB
							(b) (4)
1	REF	B	61	LF0054			
2	REF	B	62	LF0054			
3	REF	B	63	LF0054			
4	REF	B	64	LF0054			
5	REF	B	65	LF0054			
6	REF	B	66	LF0054			
7	REF	B	67	LF0054			
8	REF	B	68	LF0054			
9	REF	B	69	LF0054			
10	REF	B	70	LF0054			
11	REF	B	71	LM0080			
12	REF	B	72	LM0080			
13	REF	B	73	LM0080			
14	REF	B	74	LM0080			
15	REF	B	75	LM0080			
16	REF	B	76	LM0080			
17	REF	B	77	LM0080			
18	REF	B	78	LM0080			
19	REF	B	79	LM0080			
20	REF	B	80	LM0080			
21	TEST	B	41	GZ7634			

22	TEST	B	42	GZ7634	[redacted]
23	TEST	B	43	GZ7634	
24	TEST	B	44	GZ7634	
25	TEST	B	45	GZ7634	
26	TEST	B	46	GZ7634	
27	TEST	B	47	GZ7634	
28	TEST	B	48	GZ7634	
29	TEST	B	49	GZ7634	
30	TEST	B	50	GZ7634	
31	TEST	B	51	GZ8818	
32	TEST	B	52	GZ8818	
33	TEST	B	53	GZ8818	
34	TEST	B	54	GZ8818	
35	TEST	B	55	GZ8818	
36	TEST	B	56	GZ8818	
37	TEST	B	57	GZ8818	
38	TEST	B	58	GZ8818	
39	TEST	B	59	GZ8818	
40	TEST	B	60	GZ8818	

(b) (4)

0.25 mg/2ml strength: PBE Analysis for Mass Balance:

In Vitro PBE Analysis - Approximate Confidence Interval
Using Moment-Based Simplified Parameter Estimates
for
ANDA 78202 Cascade Impactor Mass Balance:

I. Summary

In Vitro PBE CRITERIA
MIXED SCALING APPROACH
Point Estimate and Upper Bound of 95% Confidence Interval

Linearized Theta P

Reference-scaled:	Point estimate:	0.0002
	CI:	0.0017
	Pass/Fail:	FAIL
Constant-scaled:	Point estimate:	-0.0197
	CI:	-0.0184
	Pass/Fail:	PASS
Overall Test Outcome:	Pass/Fail:	**PASS**

Notes: Constant-scaled tests are based on SigmaT0 = 0.10 and Epsilon = 0.01. Linearized tests are based on regulatory limit (Theta P) of 2.0891. For linearized theta P, if the upper bound of the confidence interval is < 0, PASS. For linearized theta P, if the upper bound of the confidence interval is > 0, FAIL. If the estimate of sigmaR > sigmaT0, use reference scaling. If sigmaR < sigmaT0, use constant scaling. If sigmaR = 0.10, sponsors should use either reference scaling or constant scaling at either side of the changeover point (0.10).

II. Statistical Details

Method of Moments Parameter Estimates

		TEST		REFERENCE		T/R Ratio
(orig scale)	Mean:	98.15	Mean:	99.01	Ratio:	99.13
				90% CI for ratio:		(97.4,100.9)
(log scale)	Mean:	4.59	Mean:	4.60	Diff:	-0.01
(log scale)	CV:	0.88	CV:	0.46		
(log scale)	SigmaBT:	-	SigmaBR:	-	Ratio:	-
(log scale)	SigmaWT:	-	SigmaWR:	-	Ratio:	-
(log scale)	SigmaT:	0.041	SigmaR:	0.021	Ratio:	1.901

Class Levels (total number samples/product = 40; number of sectors = 1):

Class Level Information for
Input Dataset ANDA 78202 Cascade Impactor Mass Balance:
By Product

Product	Class	Levels	Values
REF	product	1	REF
	container	20	21 22 23 24 25 26 27 28 29 30 31 32 33 34 35 36 37 38 39 40
	lot	2	LA1801 LM0022
TEST	product	1	TEST
	container	20	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20
	lot	2	GZ7632 GZ8410

Listing, Raw & Log Data for ANDA 78202 Cascade Impactor Mass Balance:

Obs	product	sect	container	lot	amount A	MB	lnMB
1	REF	B	21	LA1801	[redacted]		
2	REF	B	22	LA1801			
3	REF	B	23	LA1801			
4	REF	B	24	LA1801			
5	REF	B	25	LA1801			
6	REF	B	26	LA1801			
7	REF	B	27	LA1801			
8	REF	B	28	LA1801			
9	REF	B	29	LA1801			
10	REF	B	30	LA1801			
11	REF	B	31	LM0022			
12	REF	B	32	LM0022			
13	REF	B	33	LM0022			
14	REF	B	34	LM0022			
15	REF	B	35	LM0022			
16	REF	B	36	LM0022			
17	REF	B	37	LM0022			
18	REF	B	38	LM0022			
19	REF	B	39	LM0022			
20	REF	B	40	LM0022			
21	TEST	B	1	GZ7632			

(b) (4)

(b) (4)

22	TEST	B	2	GZ7632
23	TEST	B	3	GZ7632
24	TEST	B	4	GZ7632
25	TEST	B	5	GZ7632
26	TEST	B	6	GZ7632
27	TEST	B	7	GZ7632
28	TEST	B	8	GZ7632
29	TEST	B	9	GZ7632
30	TEST	B	10	GZ7632
31	TEST	B	11	GZ8410
32	TEST	B	12	GZ8410
33	TEST	B	13	GZ8410
34	TEST	B	14	GZ8410
35	TEST	B	15	GZ8410
36	TEST	B	16	GZ8410
37	TEST	B	17	GZ8410
38	TEST	B	18	GZ8410
39	TEST	B	19	GZ8410
40	TEST	B	20	GZ8410

B. Method for Cascade Impaction Analysis

APPEARS THIS WAY ON ORIGINAL

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY

TEST METHOD

TITLE:	**DETERMINATION OF AERODYNAMIC PARTICLE SIZE DISTRIBUTION IN BUDESONIDE INHALATION SUSPENSION (0.125 mg/mL, 0.25 mg/mL) USING (b) (4) CASCADE IMPACTOR**	
METHOD NO.: PD-102	**ISSUE NO.:** 3	**DATE GENERATED:** 06/26/2007
INITIATED BY:	Pharmaceutical Development	**DATE:** 06/27/2007
REVIEWED BY:	Documentation Review	**DATE:** Jun. 27/2007
APPROVED BY:	Pharmaceutical Development	**DATE:** 06/27/07
ORIGINATED BY: Phyllis Tsang, Genxiang Ma		**DATE:** 01/20/2006
		REFERENCES: GM10060006
REASON FOR REVISION: To specify compressor used. Correcting typographical and numbering through out the method.		

1.0 METHOD: HPLC

2.0 REFERENCE: House (Modified from TM-462, Issue No: 2 and PD-73, Issue No: 1).

3.0 EQUIPMENT:

HPLC with automatic injector, UV/Vis detector and suitable data processor/recorder
Column:Waters - Symmetry (b) (4) µm or equivalent
ProNeb Ultra nebulizer with Pari LC Plus nebulization kit.
(b) (4) Multistage Cascade Impactor
(b) (4)

4.0 REAGENTS:

Acetonitrile (HPLC Grade)
Methanol (HPLC Grade)
Budesonide Reference Standard

APPEARS THIS WAY ON ORIGINAL

11 Pages have been Withheld as b4 (CCI/TS) immediately following this page

BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-202

APPLICANT: Apotex Inc.

DRUG PRODUCT: Budesonide Inhalation Suspension, 0.25 mg/2 mL & 0.5 mg/2 mL

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Your particle size distribution (PSD) measured by Cascade Impaction (CI) test is **incomplete**. The DBE currently evaluates the test data using at least 30 samples for both test and reference products (3 batches from each product, 10 samples from each batch). Please repeat this test, and increase the sample size from 20 samples to 30 samples for both test and reference products (3 batches from each product, 10 samples from each batch). The DBE currently also evaluate the data at **each individual deposition site**. Please submit the CI data for ***both* the original and *repeat*** PSD by CI test results for **each individual deposition site** (i.e., nebulizer assembly, the induction port and inlet cone, S0 to filter), and the mass balance data. Please also submit the data in electronic format using similar data templates specified by the DBE in the April 27, 2007 letter

2. Your originally submitted Mean Delivered Dose (MDD) at mouthpiece test is **incomplete.** The MDD test results for the **0.25 mg/2ml strength product** did not meet the population bioequivalence criteria (PBE). For the PBE method and criteria currently used by the Agency to evaluate in vitro testing data, please see the Guidance for Industry: Statistical Information from the June 1999 Draft Guidance and Statistical Information for In Vitro Bioequivalence Data (issued April 11, 2003). Please repeat your MDD at mouthpiece test for the **0.25 mg/2ml strength product,** and increase the sample size from 20 samples to 30 samples for both test and reference products (3 batches from each product, 10 samples from each batch). You can measure the MDD test using one of the following two nebulization systems:

- Pari-LC-Jet Plus Nebulizer/Pari Master compressor system at the flow rate of 5.5 L/min, as stated in the Control 03-612; or,

- Repeat its MDD test using ProNeb Ultra Nebulizer with Pari LC Plus Nebulization at the flow rate of (b) (4) L/min, as specified in its method PD-188.

Please also submit the data for the *repeat* MDD test in electronic format using similar data templates specified by the DBE in the April 27, 2007 letter.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

H. Outcome Page

ANDA: 78-202

Completed Assignment for 78202 ID: 5534

5/18/2008 7:50:19 PM

Reviewer: Li, Bing **Date Completed:**

Verifier: **Date Verified:**

Division: Division of Bioequivalence

Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
5534	8/9/2007	Other	Study Amendment	1	1
				Bean Total:	1

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

/s/

Bing Li
6/24/2008 03:11:32 PM
BIOPHARMACEUTICS

Hoainhon T. Nguyen
6/24/2008 04:25:26 PM
BIOPHARMACEUTICS

Dale Conner
6/30/2008 10:03:53 AM
BIOPHARMACEUTICS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	78-202
Drug Product Name	Budesonide Inhalation Suspension
Strength	0.25mg/2mL and 0.5mg/2mL
Applicant Name	Apotex Inc.
	380 Elgin Mills Road East Richmond Hill, Ontario Canada L4C 5H2
Address	Authorized Agent:
	Apotex Corp. 2400 North Commerce Parkway, Suite 400 Weston, Florida 33326
	Paul Bonnici, B.Sc.,
	Tel: (905) 508-2396 Fax: (905) 508-2359
Submission Date(s)	March 31, 2006
Amendment Date(S)	NA
Reviewer	Bing V. Li, Ph.D.
First Generic	No

I. Executive Summary

This is an electronic submission.

The firm has submitted the results of *in vitro* bioequivalence testing comparing its Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL, with Astra Zeneca's Pulmicort® Respules, 0.25 mg/2 mL and 0.5 mg/2 mL, respectively. The firm did not submit its method of the particle size distribution in nebulized aerosol test, as well as the comparative results of the drug polymorph and shape between the low strength product and high strength product. In addition, the firm's particle size distribution results measured by two different methods were inconsistent.

The application is **incomplete**.

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III. Submission Summary

A. Drug Product Information

Test Product	Budesonide Inhalation Suspension, 0.25 mg/2 mL & 0.5 mg/2 mL
Reference Product	Pulmicort® Respules, 0.25 mg/2 mL & 0.5 mg/2 mL
RLD Manufacturer	Astra Zeneca
NDA No.	20-929
RLD Approval Date	08/08/2000
Indication	Indicated for the maintenance treatment of asthma and as prophylactic therapy in children 12 months to 8 years of age**.**

B. PK/PD Information

Bioavailability	6%
Food Effect	N/A
Tmax	10-30 minutes
Metabolism	*In vitro* studies with human liver homogenates have shown that budesonide is rapidly and extensively metabolized. Two major metabolites formed via cytochrome P450 (CYP) isoenzyme 3A4 (CYP3A4) catalyzed biotransformation have been isolated and identified as 16(alpha)-hydroxyprednisolone and 6(beta)-hydroxybudesonide. The corticosteroid activity of each of these two metabolites is less than 1% of that of the parent compound. No qualitative difference between the *in vitro* and *in vivo* metabolic patterns has been detected. Negligible metabolic inactivation was observed in human lung and serum preparations.
Excretion	Budesonide is excreted in urine and feces in the form of metabolites. In adults, approximately 60% of an intravenous radiolabeled dose was recovered in the urine. No unchanged budesonide was detected in the urine.
Half-life	2.3 hours
Drug Specific Issues	Budesonide is provided as a mixture of two epimers (22R and 22S). The activity of budesonide inhalation suspension drug product is due to the parent drug, budesonide. In glucocorticoid receptor affinity studies, the 22R form was two times as active as the 22S epimer. *In vitro* studies indicated that the two forms of budesonide do not interconvert.

Relevant OGD or DBE History

The First Generic is Ivax's product, ANDA 77-519, submitted on December 30, 2004. The submission is under review. There is no other earlier submission for this product in DBE's database.

Control Document No. 03-612 (Apotex, letter date 09/16/2005): The DBE recommended the following for Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL:

Depending upon your ability to determine drug particle size in the suspension and the nebulized aerosol, bioequivalence of generic versions of Pulmicort Respules® (Budesonide Inhalation Suspension) may be based on in-vitro testing alone or a combination of in-vivo and in-vitro testing:

A. Testing Requirements for the Higher Strength (0.50 mg/2 mL) Product:

i. Bioequivalence based on in-vitro testing alone:

In-vitro bioequivalence studies should be conducted using the Pari-LC-Jet Plus Nebulizer/Pari Master compressor system as necessary. The battery of in-vitro tests should include:

- *Unit dose content of drug in the ampules,*
- *Mean nebulization time and mean delivered dose at the mouthpiece (% nominal dose) at the labeled flow rate of 5.5 L/min through such time that mist is no longer coming out of the mouthpiece,*
- *Particle Size Distribution (PSD) of the active pharmaceutical ingredient (API) in the product, and comparative PSD in the suspension (in the ampoule) and in the nebulized aerosol. The PSD determination should be based on a validated method. Validation should demonstrate method sensitivity to drug particle size over the expected size range in the suspension. Drug particles and agglomerates in the suspension both in the ampoule and the nebulized aerosol should be characterized for mean size and distribution.*
- *Sameness of polymorphic form based on X-ray diffraction ,*
- *Sameness of shape (crystalline habit),*
- *Sameness of aqueous droplet size of the nebulized aerosol by a laser diffraction method.*

Please submit an in-vitro testing protocol for review prior to initiation of the study.

ii. Bioequivalence based on a combination of in-vitro and in-vivo testing:

- *Tests should include all described above in 1.A with the exception of particle size of drug and agglomerates in the nebulized aerosol.*

- *A clinical endpoint bioequivalence study for local delivery, with demonstration of acceptable dose-response for test and reference products to assure study sensitivity. At this time, the Agency has no recommendations regarding the clinical bioequivalence study design.*

- *A systemic exposure (pharmacokinetic) bioequivalence study.*

- *You may submit a protocol with your proposal for both studies to the Agency for review prior to initiating the studies.*

B. Testing Requirements for the Lower Strength (0.25 mg/2 mL) Product*:*

If the micronized budesonide (bulk drug) used in the lower strength product is the same as that used in the higher strength product, i.e., same particle size, PSD, polymorphic form, and shape, and the comparative test and reference lower strength formulations are Q1 and Q2 the same, the Division of Bioequivalence (DBE) recommends that you conduct the following tests for the lower strength:

1. *If the drug and agglomerate PSD in the nebulized aerosol of the higher and lower strength products can be determined, the following in vitro testing should be sufficient to demonstrate the equivalence of the lower strength product:*

   - *Documentation of bioequivalence of the higher strength product based on acceptable comparative in vitro data outlined above,*

   - *Comparative drug and agglomerate PSD in the suspension (in the ampoule) and in the nebulized aerosol,*

   - *Comparative data for unit dose content of drug in the lower strength ampules,*

   - *Mean nebulization time and mean delivered dose at the mouthpiece (% nominal dose) at the labeled flow rate of 5.5 L/min through such time that mist is no longer coming out of the mouthpiece for the lower strength ampules,*

   - *Proportionally similar mean delivered dose between the higher and lower strengths of the test product, and between the higher and lower strengths of the reference product.*

2. *If the drug and agglomerate PSD in the nebulized aerosols of the higher and lower strength products cannot be determined, the following abbreviated in vitro testing should be sufficient to demonstrate the equivalence of the lower strength product:*

- *Documentation of bioequivalence of the higher strength product based on acceptable comparative in-vivo and in-vitro data outlined above,*

- *Comparative data for unit dose content of drug in the lower strength ampules,*

- *Mean nebulization time and mean delivered dose at the mouthpiece (% nominal dose) at the labeled flow rate of 5.5 L/min through such time that mist is no longer coming out of the mouthpiece for the low strength ampules,*

- *Proportionally similar mean delivered dose between the high and low strengths of the test product, and between the high and low strengths of the reference product.*

C. Contents of Submission

The firm has submitted the results of the following *in vitro* tests:

- Dose Content Uniformity
- Delivered Dose and Nebulization Time
- Particle Size Distribution in suspension by Laser Diffraction
- Particle Size Distribution in nebulized aerosol by Cascade Impaction
- Droplet Size Distribution in nebulized aerosol by Laser Diffraction
- Drug Particle Size Distribution (Sameness of Shape) by Microscopy
- Sameness of Polymorphism Form by X-Ray Diffraction
- Ampules

D. In Vitro Studies

The *in vitro* tests were conducted on the following batches of the test and reference products. The tests were performed in a blinded manner to eliminate the bias during testing.

Products	**Strength**	**Batch Number**	**Manufacture Date**	**Expiry**
Reference	0.5 mg/2 mL	LF0054		October 06
	0.5 mg/2 mL	LM0080		September 07
	0.25 mg/2 mL	LA1801		July 06
	0.25 mg/2 mL	LM0022		September 07
Test	0.5 mg/2 mL	GZ7634	NA	
	0.5 mg/2 mL	GZ8818	NA	
	0.25 mg/2 mL	GZ7632	NA	
	0.25 mg/2 mL	GZ8410	NA	

Reviewer's Comments:

The firm conducted its in vitro test on the two lots of test and reference products, it is considered acceptable by DBE. However, the firm needs to provide the manufacturing date for these test products.

Method Information:

Method No.	Test Method	Validation Report
TM-462	Assay, Identification and Content Uniformity of Budesonide Inhalation Suspension	√
PD Ref. No. 21	Blinding Procedure for Bioavailability and Bioequivalency Studies for Nasal Spray Product	N/A
PD-188	Determination of Delivered Dose at Mouthpiece and Nebulization Time of Budesonide Inhalation Suspension (0.25mg/2 mL & 0.5mg/2 mL)	√
PD-102	Determination of Aerodynamic Particle Size Distribution in Budesonide Inhalation Suspension (0.125mg/mL, 0.25mg/mL & 0.5mg/mL) Using (b) (4) Cascade Impactor	√
PD-187	Particle Size Distribution Determination by Light Microscopic Image Analysis for Budesonide Inhalation Suspension	√
PD-079	Determination of Droplet Size Distribution For Liquid Inhalation Products Using the Malvern Spray Tec RT Sizer	√
QOP XRD	Examination of Apotex Budesonide Inhalation Suspension Using X-Ray Diffraction	√
BUDE-INSU-70-RH	Particle Size of Budesonide Inhalation Suspension by Laser Diffraction	√
GM-154	Operation of The Malvern Spray Tec RT Sizer (Real Time Particle Sizer)	N/A

1. Unit Dose Content of Drug in the Ampoules

Ten replicate samples for each batch of each strength of the test and reference product were measured by HPLC (method # TM-462).

The method was validated for specificity, system suitability, method precision, accuracy, linearity, range, robustness and stability. The validation results are shown as follows:

SPECIFICITY:

Stress Study:
An individual sample of Budesonide Inhalation Suspension (Lot #E080605) and Placebo (Lot #E090605) was exposed to various stress conditions such as heat, photo light irradiation, oxidation by hydrogen peroxide, acid and base hydrolysis. The resulting sample solutions were analyzed as per method.

Heat Degradation:
A sample of Budesonide Inhalation Suspension was stressed at 60°C for 1 hour.
About 4.2% of Budesonide was degraded when compared to the unstressed sample.

Photo Light Irradiation:
A sample of Budesonide Inhalation Suspension was exposed to photo light irradiation for 15 minutes. About 4.0% of Budesonide was degraded when compared to the unstressed sample.

Oxidation:
A sample of Budesonide Inhalation Suspension was oxidized with 3% hydrogen peroxide for 30 minutes at room temperature. About 1.6% of Budesonide was degraded.

Acid Hydrolysis:
A sample of Budesonide Inhalation Suspension was treated with 0.1N hydrochloric acid for 6 hours at 60°C. About 4.6% of Budesonide was degraded.

Base Hydrolysis:
A sample of Budesonide Inhalation Suspension was treated with 0.1N sodium hydroxide for 15 minutes at room temperature. About 11.4% of Budesonide was degraded.

Interference Study:

Interference of Placebo, Diluting Solvent, Mobile Phase and Related Compounds:
No interfering peaks were found which could negatively or positively bias the Assay and Content Uniformity of Budesonide Inhalation Suspension.

Filter Study: Two types of membrane filters were tested for possible interference that could affect the quantitation of Budesonide. The (%) recovery of the filtered Reference Standard Solution was calculated based on the unfiltered standard and sample solutions respectively. No significant interference was observed.

SYSTEM SUITABILITY:

System Analysis:

The HPLC system was equilibrated using the Mobile Phase as described in the Assay method. Repeat injections were made with the Reference Standard Solution until the

Coefficient of Variation (CV) of the Budesonide peak area of 5 consecutive injections was NMT (b) %. Under these conditions, the system analysis showed the Tailing Factor (T) was NMT (b), and Number of Theoretical Plates (N) was NLT (b) (4), based on the Budesonide peak.

SYSTEM PRECISION:

TABLE 2 – System Precision

Injection No.	Observed Peak Area
1 2 3 4 5	(b) (4)
Mean: CV (%):	1047.10083 0.0
Reference: JH12050015, p.97; ID #5	

METHOD PRECISION:

TABLE 3a - Method Precision (Intra-Day)

Sample No.	(%) Label Claim		
Label claim:	0.125 mg/mL	0.25 mg/mL	0.5 mg/mL
1 2 3 4 5 6	(b) (4)	(b) (4)	(b) (4)
Mean: CV (%):	93.9 1.7	91.7 1.7	90.6 1.3
Reference: FND12980067, p.129; FND12980092, p.38			

Content Uniformity:

TABLE 3b - Method Precision (Intra-Day)

Label Claim	0.125 mg/mL	0.25 mg/mL	0.5 mg/mL
(%) Label Claim:	(b) (4)	(b) (4)	(b) (4)
CV (%):	2.1	4.1	1.8
Reference: FND12980067, p.151, 152; FND12980092, p.24 to 26, 82			

Inter-Day:

TABLE 3c - Method Precision (Inter-Day)

Day	(%) Label Claim		
Label Claim:	0.125 mg/mL	0.25 mg/mL	0.5 mg/mL
First	(b) (4)	(b) (4)	(b) (4)
Second			
Third			
Mean: CV (%):	95.0 2.0	91.6 2.2	91.4 0.2
Reference: FND12980067, p.148; FND12980092, p.38			

Repeatability:

TABLE 3d – Method Precision (Repeatability)

Sample No.	Label Claim of Budesonide (%)
1 2 3 4 5 6	(b) (4)
Mean: CV (%):	103.4 1.2
Reference: JH12050015, p.97 to 104; ID #5	

Intermediate Precision:

TABLE 3e – Method Precision (Intermediate Precision)

Sample No.	Label Claim of Budesonide (%)	
	Instrument: HPLC Unit #121 Column: Water Symmetry, C18 Serial No.: T80421K36	Instrument: HPLC Unit #160 Column: Water Symmetry, C18 Serial No.: W4056U071
	Chemist 1	Chemist 2
1 2 3 4 5 6	(b) (4)	(b) (4)
Mean: CV (%):	103.4 1.2	103.7 0.7
Difference (%):	N/A	0.3
References:	JH12050015, p. 97 to 104; ID #5	SB13050071, p.27 to 33; ID #1 (RH_SP_Budesonide_Inh)

ACCURACY:

TABLE 4 – Accuracy (Recovery) Test

(%) Level	Spiking Concentration (µg/mL)	Recovered Concentration (µg/mL)	Recovery (%)	Mean Recovery (%)	CV (%)
50	(b) (4)			98.3	0.2
100				100.5	1.2
150				101.0	0.8
Reference: JH12050035, p. 76 to 80; ID #5					

LINEARITY:

TABLE 5 – Linearity of Detector Response for Budesonide

Theory (%)	Concentration (mg/mL x 10^{-2})	Observed Average Area	Concentration Response (x 10^4)
(b) (4)	(b) (4)		
For Concentration Response: Mean:			4.09×10^4
CV(%):			0.5
Coefficient of Determination (R^2)			1.000
y-Intercept:			6.15
Slope:			4.07×10^4
Reference: FND12980092, p.90			

RANGE:

TABLE 6 – Precision of the method at Ranges of 50% and 150%

Injection No.	Observed Area	
(%) Level:	50	150
1	(b) (4)	(b) (4)
2		
3		
4		
5		
Mean:	510.91868	1531.90661
CV (%)	0.1	0.1
Reference: FND12980067, p.109, 115		

ROBUSTNESS:

The robustness test of the method for the Assay and Content Uniformity of Budesonide Inhalation Suspension provides the data which verifies the reproducibility of the method.

Level 1: Effect of Modification of Mobile Phase:

The same lots of Budesonide Inhalation Suspension were analyzed by changing the Mobile Phase ratio of acetonitrile:purified water 70:30 to 75:25. The (%) difference in (%) LC between mobile phases was (b) (4)% for both 0.125 mg/mL and 0.25 mg/mL strengths and (b) (4)% for the 0.5 mg/mL strength.

TABLE 7a – Robustness Test Results

Mobile Phase	Acetonitrile:Purified Water = 70:30			Acetonitrile:Purified Water = 75:25		
Reference	FND12980092, p.12, 39			FND12980092, p.41, 91, 92		
Label Claim (mg/mL)	0.125	0.25	0.5	0.125	0.25	0.5
(%) Label Claim:	(b) (4)		(b) (4)	(b) (4)		(b) (4)

Level 2: Effect of Variation of Column, System and Analyst:

The second chemist analyzed the same lots of Budesonide Inhalation Suspension using a different HPLC system and column with the same packing material. Similar results were obtained.

TABLE 7b – Robustness Test Results

	HPLC System Unit #75 Column Serial No.: T71911D23 Waters Symmetry C18 Chemist: FND12980067, p.148; FND12980092, p.38			HPLC System Unit #63 Column Serial No.: T81051012 Waters Symmetry C18 Chemist: DS12980093, p.124		
Label Claim (mg/mL)	0.125*	0.25*	0.5*	0.125	0.25	0.5
(%) Label Claim:	(b) (4)	(b) (4)	(b) (4)	(b) (4)		(b) (4)

*Mean of Inter-Day Method Precision Day 2 was used.

STABILITY:

TABLE 8a – Stability of Standard Solution

Day	Recovery (%)	
	Stability of Stock Standard Solution	Stability of Working Standard Solution
0	(b) (4)	(b) (4)
1		
2		
3		
6		
7		
9		
Reference: JH12050014, p.58; ID #38		

TABLE 8b – Stability of Sample Solution

	0.125 mg/mL Strength		0.25 mg/mL Strength		0.5 mg/mL Strength	
Day	Label Claim (%)	Recovery (%)	Label Claim (%)	Recovery (%)	Label Claim (%)	Recovery (%)
0	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
3						
4						
5						
7						
Reference: JH12050014, p.58; ID #38						

N/A = Not Applicable

Study Results:

- For 0.25 mg/2 mL Strength:

Table# I-A-2
Comparative Summary Table of Dose Content Uniformity of Drug in the Ampoules between Apotex product and Reference product for Budesonide Inhalation Suspension 0.25mg/2mL

Apotex		AstraZeneca	
Lot_No	assay %	Lot_No	assay %
GZ7632	(b) (4)	LA1801	(b) (4)
GZ8410		LM0022	
Average:	106.85	Average:	102.78
SD:	1.82	SD:	1.73
%CV:	1.7	%CV:	1.70
Min:	102.80	Min:	100.0
Max:	111.00	Max:	106.10

- For 0.5 mg/2 mL Strength:

Table# I-B-2
Comparative Summary Table of Dose Content Uniformity of Drug in the Ampoules between Apotex product and Reference product for Budesonide Inhalation Suspension 0.5mg/2mL

Apotex		AstraZeneca	
Lot_No	assay_%	Lot_No	assay_%
GZ7634	(b) (4)	LF0054	(b) (4)
GZ8818		LM0080	
Average:	108.96	Average:	102.78
SD:	2.54	SD:	1.73
%CV:	2.3	%CV:	1.70
Min:	105.00	Min:	100.0
Max:	112.50	Max:	106.10

2. Mean Nebulization Time and Mean Delivered Dose at the Mouthpiece

Ten replicate samples for each batch of each strength of the test and reference product were measured. A ProNeb Ultra nebulizer with Pari LC plus nebulization kit with a (b) (4) with flow control valve was used. Flow rate was set at 5.5± 5 L/min. Nebulization time was recorded from the time when the nebulizer compressor was turned on to the time when no more drug product in the sample cup is nebulized, or the nebulization has ceased. Samples were collected by setting up a sample collection tube on the mouthpiece adaptor. Samples were analyzed by HPLC. Photo of instrument setup were provided (method PD-188).

The method was validated for system precision, method precision, linearity, limit of quantitation, selectivity, stability, and filter recovery. The validation results are shown as follows:

System Precision:

Table 1- System Precision

Injection No.	Observed Area
1 2 3 4 5 6	(b) (4) [redacted]
Mean CV (%)	120.04304 0.1
Reference: Project: RH_PD_Budesonide_INH ID#102, RH ID# ZF013006	

Repeatability:

Table 2- Repeatability

Injection No.	Lot# GZ8410 (0.25 mg/2 mL)		Lot# GZ7634 (0.50 mg/2 mL)	
	Observed Area	Nebulization time (min)	Observed Area	Nebulization time (min)
1 2 3 4 5 6	(b) (4) [redacted]			
Mean CV (%)	168.41587 5.9	10.77 6.6	166.76567 5.2	10.37 5.3
Reference	Project:RH_PD_Budesonide_INH ID#102, RH ID# ZF013006		Project: RH_PD_Budesonide_INH ID#107, RH ID# ZF020106	

Intermediated Precision:

Table 3- Intermediated Precision

		First Chemist	Second Chemist	% Difference
Lot# GZ8410 (0.25mg/2mL)	Average peak area	168.41587 CV: 5.9%	187.48024 CV: 3.1%	11.3
	Average Nebulization time	10.77 min CV: 6.6%	12.17 min CV: 5.4%	13.0
Lot# GZ7634 (0.50mg/2 mL)	Average peak area	166.76567 CV: 5.2%	181.21639 CV: 3.7%	8.7
	Average Nebulization time	10.37 min CV: 5.3%	11.43 min CV: 2.4%	10.3
Reference		Project: RH_PD_Budesonide_INH ID#102, RH ID# ZF013006 ID#107, RH ID# ZF020106	Project: RH_PD_Budesonide_INH ID#110, RH ID#YL020206 ID#112, RH ID#YL020306	

Linearity:

Table 4- Linearity of Detector Response for Budesonide

% Level	Concentration (mg/mL)	Observed Area	Concentration Response
1(LOQ) 50 80 100 125 150	[redacted] (b) (4)		
Mean CV (%)			2.52360×10^{-5} 0.4
R^2 Y-intercept Slope			1.00000 0.0130049 39562.89099
Reference: Project: RH_PD_Budesonide_INH ID#106, RH ID# ZF013106			

Limit of Quantitation:

Table 5- Limit of Quantitation

Injection No.	Observed Area
1 2 3 4 5 6	[redacted] (b) (4)
Mean CV (%)	1.25318 1.8
Reference: Project: RH_PD_Budesonide_INH ID#109, RH ID# ZF020206	

Selectivity: Two placebo samples were collected with one sample collection in between and chromatographed under the HPLC conditions. No interfering peaks were observed in placebo.

Stability of Samples:

Table 6. Stability of Working Standard Solution and Sample Soluition

	Day 0	Day 1		Day 2		Day 3	
	Peak area	Peak area	% recovery	Peak area	% recovery	Peak area	% recovery
Working standard solution	120.04304	118.83111	(b) (4)	119.99157	(b) (4)	119.50643	(b) (4)
Reference	Project: RH_PD_Budesonide_INH ID#102, RH ID# ZF013006	Project: RH_PD_Budesonide_INH ID#106, RH ID# ZF013106		Project: RH_PD_Budesonide_INH ID#107, RH ID# ZF020106		Project: RH_PD_Budesonide_INH ID#109, RH ID# ZF020206	
Sample solution Lot#GZ7634	183.31784	184.09647	(b) (4)	186.78220	(b) (4)	189.34906	(b) (4)
Reference	Project: RH_PD_Budesonide_INH ID#112, RH ID# YL020306	Project: RH_PD_Budesonide_INH ID#115, RH ID# ZF020406		Project: RH_PD_Budesonide_INH ID#113, RH ID# ZF020506		Project: RH_PD_Budesonide_INH ID#116, RH ID# YL020606	

Filter Study: (b) (4) um filter were studied:

Table 7. Filter Study of (b) (4) Filter and (b) (4) Filter

	Unfiltered	(b) (4) filter	(b) (4) filter
Injection 1	(b) (4)		
Injection 2			
Average	119.83142	119.52926	119.39780
% Recovery	N/A	(b) (4)	(b) (4)
Reference	Project: RH_PD_Budesonide_INH, ID#109, RH ID# ZF020206		

Study Results:

- For 0.25 mg/2 mL Strength:

Table# II-A-2

Comparative Summary Table of Delivered Dose and Nebulization Time of Drug in the Ampoules between Apotex product and Reference product for Budesonide Inhalation Suspension 0.25mg/2mL

Manufacturer	Lot_No	Time_min	assay_%
Apotex	GZ7632	11.17	(b) (4)
		10.15	
		11.60	
		10.53	
		10.56	
		10.35	
		10.43	
		10.13	
		9.92	
		10.37	
	GZ8410	10.13	
		9.53	
		11.20	
		10.43	
		10.13	
		10.37	
		10.75	
		10.10	
		10.37	
		10.25	
	Average:	10.42	41.4
	SD:	0.47	2.74
	%CV:	4.5	6.6
	Min:		(b) (4)
	Max:		

Table# II-A-2

Comparative Summary Table of Delivered Dose and Nebulization Time of Drug in the Ampoules between Apotex product and Reference product for Budesonide Inhalation Suspension 0.25mg/2mL

Manufacturer	Lot_No	Time_min	assay_%
AstraZeneca	LA1801	10.38	(b) (4)
		10.52	
		10.40	
		10.33	
		11.30	
		10.37	
		9.25	
		10.70	
		10.92	
		10.97	
	LM0022	10.30	
		10.18	
		10.33	
		10.18	
		10.93	
		10.17	
		10.43	
		10.27	
		9.73	
		10.45	
	Average:	10.41	34.6
	SD:	0.44	1.58
	%CV:	4.3	4.6
	Min:		(b) (4)
	Max:		

- For 0.5 mg/2 mL Strength:

Table# II-B-2

Comparative Summary Table of Delivered Dose and Nebulization Time of Drug in the Ampoules between Apotex product and Reference product for Budesonide Inhalation Suspension 0.5mg/2mL

Manufacturer	Lot_No	Time_min	assay_%
Apotex	GZ7634	10.08	(b) (4)
		10.02	
		10.32	
		10.68	
		9.42	
		10.27	
		10.48	
		10.20	
		10.22	
		10.05	
	GZ8818	10.30	
		10.63	
		10.33	
		10.07	
		10.23	
		10.07	
		10.73	
		10.17	
		10.18	
		10.32	
	Average:	10.24	39.8
	SD:	0.28	2.04
	%CV:	2.8	5.1
	Min:	(b) (4)	
	Max:		

Table# II-B-2

Comparative Summary Table of Delivered Dose and Nebulization Time of Drug in the Ampoules between Apotex product and Reference product for Budesonide Inhalation Suspension 0.5mg/2mL

Manufacturer	Lot_No	Time_min	assay_%
AstraZeneca	LF0054	9.88	(b) (4)
		11.77	
		10.58	
		10.32	
		10.48	
		10.27	
		10.48	
		10.18	
		10.10	
		10.65	
	LM0080	10.73	
		10.00	
		10.62	
		10.57	
		10.48	
		10.90	
		10.67	
		10.67	
		10.52	
		10.87	
	Average:	10.54	36.00
	SD:	0.40	1.42
	%CV:	3.8	4.0
	Min:	(b) (4)	
	Max:		

- Comparison of Mean Delivered Dose between Lower Strength and Higher Strength For Budesonide Inhalation Suspension 0.25 mg/2 mL and 0.5 mg/2 mL:

Strength/	Lot Number	Delivered Dose (mg/2 mL)	Mean Delivered Dose (mg/ 2mL)	Ratio (High Dose/Low Dose)
Test Product 0.25 mg/2 mL	(L) GZ7632	(b) (4)	0.104	1.9
	(L) GZ8410			
Test Product 0.5 mg/2 mL	(L) GZ7634		0.200	
	(L) GZ8818			
Reference Product 0.25 mg/2 mL	(L) LA1801		0.087	2.1
	(L) LM0022			
Reference Product 0.5 mg/2 mL	(L) LF0054		0.180	
	(L) LM0080			

The above data show that the mean delivered dose between the higher and lower strengths of the test product, and between the higher and lower strengths of the reference product are proportionally similar.

3. Particle Size of Budesonide Inhalation Suspension by Laser Diffraction (API in suspension/ampoule)

Laser Diffraction method was used to demonstrate the particle size in Budesonide inhalation suspension by a Malvern Mastersizer S (method BUDE-INSU-70-RH). The content of the sample ampoule was transferred directly to a dispersion unit. The samples were measured at (b) (4) Ten replicate samples for each batch of each strength of the test and reference product were measured.

The individual and mean results expressed in *micrometer* for the 10th percentile (D_{10}), 50th percentile (D_{50}), 90th percentile (D_{90}) and Dmean 4,3] were submitted. The method was validated for precision (repeatability) and intermediate precision (ruggedness). The validation results are shown as follows:

The firm stated in the summary of the validation report that "*after additional information was provided on the solubility/degradation of the budesonide inhalation suspension after exposed to light, only the initial run/measurement should be used for these samples to reduce exposure to the laser and provide and accurate particle size distribution of the samples. The initial run/measurement for each samples run will be reported.*"

Method Precision (repeatability):

For Budesonide Inhalation Suspension, Batch No. GZ7634:

Method Precision (repeatability) (n=6)	D [v, 0.1] (μm)	D [v, 0.5] (μm)	D [v, 0.9] (μm)
Mean	(b) (4)		
%RSD	5.47	4.76	3.69

For Budesonide Inhalation Suspension, Batch No. GZ7632:

Method Precision (repeatability) (n=6)	D [v, 0.1] (μm)	D [v, 0.5] (μm)	D [v, 0.9] (μm)
Mean	(b) (4)		
%RSD	10.01	7.68	6.70

Intermediate Precision:

For Budesonide Inhalation Suspension, Batch No. GZ7634:

Intermediate Precision (ruggedness) (n=3) Inter-Day Variation	D [v, 0.1] (μm)	D [v, 0.5] (μm)	D [v, 0.9] (μm)
Mean	(b) (4)		
%RSD	8.86	9.11	9.89

For Budesonide Inhalation Suspension, Batch No. GZ7632:

Intermediate Precision (ruggedness) (n=3) Inter-Day Variation	D [v, 0.1] (μm)	D [v, 0.5] (μm)	D [v, 0.9] (μm)
Mean	(b) (4)		
%RSD	5.79	4.62	3.96

Study Results:

- For 0.25 mg/2 mL Strength:

Table# IV-A-2
Comparative Summary Table of Particle Size Distribution by Malvern MasterSizer S
between Apotex product and Reference product for
Budesonide Inhalation Suspension 0.25mg/2mL

Manufacturer	Lot_No	Dv_01	Dv_05	Dv_09	Dmean_43
Apotex	GZ7632	(b) (4)			
	GZ8410				
	Average:				
	SD:	0.31	0.61	1.03	0.64
	%CV:	8.2	7.4	6.9	7.2
	Min:	(b) (4)			
	Max:				

Table# IV-A-2
Comparative Summary Table of Particle Size Distribution by Malvern MasterSizer S
between Apotex product and Reference product for
Budesonide Inhalation Suspension 0.25mg/2mL

Manufacturer	Lot_No	Dv_01	Dv_05	Dv_09	Dmean_43
AstraZeneca	LA1801	(b) (4)			
	LM0022				
	Average:				
	SD:	0.32	0.46	0.77	0.48
	%CV:	9.3	5.7	4.8	5.4
	Min:	(b) (4)			
	Max:				

❖ For 0.5 mg/2 mL Strength:

Table# IV-B-2
Comparative Summary Table of Particle Size Distribution by Malvern MasterSizer S
between Apotex product and Reference product for
Budesonide Inhalation Suspension 0.5mg/2mL

Manufacturer	Lot_No	Dv_01	Dv_05	Dv_09	Dmean_43
Apotex	GZ7634	(b) (4)			
	GZ8818				
	Average:	(b) (4)			
	SD:	0.35	0.60	0.97	0.63
	%CV:	8	6.4	5.7	6.2
	Min:	(b) (4)			
	Max:				

Table# IV-B-2
Comparative Summary Table of Particle Size Distribution by Malvern MasterSizer S
between Apotex product and Reference product for
Budesonide Inhalation Suspension 0.5mg/2mL

Manufacturer	Lot_No	Dv_01	Dv_05	Dv_09	Dmean_43
AstraZeneca	LF0054	(b) (4)			
	LM0080				
	Average:				
	SD:	0.27	0.51	0.87	0.54
	%CV:	7	5.9	5.4	5.7
	Min:	(b) (4)			
	Max:				

4. Particle Size Distribution in Nebulized Aerosol by Cascade Impaction

The aerodynamic particle size distribution was determined using (b) (4) Multistage Cascade Impactor and Pari LC Plus Nebulizer (Method PD-102). HPLC was used for samples analysis. Cascade impaction performed on the product has been done by analyzing the amount of drug deposited on various stages of the impactor.

Method was validated for system precision, method precision, linearity, limit of quantitation, selectivity, and stability of samples. The validation results are shown as follows:

System Precision:

Table 1- System Precision

Injection No.	Observed Area
1 2 3 4 5 6	(b) (4)
Mean CV (%)	205.69059 0.1
Reference: Project: RH_PD_Budesonide_INH ID#85, RH ID# gm011006, Book #: GM 10060006, P6	

Method Precision:

Repeatability:

Table 2- Repeatability

Summary results for six sample collections__Lot GZ8410 (0.125mg/mL)

Sample No	1	2	3	4	5	6	Mean	CV, %
MMAD						(b) (4)	(b) (4)	12.3
GSD							**2.07**	3.4
% up to (b) (4)							**65.77**	8.5
% up to							**91.24**	2.1
Material balance (100*C/D)							**86.60**	1.3
Respirable Fraction (R/A)							**0.63**	5.2
Fine Particle Dose (□g) R/N							**56.62**	7.8
Delivered from Mouthpiece (100*A/C)							**40.02**	3.4

Summary results for six sample collections__Lot GZ8818 (0.25mg/mL)

Sample No	1	2	3	4	5	6	Mean	CV, %
MMAD						(b) (4)	(b) (4)	4.0
GSD							**2.13**	2.3
% up to (b) (4)							**58.31**	3.6
% up to							**86.95**	1.5
Material balance (100*C/D)							**87.67**	1.5
Respirable Fraction (R/A)							**0.62**	2.8
Fine Particle Dose (□g) R/N							**102.90**	4.5
Delivered from Mouthpiece (100*A/C)							**37.38**	2.5

Intermediate Precision:

Table 3 Difference Between Two Chemist Results

Batch # of Product: GZ8818 (0.25mg/mL)	Chemist: GM		Chemist: VJ		Difference, %
	Mean results	CV, %	Mean results	CV, %	
MMAD	(b) (4)	4.0	(b) (4)	1.7	15.5
GSD	2.13	2.3	2.10	1.1	1.4
% up to (b) (4)	58.31	3.6	66.99	1.5	13.0
% up to	86.95	1.5	91.52	0.7	5.0
Material balance (100*C/D)	87.67	1.5	92.50	1.6	5.2
Respirable Fraction (R/A)	0.62	2.8	0.70	6.7	11.4
Fine Particle Dose (μg) R/N	102.90	4.5	132.97	8.6	22.6
Delivered from Mouthpiece (100*A/C)	37.38	2.5	39.23	0.9	4.7
Batch # of Product: GZ8410 (0.125mg/mL)	**Chemist: GM**		**Chemist: VJ**		**Difference, %**
	Mean results	**CV, %**	**Mean results**	**CV, %**	
MMAD	(b) (4)	12.3	(b) (4)	5.4	15.9
GSD	2.07	3.4	2.11	1.5	1.9
% up to (b) (4)	65.77	8.5	73.53	3.6	10.6
% up to	91.24	2.1	94.00	1.3	2.9
Material balance (100*C/D)	86.60	1.3	88.77	2.8	2.4
Respirable Fraction (R/A)	0.63	5.2	0.75	4.2	16.0
Fine Particle Dose (μg) R/N	56.62	7.8	75.80	5.6	25.3
Delivered from Mouthpiece (100*A/C)	40.02	3.4	41.52	2.6	3.6
HPLC Unit #	169		97		NA
Cascade Unit #	1		3		
Column S/N# (waters Symmetry C18, (b) (4) (b) (4)	WW01441S004		T4249S05		
Nebulizer Unit #	5		7		

Linearity:

Table 4- Linearity of Detector Response for Budesonide

% Level	Concentration (ug/mL)	Observed Area	Concentration Response
1(LOQ) 12.5 25 50 100 150	(b) (4)		
Mean CV (%)			99.38104 3.0
R^2 Y-intercept Slope			0.99994 0.14963 100.12446
Reference: GM10060006, p.10			

Limit of Quantitation:

The lowest level of Budesonide's concentration at which a linear relationship with detection response exists and that can be quantitated with acceptable accuracy and precision was 0.020521 ug/ml.

Table 5- Limit of Quantitation

Injection No.	Observed Area
1	(b) (4)
2	
3	
4	
5	
6	
Mean	1.92205
CV (%)	1.9
Reference: Project: RH_PD_Budesonide_INH ID#85, RH ID# gm011006, Book #: GM 10060006, 9 – 10.	

Selectivity:

One placebo sample was collected as per method into the Cascade Impactor and chromatographed under the HPLC conditions. No interfering peaks were observed in placebo and diluting solvent.

Stability of the Sample:

Table 6. Stability of Sample Using Lot GZ8818

Sample No.	Area (Day 1)	Area (Day 2)	Recovery,%	Area (Day 3)	Recovery,%
S0		(b) (4)	(b) (4)	(b) (4)	(b) (4)
S1					
S2					
S3					
S4					
S5					
S6					
S7					
Filter Assembly					
Induction Port					

Study Results:

- For 0.25 mg/2 mL Strength:

Table# III-A-6

Summary of Drug Particle Size Distribution by Cascade Impactor for Budesonide Inhalation Suspension, 0.25mg/2mL

Reference Product: Pulmicort Respules (Budesonide) Inhalation Suspension 0.25mg/2mL
Apotex Product: GZ7632, GZ8410
Innovator Product: LA1801 exp.: 07/06; LM0022 exp.:09/07

Manufacturer	Batch #	Weight (g)	Volume (mL)	A (ug)	B (ug)	C (ug)	D (ug)	R (ug)
Apotex	GZ7632	(b) (4)						
	GZ8410							
	Average:							
	%RSD:	0.0	0.0	2.6	0.3	1.8	0.8	3.2
AstraZeneca	LA1801	(b) (4)						
	LM0022							
	Average:							
	%RSD:	1.1	1.1	1.3	0.1	2.7	0.7	1.0

Table# III-A-6

Summary of Drug Particle Size Distribution by Cascade Impactor for Budesonide Inhalation Suspension, 0.25mg/2mL

Reference Product: Pulmicort Respules (Budesonide) Inhalation Suspension 0.25mg/2mL
Apotex Product: GZ7632, GZ8410
Innovator Product: LA1801 exp.: 07/06; LM0022 exp.:09/07

Manufacturer	Batch #	MMAD (um)	GSD	% up to (b) (4)	% up to (b) (4)	Material balance (100*C/D)	Respirable Fraction (R/A)	Fine Particle Dose (ug) R/N	Delivered from Mouthpiece (100*A/C)
Apotex	GZ7632	(b) (4)							
	GZ8410								
	Average:								
	%RSD:	5.9	1.7	3.8	1.2	2.6	1.0	3.1	0.7
AstraZeneca	LA1801	(b) (4)							
	LM0022								
	Average:								
	%RSD:	0.7	0.0	0.5	0.1	2.0	0.0	1.1	1.3

❖ For 0.5 mg/2 mL Strength:

Table# III-B-6

Summary of Drug Particle Size Distribution by Cascade Impactor for Budesonide Inhalation Suspension, 0.5mg/2mL

Reference Product: Pulmicort Respules (Budesonide) Inhalation Suspension 0.5mg/2mL
Apotex Product: GZ7634, GZ8818
Innovator Product: LF0054 exp.: 10/06; LM0080 exp.:09/07

Manufacturer	Batch #	Weight (g)	Volume (mL)	A (ug)	B (ug)	C (ug)	D (ug)	R (ug)
Apotex	GZ7434	(b) (4)						
	GZ8818							
	Average:							
	%RSD:	1.5	1.5	3.9	5	2.5	5.3	2.6
AstraZeneca	LF0054	(b) (4)						
	LM0080							
	Average:							
	%RSD:	1.0	1.0	0.7	1.0	0.8	1.0	3.6

Table# III-B-6

Summary of Drug Particle Size Distribution by Cascade Impactor for Budesonide Inhalation Suspension, 0.5mg/2mL

Reference Product: Pulmicort Respules (Budesonide) Inhalation Suspension 0.5mg/2mL
Apotex Product: GZ7634, GZ8818
Innovator Product: LF0054 exp.: 10/06; LM0080 exp.:09/07

Manufacturer	Batch #	MMAD (um)	GSD	% up to (b) (4)	% up to (b) (4)	Material balance (100*C/D)	Respirable Fraction (R/A)	Fine Particle Dose (ug) R/N	Delivered from Mouthpiece (100*A/C)
Apotex	GZ7434	(b) (4)							
	GZ8818								
	Average:								
	%RSD:	3.4	0.0	2.5	0.7	2.9	1.0	2.6	1.5
AstraZeneca	LF0054	(b) (4)							
	LM0080								
	Average:								
	%RSD:	5.8	1.9	4.6	2.1	0.2	3.2	3.6	0.0

Reviewer's Comments:

1. The drug particle and aggregate distribution in nebulized aerosol is the key test to determine whether the in vivo BE study could be waived. Currently, the DBE does not recommend a specific method for this test. In an earlier submission (ANDA 77-519, first Generic by Ivax), Ivax described its method as followings: "*The nebulized aerosol was collected by nebulizing one ampoule and collecting the nebulized droplets by impacting/impinging the droplets in placebo solution located in the cups (4 cups) of a Next Generation Impactor/HEPA filtered compressed air supply (at flow rate of 5.5 L/min). The captured suspension was combined and transferred to a volumetric flask and made up to the mark. The particle size distribution of the captured nebulized*

aerosol was measured using a [redacted] *Coulter Counter*". Ivax has provided it's rational in selecting this method (see the attachment) and it was found acceptable by DBE.

2. A seminar by [redacted] (b) (4). introducted an "Aerosizer particle measuring system" which is capable of measuring the individual size of particles in the range of less than [redacted] (b) (4) micrometers. The particles may be in the form of a dry powder, may be suspended in a gas or may be sprayed from a liquid suspension. For the nebulizer aerosol measurement, the fine mist of liquid is generated and the suspending liquid is evaporated off in the drying stack leaving the dry particles suspended in air. It appears as a feasible method to conduct this test; however, the method may need further validation.

3. Apotex used [redacted] (b) (4) Cascade Impactor in determining the particle/aggregate in the nebulized aerosol. Apotex did not submit the method of particle/aggregate size distribution measurement using cascade impaction (method PD 102). Instead, the firm submitted two copies of the method validation report. The firm should submit the method describing the procedures of how the measurement was done and how the data were collected and analyzed. The firm should also provide the rational of using this method for the measurement of <u>particle size of drug and agglomerates</u> in the nebulized aerosol.

4. The Cascade impactor (CI) determines the aerodynamic diameter of the particle size distribution. It has been used for particle size analysis of most inhaler aerosols. It can provide information that may be indicative for lung deposition. However, it might not be truly reflecting the drug particle/aggregates distribution in aerosol.

5. In the draft guidance *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action (April, 2003), section for* "Nasal aerosols: Particle/Droplet Size Distribution", FDA recommends that for the nasal aerosol, the firm should report the drug deposition at 11 sites (1) sum of valve stem plus actuator; (2) induction port; (3 - 10) eight individual stages; and (11) filter, using USP 25 Apparatus 1 (<601>) operated at the standard 28.3 liter per minute configuration. The number of actuations recommended for the CI study of aerosols is described in the draft guidance *Metered Dose Inhaler (MDI) and Dry Powder Inhaler (DPI) Drug Products Chemistry, Manufacturing, and Controls Documentation (Oct. 1998).*

6. The DBE will determine the feasibility of the firm's CI test in determining drug/aggregates distribution upon receiving the firm's details of method description (method PD 102).

5. Droplet Size Distribution of the Nebulized Aerosol by Laser Diffraction

Droplet size distribution of the Nebulized Aerosol was measured by Laser Diffraction. Malvern Spray Tec Sizer was utilized to perform the droplet size distribution test (method PD-079). This equipment measures the droplet size by the degree of obscuration of the laser beam caused by the nebulization of the product from a single ampoule. PARI LC PLUS Reusable Nebulizer

was used and the flow rate was set at 5.5L/min. The average of 10th percentile (D_{10}), 50th percentile (D_{50}), 90th percentile (D_{90}) and SPAN [$(D_{90} - D_{10})/D_{50}$] of three sample collections were submitted.

The method was validated for system precision and method precision. The firm also submitted 20% representative Time History plots of droplet size distribution data for 0.5 mg/2 ml strength. The validation results are shown as follows:

System Precision:

Table 1- System Precision

Lot Number of Product	Collection No.	Fully Developed Plume of Spray (μm)			
		Dv(10)	Dv(50)	Dv(90)	Span
GZ7634	1	[redacted]			(b) (4)
	2				
	3				
	4				
	5				
	6				
Average:		[redacted]			
RSD, %		1.38	3.12	2.86	0.85
Min		[redacted]			
Max					

Repeatability:

Table 2- Repeatability

Lot Number of Product	Sample No.	Fully Developed Plume of Spray (μm)			
		Dv(10)	Dv(50)	Dv(90)	Span
GZ7634	1	[redacted]			(b) (4)
	2				
	3				
	4				
	5				
	6				
Average:		[redacted]			
RSD, %		4.57	4.07	3.54	3.33
Min		[redacted]			(b) (4)
Max					

Intermediate Precision:

Table 3 Difference Between Two Chemist Results

Chemist	Lot Number of Product	Nebulizer Set	Sample #	Fully Developed Plume of Spray (μm)			
				Dv(10)	Dv(50)	Dv(90)	Span
GM	GZ7634	Unit #7	1	[redacted]			(b) (4)
			2				
			3				
			4				
			5				
			6				
	Average:						
	RSD, %			4.57	4.07	3.54	3.33
	Min			[redacted]			(b) (4)
	Max						
Chemist	Lot Number of Product	Nebulizer Set	Sample #	Fully Developed Plume of Spray (μm)			
				Dv(10)	Dv(50)	Dv(90)	Span
MN	GZ7634	Unit #6	1	[redacted]			(b) (4)
			2				
			3				
			4				
			5				
			6				
	Average:						
	RSD, %			5.50	5.20	4.16	3.80
	Min			[redacted]			(b) (4)
	Max						
Difference for mean results between GM and MN, %				**1.4**	**1.1**	**1.3**	**2.7**

Study Results:

For 0.5 mg/2 ml:

Table# V-2
Comparative Summary Table of Droplet Size Distribution by Laser Diffraction between Apotex product and Reference product for Budesonide Inhalation Suspension 0.5mg/2mL

Manufacturer	Lot_No	Dv(10)	Dv(50)	Dv(90)	Span
Apotex	GZ7634	(b) (4)			
	GZ8818				
	Average:				
	SD:	0.03	0.15	0.49	0.12
	%CV:	5.4	4.8	4.8	4.1
	Min:	(b) (4)			
	Max:				

Table# V-2
Comparative Summary Table of Droplet Size Distribution by Laser Diffraction between Apotex product and Reference product for Budesonide Inhalation Suspension 0.5mg/2mL

Manufacturer	Lot_No	Dv(10)	Dv(50)	Dv(90)	Span
AstraZeneca	LF0054	(b) (4)			
	LM0080				
	Average:				
	SD:	0.05	0.20	0.39	0.11
	%CV:	7.3	6.1	3.9	3.7
	Min:	(b) (4)			
	Max:				
Ratio of Means:		1.00	0.99	1.02	1.03

Reviewer's Comments:

The firm did not submit droplet size distribution by laser diffraction data for 0.25 mg/2 ml strength. It is acceptable since the control document did not require this information.

6. Sameness of Shape: Particle Size Distribution Determination by Light microscopic Image Analysis (Method PD-187)

A Microscopic Image Analysis method was employed for the determination of particle size distribution of Budesonide Inhalation Suspension (Method PD-187). The suspension was sonicated, and transferred (10ul) onto a microscope slide and examined under microscope. Ten random fields for each slide were examined. Data were acquired and process with Northern Eclipse software. Mean diameter and Dv(50) were reported. Frequency count and Frequency (%) at the particle sized range of (b) (4) were computed. Typical image of the microscope slide was submitted.

The method was validated for system precision, method precision specificity, and robustness. The validation results are shown as follows:

System Precision:

TABLE 1 - System Precision

Sample No.	Mean Diameter (μm)	Dv(50) (μm)	Frequency (%)			Total Particle Count
			(b) (4)			(b) (4)
1						
2						
3						
4						
5						
6						
Mean:						
RSD(%):	3.9	4.5	3.9	17.4	N/A	5.4

Repeatability:

TABLE 2 – Repeatability

Sample No.	Mean Diameter (μm)	Dv(50) (μm)	Frequency (%)			Total Particle Count
			(b) (4)			(b) (4)
1						
2						
3						
4						
5						
6						
Mean:						
RSD(%):	6.0	6.5	5.9	25.6	N/A	4.5
Reference:	TZ10060023, p. 32					

Intermediate Precision:

TABLE 3a - Intermediate Precision (Diameter)

	Chemist 1: T. ZHAO			Chemist 2: S. QUANG		
Sample No.	Mean Diameter (um)	Dv(50) (um)	Total Particle Count	Mean Diameter (um)	Dv(50) (um)	Total Particle (Count)
						(b) (4)
1						
2						
3						
4						
5						
6						
Mean:						
RSD(%):	6.0	6.5	4.5	7.1	10.4	17.6
Difference(%):	NA	NA	N/A	2.7	5.7	0.6

TABLE 3b - Intermediate Precision (Frequency)

Sample No.	Chemist 1: T. ZHAO Frequency (%)			Chemist 2: S. QUANG Frequency (%)		
1	(b) (4)					
2						
3						
4						
5						
6						
Mean:						
RSD(%):	5.9	25.6	N/A	6.7	24.7	N/A
Difference(%):	NA	NA	N/A	3.3	12.6	N/A
Reference:	TZ10060023, p. 32			SQ10060020, p.42		

Specificity: No particles were found in the placebo that can affect the quantitation of particles in the product samples.

Robustness: the robustness of the method was determined by varying the sonication time from 1.0 min to 2.0 min.

TABLE 4a – Robustness (Diameter)

Time	1.5 min			1.0 min			2.0 min		
Sample No.	Mean Diameter (um)	Dv(50) (um)	Total Particle Count	Mean Diameter (um)	Dv(50) (um)	Total Particle Count	Mean Diameter (um)	Dv(50) (um)	Total Particle (Count)
1	(b) (4)								
2									
Mean:									
RSD(%):	8.5	1.2	7.3	1.3	1.5	3.4	11.4	16.1	0.0
Difference(%):	N/A	N/A	N/A	7.0	3.7	4.6	11.7	2.0	2.9
Reference:	TZ10060023, p.32								

TABLE 4b – Robustness (Frequency)

Time	1.5 min			1.0 min			2.0 min		
Sample No.	Frequency (%)			Frequency (%)			Frequency (%)		
1	(b) (4)								
2									
Mean:									
RSD(%):	7.7	32.4	N/A	0.2	0.8	N/A	2.4	17.4	N/A
Difference(%):	N/A	N/A	N/A	2.3	9.9	N/A	8.0	36.5	N/A
Reference:	TZ10060023, p.32								

Study Results:

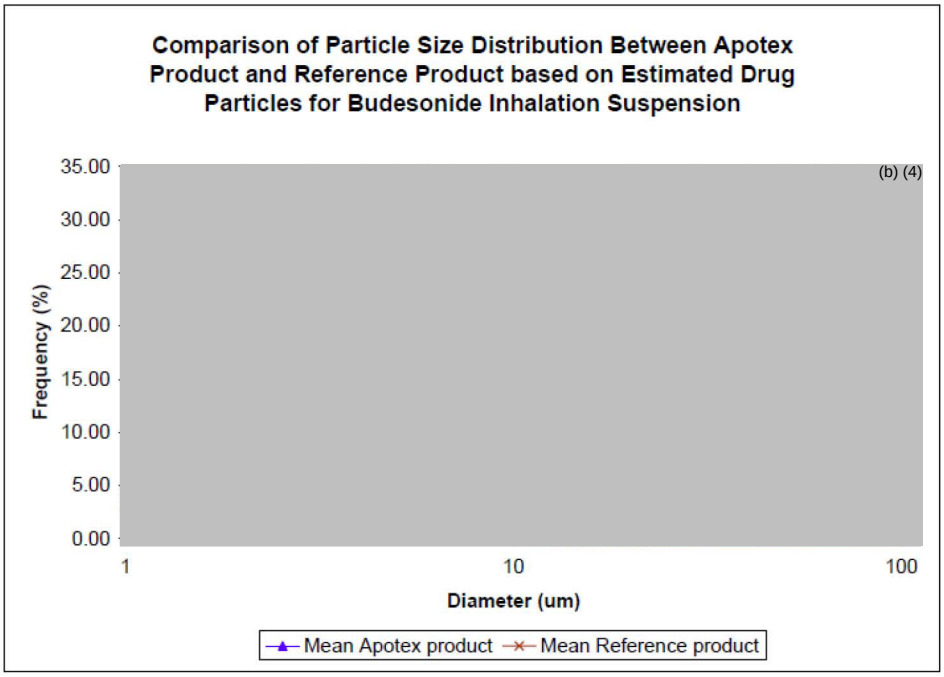
Table# VI-4

Summary of Apotex Product versus Reference Product

Particle Size by Microscopic Image Analysis for Budesonide Inhalation Suspension, 0.5mg/2mL

Manufacturer	Batch_No	Mean_Dia	MeanDv50	Mean_Par
Apotex	GZ7634		(b) (4)	
	GZ8818			
	Mean			
AstraZeneca	LF0054			
	LM0080			
	Mean			
	Ratio			

Figure# VI-1



The firm also submitted few representative 2-demission images acquired by image analyzer.

Reviewer's Comments:

1. The firm stated that "*particles are mainly shown round and oval in crystal shape. The crystalline habit of Innovator and Apotex's product is matched*".
2. The firm did not submit the Particle Size Distribution Determination by Light microscopic Image Analysis results for the 0.25 mg/2 ml product. The firm needs to submit information to prove that "*the budesonide (bulk drug) used in the lower strength*

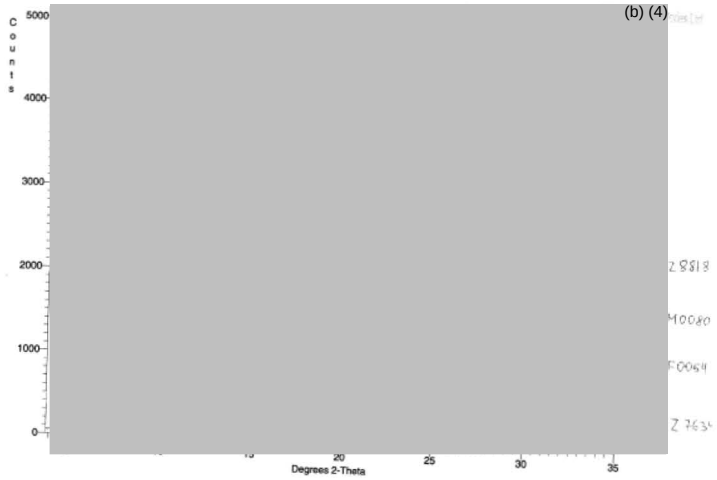
is the same as that used in the higher strength product, i.e., same particle size, PSD, polymorphic form, and shape", according to the control document.

7. Sameness of Polymorphic Form Based on X-ray Diffraction

Twenty ml of Budesonide inhalation suspension were filtered through a (b) (4) um silver membrane. The membrane was mounted into the X-ray holder. The filtered material is examined directly on the membrane using X-ray diffraction using the following instrument settings (Method QOP XRD):
Voltage: (b) (4) kV
Current: (b) (4) mA
Scan range: (b) (4) deg, (b) (4)
Scan speed: (b) (4) deg/min
Step (b) (4) deg, (b) (4)
The diffraction patterns from the samples were visually compared with the diffraction pattern of budesonide standard. The method was validated for specificity, repeatability and robustness.

Study Results:

Diffraction Pattern For the test and reference products of 0.5 mg/2 ml strength



Reviewer's Comments:

1. The X-ray diffraction spectrum exhibits identical patterns for the test and reference products for 0.5 mg/2ml product.

2. The firm also indicated in its Chemistry report that "*from TGA, IR, And XRD spectra it appears that no polymorphic forms are present*".

3. The firm did not submit the X-ray Diffraction results for the 0.25 mg/2 ml product. The firm needs to submit information to prove that "*the budesonide (bulk drug) used in the*

lower strength is the same as that used in the higher strength product, i.e., same particle size, PSD, polymorphic form, and shape".

8. Ampoules:

The firm submitted data of the DSC scans of Apotex Inc.'s ampoule and the Reference Listed Drug. A photographic presentation of the ampoules used in both the Apotex Inc.'s product and Reference Listed Drug were also are included. The firm concluded that the ampules are of a similar resin. This data is not reviewed.

E. Formulation

0.25 mg/2 mL Strength:

Components	Function	Test mg/mL	Reference mg/mL	%Difference
Budesonide, EP (Micronized)	Active ingredient	0.125	0.125	0
Sodium Chloride, USP/EP	(b) (4)			
Citric Acid (b) (4) USP				
Sodium Citrate (b) (4) USP				
Edetate Disodium, Dihydrate USP/EP				
Polysorbate 80 NF (b) (4)				
Water for Injection, USP/EP				

0.50 mg/2 mL Strength:

Components	Function	Test mg/mL	Reference mg/mL	%Difference
Budesonide, EP (Micronized)	Active ingredient	0.25	0.25	0
Sodium Chloride, USP/EP	(b) (4)			
Citric Acid (b) (4) USP				
Sodium Citrate (b) (4) USP				
Edetate Disodium, Dihydrate USP/EP				
Polysorbate 80 NF (b) (4)				
Water for Injection, USP/EP				

Reviewer's Comments on Formulation:

The firm's formulations are Q1 & Q2 same as the reference product for both strengths, and thus are acceptable.

F. Waiver Request(s)

Strengths for which waivers are requested	0.25 mg/2 mL & 0.50 mg/2 mL
Regulation cited	21 CFR 320.22 (b) (3)
Proportional to strength tested in vivo?	Q1&Q2 same with the respective strengths of the RLD product.
Is dissolution acceptable?	N/A
Waivers granted?	See Deficiency Comments
If not then why?	

G. Reviewer's Comments to the Overall Particle Size Studies:

The reviewer examined the particle size distribution (PSD) data from NDA 20-929 (RLD), ANDA 77-519 (Ivax, first Generic), and this application (Apotex), and have the following observations:

1. The firm (Apotex)'s specification on the drug substance (API) was set as:

   D10:< (b) (4) um
   D50 (b) (4) um
   D90:< (b) (4) um

2. The firm's PSD in suspension by light microscope results indicated that the D50 is (b) (4) um for test product and (b) (4) um for the reference product.

3. However, the firm's particle size distribution in suspension by laser diffraction study showed a significant greater PSD for both the test and reference product, that is: the D50 was (b) (4) um for the test product and (b) (4) um for the reference product. This result is inconsistent with the firm's PSD results by light microscopy study.

4. The reviewer checked the Chemical stability of the firm's product in terms of particle size, and found that the PSD increased significantly during a short storage time period (shown below).

PSD during cycle studies (-22°C for 2 days and 40°C for 2 days for 3 cycles)			
Drug Product/Lot	Distribution	Initial PSD	PSD after 3 cycles
0.25 mg/2 mL/#GZ8810	D10	(b) (4) um	(b) (4) um
	D50	um	(b) (4) um
	D90	um	um
0.5 mg/2 mL/GZ8818	D10	um	(b) (4) um
	D50	um	(b) (4) um
	D90	(b) (4) um	(b) (4) um

* Table cited from the chemistry Review located in DFS.

5. To check whether the same phenomena also occur in the reference product, the reviewer checked the chemistry review of the RLD product (Chemistry review for NDA 20-929, DFS

N 020929 N000 18-Nov-1997). It was stated that "*There is no significant change in particle size distribution for samples stored 24 months at 25ºC/60% RH' and "It is highly unlikely that any agglomerates are formed during the expiration dating period"*

6. The reviewer also checked the first generic application for this product (ANDA 77-519 Ivax), and found that the PSD for both test and reference products in this application were at the range of (b) (4) um (for D50) approximately (see summary table below for details).

7. Therefore, it is likely that the Apotex's method in particle size distribution in suspension measurement has problem and thus did not accurately reflect the particle size of both test and reference products. The firm should further investigate its particle size distribution in suspension study. The firm may use other alternative particle size measurement method, such as Coulter Multisizer, to confirm the study results.

Table: Comparative Summary of the D50 data of the 0.5 mg/2 ml strength Budisonide Inhalation Suspensions*:

Methods	**ANDA 78-202 (Apotex)**		**ANDA 77-519 (Ivax)**	
	TEST	REF	TEST	REF
PSD in suspension by Laser Diffraction	(b) (4) µm	(b) (4) µm	(b) (4) µm	(b) (4) µm
PSD in suspension by light microscopy	(b) (4) µm	(b) (4) µm	NA	NA
Droplet size dist'n in Aerosol	(b) (4) µm	(b) (4) µm	(b) (4) µm	(b) (4) µm
Specification	For API: D10:< (b) µm D50 (b) (4) µm D90:< (b) (4) µm	NA	For drug product: D10:< (b) (4) µm D50:< (b) (4) µm D90:< (b) (4) µm	NA
PSD after storage (Chemistry review)	(b) (4) µm at -22ºC for 2 days; (b) (4) µm at 40ºC for 2 days for 3 cycles	NA	NA	NA

* The reviewer quotes D50 data in this table as a representative. Same trends were observed for D10 and D90.

H. Deficiency Comments

1. The firm did not submit the method of particle size distribution <u>in the nebulized aerosol</u> using cascade impactor (method PD 102). Instead, the firm submitted two copies of the method validation report. The firm should submit the method describing the procedures of how the measurement was done and how the data were collected and analyzed. The firm should provide the rational of using this method for the measurement of <u>particle size of drug and agglomerates</u> in the nebulized aerosol.

2. The firm did not submit the X-ray Diffraction results and the Particle Size Distribution Determination by Light microscopic Image Analysis results for the 0.25 mg/2 ml product. The firm needs to submit information to prove that "*the budesonide (bulk drug) used in the lower*

strength is the same as that used in the higher strength product, i.e., same particle size, PSD, polymorphic form, and shape". Alternatively, the firm should submit the comparison between the high strength product and low strength product.

3. Since the Mean Delivered Dose obtained by the firm ranged (b) (4) (% nominal) for the test and RLD products, compared with 17 (% nominal) specified in the RLD product labeling, the firm is asked to explain the difference.

4. Since the mean nebulization time obtained by the firm was around 10 minutes for the test and RLD products, compared with 5 minutes or less specified in the RLD product labeling, the firm is asked to explain the difference.

5. The firm's particle size distribution (PSD) in suspension measured by different methods is inconsistent. The PSD measured by Laser Diffraction is significantly greater than that measured by light microscopy. The firm should investigate its method of PSD measurement by laser diffraction. The firm may use other alternative particle size measurement method, such as Coulter Multisizer, to confirm the study results.

6. The firm should provide the raw data for all the in vitro tests (Unit Dose Content of Drug in the Ampoules, Mean Nebulization Time and Mean Delivered Dose at the Mouthpiece, Particle Size Distribution of the Active Ingredient in the Suspension, Droplet Size Distribution of the Nebulized Aerosol) of the test and reference products, in electronic SAS Transport files, in the format of recommended tables provided.

7. The firm should submit the batch sizes and manufacturing dates of the test product.

8. The firm should submit the study site information for each in vitro test.

I. Recommendations

The *in vitro* bioequivalence testing conducted by Apotex Inc. comparing its test product, Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL, with the reference product, Pulmicort Respules, 0.25 mg/2 mL and 0.5 mg/2 mL, respectively, manufactured by Astra Zeneca, is **incomplete** for the reasons cited in the Deficiency Comments above.

J. Attachment:

Ivax (ANDA 77-519)'s Discussion of Method Development for the Test of Particle Size Distribution of the Active Ingredient in the Nebulized Aerosol:

Doc. Ref. D138 (version 01)	Validation of Procedure for Determination of Particle Size Distribution of the Nebulized Budesonide Inhalation Suspension Particles within the Nebulized Aerosol.	Page 2 of 13
Author: H. Gill		Authorised By:
Site: Manor Park, Runcorn.		Date: 21 Jun 04

Product : **Budesonide Inhalation Suspension**

Strengths : **1.0mg/2ml, 0.5mg/2ml and 0.25mg/2ml**

Method : **Particle Size Distribution of Budesonide Inhalation Suspension Particles within the Nebulized Aerosol.**

AIM

To validate the procedure for determination of particle size distribution of the nebulized Budesonide Inhalation Suspension particles within the nebulized aerosol.

Budesonide Inhalation Suspension is presented as a 2ml ampoule, containing (b) (4) 0.5, or 0.25mg of budesonide as the active ingredient. Inactive ingredients are sodium chloride, polysorbate 80, citric acid (b) (4) (b) (4) citrate (b) (4) disodium edetate dihydrate and Water for Injections (WFI).

The principal route of administration is by inhalation via the oropharynx into the lung. The product is administered to the patient by nebulisation.

The proposed analytical procedure is designed to provide data on the distribution of particle sizes of the insoluble Budesonide crystal in the nebulized aerosol.

Method Development

Collection of the Nebulized Sample:

(b) (4)

Doc. Ref. D138 (version 01)	Validation of Procedure for Determination of Particle Size Distribution of the Nebulized Budesonide Inhalation Suspension Particles within the Nebulized Aerosol.	Page 3 of 13
Author: H. Gill		Authorised By:
Site: Manor Park, Runcorn.		Date: 21 Jun 04

(b) (4)

[redacted]

Sample analysis:

(b) (4)

[redacted]

Coulter Counting is closely related to particle counting by light obscuration but is able to overcome the above deficiencies. Incidences of multiple particles flowing through the detector and being counted as one is less likely as the orifice used is only (b) µm wide and the equipment monitors the number of particles in real time so that if the concentration is too high the equipment will indicate this. The Coulter technique uses the impedance generated by a particle as it flows through an orifice in an electrolyte to determine the volume of the particle, orientation of the particle to the detector will not influence the result.

The Coulter Counter analysis was determined to be the most appropriate analysis technique for this application. The counter is calibrated with NIST traceable standard prior to running each batch of samples and uses a UKCAS approved method. As the instrument is a direct measurement of each particle size within the sample presented no further validation exercise will be performed.

BIOEQUIVALENCY DEFICIENCIES

ANDA: 78-202 APPLICANT: Apotex Inc.

DRUG PRODUCT: Budesonide Inhalation Suspension, 0.25 mg/2 mL & 0.5 mg/2 mL

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You did not submit the method of particle size distribution in the nebulized aerosol using cascade impactor (method PD 102). Instead, you submitted two copies of the method validation report. Please submit the method describing the procedures of how the measurement was conducted and how data were collected and analyzed for this test. In addition, please provide the rational of using this method for the measurement of <u>particle size of drug and agglomerates</u> in the nebulized aerosol.

2. You did not submit the X-ray Diffraction results and the Particle Size Distribution Determination by Light microscopic Image Analysis results for the 0.25 mg/2 ml product. Please submit information to prove that "*the budesonide (bulk drug) used in the lower strength is the same as that used in the higher strength product, i.e., same particle size, PSD, polymorphic form, and shape*". Alternatively, you submit the comparison between the high strength product and low strength product.

3. Your Mean Delivered Dose values obtained for the test and reference listed drug (RLD) products ranged (b) (4) (% nominal), compared with 17(% nominal) specified in the RLD product labeling. Please explanation for the difference between your test results and the Mean Delivered Dose specified in the labeling.

4. Your mean nebulization time obtained for the test and RLD was ten (10) minutes, compared with 5 minutes or less specified in the RLD product labeling. Please provide

explanation for the difference between your test results and the mean nebulization time specified in the labeling.

5. The results of your particle size distribution (PSD) in suspension measured by two different methods are inconsistent. The PSD measured by Laser Diffraction is significantly greater than that measured by light microscopy. Please investigate your method of PSD measurement by laser diffraction. You may use other alternative particle size measurement method, such as Coulter Multisizer, to confirm the study results.

6. Please re-submit raw data for the in vitro tests (Unit Dose Content of Drug in the Ampoules, Mean Nebulization Time and Mean Delivered Dose at the Mouthpiece, Particle Size Distribution of the Active Ingredient in the Suspension, Droplet Size Distribution of the Nebulized Aerosol) of the test and reference products, in electronic SAS Transport files, in the format of recommended tables provided.

7. Please submit the batch sizes and manufacturing dates of the test product.

8. Please submit the study site information for each in vitro test.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

SAS Data Definition Tables for in Vitro Nasal Nebulized Aerosol Data

Data in these tables should be arranged in columns as shown in examples. Data sets should be submitted as SAS Transport files. Each separate table should be used for data from each strength.

Table 1. Unit Dose Content of Drug in the Ampoules

Variable Name	**Variable Label**	**Variable Type**	**Content**	**Notes**
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
LOT	Lot number	Alphanumeric/ Numeric	Alphanumeric/ Numeric	Identifier for product lot
CONTAINER	Ampoule Number	Numeric	Numeric values	Identifier for ampoule. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
AMOUNT	Actual measured amount of drug mass	Numeric	Numeric values	Drug mass per ampoule
PCTLABEL	Percentage of label claim	Numeric	Numeric values	Percentage of drug mass per single actuation

Example

PRODUCT	LOT	CONTAINER	AMOUNT	PCTLABEL
TEST	1234	1		
		2		
		3		
		4		
		5		
		6		
		7		
		8		
		9		
		10		

Table 2. Mean Nebulization Time and Mean Delivered Dose at the Mouthpiece

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
LOT	Lot number	Alphanumeric/ Numeric	Alphanumeric/ Numeric	Identifier for product lot
CONTAINER	Ampoule Number	Numeric	Numeric values	Identifier for ampoule. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
DELIVERED DOSE	Dose delivered expressed in % of Nominal Dose	Numeric	Numeric values	Percent dose delivered
NEBULIZATION TIME	Nebulization time expressed in minutes or seconds	Numeric	Numeric values	Nebulized time expressed in minutes or seconds

Example

PRODUCT	LOT	CONTAINER	DOSE%	NEBULIZATION TIME
TEST	1234	1		
		2		
		3		
		4		
		5		
		6		
		7		
		8		
		9		
		10		

Table 3. Particle Size Distribution of the Active Ingredient in the Suspension

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
LOT	Lot number	Alphanumeric/ Numeric	Alphanumeric/ Numeric	Identifier for product lot
CONTAINER	Ampoule Number	Numeric	Numeric values	Identifier for ampoule. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
D10	D10	Numeric	Numeric values	D10
D50	D50	Numeric	Numeric values	D50
D90	D90	Numeric	Numeric values	D90
SPAN	SPAN	Numeric	Numeric values	SPAN calculated as ((D90-D10)/D50)

Example

PRODUCT	LOT	CONTAINER	D10	D50	D90	SPAN
TEST	1234	1				
		2				
		3				
		4				
		5				
		6				
		7				
		8				
		9				
		10				

Table 4. Droplet Size Distribution of the Nebulized Aerosol

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
LOT	Lot number	Alphanumeric/ Numeric	Alphanumeric/ Numeric	Identifier for product lot
CONTAINER	Ampoule Number	Numeric	Numeric values	Identifier for ampoule. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
D10	D10	Numeric	Numeric values	D10
D50	D50	Numeric	Numeric values	D50
D90	D90	Numeric	Numeric values	D90
SPAN	SPAN	Numeric	Numeric values	SPAN calculated as ((D90-D10)/D50)

Example

PRODUCT	LOT	CONTAINER	D10	D50	D90	SPAN
TEST	1234	1				
		2				
		3				
		4				
		5				
		6				
		7				
		8				
		9				
		10				

ANDA 78-202

BIOEQUIVALENCE - INCOMPLETE Submission date: March 31, 2006

1. *IN VITRO* STUDY (OTH) Strength: 0.5 mg/2 mL
Outcome: IC

2. *IN VITRO* STUDY (OTH) Strength: 0.25 mg/2 mL
Outcome: IC

OUTCOME DECISIONS: **IC** - Incomplete

WINBIO COMMENTS: IC.

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

/s/

Bing Li
4/23/2007 10:16:25 AM
BIOPHARMACEUTICS

Moheb H. Makary
4/23/2007 10:24:47 AM
BIOPHARMACEUTICS

Barbara Davit
4/23/2007 04:30:54 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-202

MICROBIOLOGY REVIEWS

Product Quality Microbiology Review

September 3, 2008

ANDA: 78-202

Drug Product Name
Proprietary: N/A
Non-proprietary: Budesonide Inhalation Suspension
Drug Product Classification: N/A
Review Number: #2

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
August 7, 2008	August 7, 2008	N/A	August 12, 2008
August 27, 2008	August 27, 2008	N/A	August 27, 2008

Submission History (for amendments only)

Submission Date(s)	Microbiology Review #	Microbiology Review Date(s)
March 31, 2006*[1]	1	June 30, 2008
June 20, 2006	1	June 30, 2008
February 21, 2007*[2]	1	June 30, 2008
November 5, 2007	1	June 30, 2008

*[1] Submission was RTF *[2] Comparability Study

Applicant/Sponsor
Name: Apotex Inc.
Address: 380 Elgin Mills Road East
Richmond Hill, Ontario. Canada L4C SH2
Representative: Kiran Krishnan
2400 North Commerce Parkway, Suite 400
Weston, Florida 33326
Telephone: 954-349-4217

Name of Reviewer: George K. Arhin, Ph.D.

Conclusion: The submission **is recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original Amendment

2. SUBMISSION PROVIDES FOR: Response to Agency's deficiency letter.

3. MANUFACTURING SITE:

Apotex Inc.
380 Elgin Mills Road East
Richmond Hill, Ontario
Canada, L4C 5H2

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile suspension in strengths 0.25 mg/2 ml and 0.5 mg/2 ml, filled into translucent LDPE plastic ampules and given by inhalation.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Budesonide inhalation suspension (contains the API Budesonide, a cortisteroid) is an anti-inflammatory cortisteroid indicated for the maintenance treatment of asthma and as prophylactic therapy in children (1-8 years of age)

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: The firm's representative (K. Krishnan) was contacted by this Microbiology Reviewer (G. Arhin) on 8/20/2008 to request additional information regarding the description of manufacturing facility. The representative indicated that the requested information would be provided by e-mail. The information was received on 8/27/2008.

filename: 78-202a1.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

The submission is **recommended** for approval on the basis of sterility assurance.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology

The subject drug is manufactured (b) (4). The API is (b) (4)

B. Brief Description of Microbiology Deficiencies - None identified

C. Assessment of Risk Due to Microbiology Deficiencies

No microbiology deficiencies were identified. The applicant demonstrates an adequate level of sterility assurance for the manufacturing process.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist / George. K. Arhin, Ph.D.
Microbiology Team Leader / Brenda Pillari, Ph.D.

C. CC Block

cc: Field Copy

3 Pages have been Withheld as b4 (TS/CCI) immediately following this page

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/s/

George K. Arhin
9/4/2008 12:46:39 PM
MICROBIOLOGIST

Kun Shen
9/4/2008 02:36:02 PM
MICROBIOLOGIST

checked for correct linking

Neal Sweeney
9/4/2008 03:03:10 PM
MICROBIOLOGIST

Brenda Pillari
9/4/2008 04:58:48 PM
MICROBIOLOGIST

Product Quality Microbiology Review

June 30, 2008

ANDA: 78-202

Drug Product Name
Proprietary: N/A
Non-proprietary: Budesonide Inhalation Suspension
Drug Product Classification: N/A
Review Number: #1

Dates of Submission(s) Covered by this Review

Letter	Stamp	Consult Sent	Assigned to Reviewer
March 31, 2006*[1]	April 3, 2006	N/A	January 2, 2008
June 20, 2006	June 21, 2006	N/A	January 2, 2008
February 21, 2007*[2]	February 23, 2007	N/A	January 2, 2008
November 5, 2007	November 6, 2007	N/A	April 14, 2008

*[1] Submission was RTF
*[2] Comparability Study

Submission History (for amendments only) – None

Applicant/Sponsor
Name: Apotex Inc.
Address: 380 Elgin Mills Road East
Richmond Hill, Ontario
Canada L4C SH2
Representative: Tammy McIntire
Apotex Corp
2400 North Commerce Parkway, Suite 400
Weston, Florida 33326
Telephone: 954-349-4217

Name of Reviewer: George K. Arhin, Ph.D.

Conclusion: The submission **is not recommended** for approval on the basis of sterility assurance.

Product Quality Microbiology Data Sheet

A. 1. TYPE OF SUBMISSION: Original ANDA

2. SUBMISSION PROVIDES FOR: Initial marketing of sterile drug product

3. MANUFACTURING SITE:

Apotex Inc.
380 Elgin Mills Road East
Richmond Hill, Ontario
Canada, L4C 5H2

4. DOSAGE FORM, ROUTE OF ADMINISTRATION AND STRENGTH/POTENCY: Sterile suspension in strengths 0.25 mg/2 ml and 0.5 mg/2 ml, filled into translucent LDPE plastic ampules and given by inhalation.

5. METHOD(S) OF STERILIZATION: (b) (4)

6. PHARMACOLOGICAL CATEGORY: Budesonide inhalation suspension (contains the API Budesonide, a cortisteroid) is an anti-inflammatory cortisteroid indicated for the maintenance treatment of asthma and as prophylactic therapy in children (1-8 years of age)

B. SUPPORTING/RELATED DOCUMENTS: None

C. REMARKS: None

filename: 78-202.doc

Executive Summary

I. Recommendations

A. Recommendation on Approvability -

The submission is **not recommended** for approval on the basis of sterility assurance. Specific comments and deficiencies are provided in the "Product Quality Microbiology Assessment" and "List of Microbiology Deficiencies and Comments" sections.

B. Recommendations on Phase 4 Commitments and/or Agreements, if Approvable – N/A

II. Summary of Microbiology Assessments

A. Brief Description of the Manufacturing Processes that relate to Product Quality Microbiology

The subject drug is manufactured (b) (4). The API is (b) (4)

B. Brief Description of Microbiology Deficiencies

Clarification is needed for the comparability studies with regard to the (b) (4)

C. Assessment of Risk Due to Microbiology Deficiencies

The safety risk associated with the microbiology deficiencies is considered moderate.

III. Administrative

A. Reviewer's Signature _____

B. Endorsement Block

Microbiologist / George. K. Arhin, Ph.D.
Microbiology Team Leader / Brenda Pillari, Ph.D.

C. CC Block

cc: Field Copy

20 Pages have been Withheld as b4 (CCI/TS) immediately following this page

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/s/

George K. Arhin
7/21/2008 11:16:51 AM
MICROBIOLOGIST

Kun Shen
7/21/2008 11:40:00 AM
MICROBIOLOGIST

Neal Sweeney
7/21/2008 12:43:53 PM
MICROBIOLOGIST

Brenda Pillari
7/21/2008 01:10:07 PM
MICROBIOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 78-202

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

OGD APPROVAL ROUTING SUMMARY

ANDA # 78-202 Applicant Apotex Inc.
Drug Budesonide Inhalation Suspension Strength(s) 0.25 mg/2 mL and 0.5 mg/2 mL

APPROVAL ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. **Martin Shimer** Date 5 March 2009 Date 3/29/09
Chief, Reg. Support Branch Initials MHS Initials rlw

Contains GDEA certification: Yes ☒ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92) Pediatric Exclusivity System
RLD = Pulmicort NDA# 20-929
Patent/Exclusivity Certification: Yes ☒ No ☐ Date Checked Previously granted
If Para. IV Certification- did applicant Nothing Submitted ☐
Notify patent holder/NDA holder Yes ☐ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☐ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☒
Date of latest Labeling Review/Approval Summary _____
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒
Type of Letter: Full Approval.
Comments: ANDA submitted on 4/3/2006, BOS=Pulmicort Respules NDA 20-929, PIII to the '536, PIV to the '603 and '099, MOU also submitted to the '603 and '099 solely for claims related to once daily dosing of the drug product. RTR issued on 6/8/2006. On 6/12/2006 the sponsor revised their certs to the '603 and '099 patents to MOU statements only. Then on 6/21/2006 the firm further amended their certs to provide a PIII to the '099 and a MOU to the '603. ANDA ack for filing on 6/21/2006 (LO dated 7/11/2006). On 8/29/2006 the firm then switched back their certification on the '099 patent from PIII to MOU (this switch was related to a change in the use code defined in the OB). Firm has addressed both listed patents with MOUs (MOU to the '603 on 6/21/06; MOU to the '099 on 8/29/2006), and has carved out the "once daily treatment" use information from their labeling. IVAX, the sponsor of ANDA 77-519, was approved on 11/18/2008. IVAX is not eligible for 180 day exclusivity as they also provided MOU statements to both the '603 and '099 patents.
ANDA is eligible for immediate Full Approval.

2. Project Manager, Esther Chuh Team 2 Review Support Branch Date 2/24/2008 Date _____
Initials EC Initials _____

Original Rec'd date 3/31/2006
Date Acceptable for Filing 6/21/2006
Patent Certification (type) IV, MOU
Date Patent/Exclus.expires 6/23/2019
Citizens' Petition/Legal Case Yes ☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒
Priority Approval Yes ☐ No ☒
(If yes, prepare Draft Press Release, Email it to Cecelia Parise)
Acceptable Bio reviews tabbed Yes ☐ No ☐

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 5/20/2008
Date of Office Bio Review 2/10/2009
Date of Labeling Approv. Sum 12/5/2008
Date of Sterility Assur. App. 9/4/2008
Methods Val. Samples Pending Yes ☐ No ☒
MV Commitment Rcd. from Firm Yes ☐ No ☐
Modified-release dosage form: Yes ☐ No ☒
Interim Dissol. Specs in AP Ltr: Yes ☐

Bio Review Filed in DFS: Yes ☐ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. Labeling Endorsement
Reviewer: Labeling Team Leader:
Date 3/5/2009 Date 3/5/2009
Name/Initials Angela Payne Name/Initials John Grace
Comments:

From: Grace, John F
Sent: Thursday, March 05, 2009 1:25 PM
To: Payne, Angela; Chuh, Esther
Subject: RE: ANDA 78-202 Apotex/ Budesonide Inh Susp

concur.

From: Payne, Angela
Sent: Thursday, March 05, 2009 10:58 AM
To: Chuh, Esther; Grace, John F
Subject: RE: ANDA 78-202 Apotex/ Budesonide Inh Susp

John/Esther,

The labeling approval summary signed on 12/5/08 remains acceptable. There are no new changes to the labeling of the RLD, Comis, or USP.

Angela

4. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date 3/29/09
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials rlw/for
Comments:N/A. Apotex provided method-of-use statements to the '603 and '099 patents listed in the "Orange Book".

5. Div. Dir./Deputy Dir. Date 3/25/09
Chemistry Div. I Initials PS

Comments:CMC OK.

6. Frank Holcombe **First Generics Only** Date 3/29/09
Assoc. Dir. For Chemistry Initials rlw/for Comments: (First generic drug

review)

N/A. IVAX's ANDa for this drug product was approved on November 18, 2008.

7. Vacant Date_____ Deputy Dir., DLPS
Initials_____

RLD = Pulmicort Respules 0.25 mg/2 mL and 0.5 mg/2 mL
AstraZeneca NDA 20-929 (001, 002)

8. Peter Rickman Date3/29/09
Director, DLPS Initials rlw/for

Para.IV Patent Cert: Yes☐ No☐;Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐ Comments: Bioequivalence studies (in vitro) found acceptable for approval. Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 4/23/07 and 2/10/09.

Final-printed labeling found acceptable for approval 12/5/08, as endorsed 3/5/09, above.

Microbiology/Sterility assurance found acceptable for approval (Micro Review #2) 9/4/08.

CMC found acceptable for approval (Chemistry Review #4, addendum #1).

OR

8. Robert L. West Date 3/29/09
Deputy Director, OGD Initials RLWest

Para.IV Patent Cert: Yes☐ No☒; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☒
Press Release Acceptable ☐
Comments: Acceptable EES dated 8/29/08 (Verified 3/29/09). No "OAI" Alertsd noted.

Apotex has provided method-of-use statements to the '603 and '099 patents listed in the "Orange Book". Apotex has "carved-out" the use associated with these patents (Once a day treatment of asthma with nebulized budesonide) from its package insert labeling. This is acceptable and supported by a memorandum dated 3/13/07 filed in DFS from DPAP. There are no additional patents or exclusivity listed in the current "Orange Book" for this drug product.

This ANDA is recommended for approval.

9. Gary Buehler Date 3/29/09
Director, OGD Initials rlw/for
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

10. Project Manager, Esther Chuh Team 2 Date3/30/2009

Review Support Branch Initials EC
Date PETS checked for first generic drug (just prior to notification to firm)

Applicant notification:
9:50 AM Time notified of approval by phone
10:00AM Time approval letter faxed

FDA Notification:
3/30/2009 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
3/30/2009 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

EER DATA:

EES Data for: 078202

**** Compliance Recommendations ****

App No	Doc Seq No	Date	OC Recommendation
078202	000	8/29/2008	ACCEPTABLE
078202	000	5/20/2008	ACCEPTABLE
078202	000	2/14/2007	WITHHOLD

**** EER Table ****

CFN	Name	Profile Code	Last Milestone Name	Last Milestone Date	Last Status	Last Status Date	OAI Alert/ Effective Date
[redacted]	(b) (4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	None
9611083	APOTEX INC	CTL	OC RECOMMENDATION	8/10/2006	AC	8/10/2006	None

	(b) (4)						None
9615251	APOTEX INC	LIQ	OC RECOMMENDATION	6/1/2006	AC	6/1/2006	None
						(b) (4)	None
							None
							None
							None
							None
							None

COMIS TABLE:

Comis Application Table Data for Application No: 078202

***** Note: For Enterprise Search Files you may have to click and close the new window on first use***

Back to Search Form ***COMIS Pool Reviewers*** **ES DFS Files Only** **ES - All Files** **EDR** **Cycles**

Drug Name: BUDESONIDE

Potency: 0.25MG/2ML & 0.5MG/2ML Dosage Form: SUS APPL Type: N

Applicant: APOTEX

Status Code: PN Status Date: 11/14/2008 Clock Date: 4/3/2006 USP: N Org: 600

Therapeutic Drug Class: MISCELLANEOUS RESPIRATORY

Patent Certification: 4 Patent Expiration Date: PEPFAR:

Incom Doc Type	Supp Mod Type	Decision Code	Status code

(b) (4)

(b) (4)

Comis

Document Table Data

ORANGE BOOK PRINT OFF:

Patent and Exclusivity Search Results from query on Appl No 020929 Product 002 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
020929	002	6598603	Dec 23, 2018			**U-529**	
020929	002	6598603*PED	Jun 23, 2019				
020929	002	6899099	Dec 23, 2018			**U-529**	
020929	002	6899099*PED	Jun 23, 2019				

Exclusivity Data

There is no unexpired exclusivity for this product.

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through February, 2009
Patent and Generic Drug Product Data Last Updated: March 27, 2009

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

/s/

Esther Chuh
3/30/2009 10:03:44 AM

RECORD OF TELEPHONE CONVERSATION

Reference is made to ANDA #78-202; Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL; Apotex, Inc.

I called Ms. Bernice Tao of Apotex on 3/9/09 regarding a final issue regarding [redacted] (b) (4)

Apotex addressed [redacted] (b) (4) compliance in their drug product Test and Specifications sheet, however, they indicated it as a comment at the bottom of their Finished Drug Product Tests and Specifications. Upon further review it was determined that they would need to incorporate [redacted] (b) (4) [redacted] as a specifications similar to all other specifications for the drug product.

We recommended that she FAX us a copy of the information in addition to submitting it as an amendment to the ANDA.

Bernice Tao returned my call on 3/9/09 indicating she would provide the response, but it might be delayed due to issues with their LIMS system and difficulty in changing the forms.

Apotex provided the appropriate document on 3/18/09 as a FAX with an additional update to their eCTD application.

DATE:
March 18, 2009

ANDA NUMBER
78-202

TELECON INITIATED BY
FDA

PRODUCT NAME:
Budesonide Inhalation Suspension
0.25 mg/mL & 0.5 mg/mL

FIRM NAME:
Apotex Inc.

FIRM REPRESENTATIVES:
Ms. Bernice Tao, Ph.D.
Executive Vice President

PHONE NUMBER:
(416) 401-7889

FDA REPRESENTATIVE(S)
Ken Furnkranz

SIGNATURES:

_____
Kenneth J. Furnkranz

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/s/

Kenneth Furnkranz
3/18/2009 04:37:29 PM
CHEMIST

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

FROM: Hoainhon Nguyen
Acting Deputy Director
Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

THROUGH: Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

SUBJECT: Current Recommendations for BE Testing of Budesonide Inhalation Suspension (BIS) Drug Products

TO: ANDA 77-519 – Ivax's Budesonide Inhalation Suspension
ANDA 78-202 – Apotex's Budesonide Inhalation Suspension
ANDA (b) (4)

I. Scientific Basis for the Current BE Recommendations As Response to Citizen Petition FDA-2006-P-073

The following is the summary of the Agency's response to the Citizen Petition Docket No. FDA-2006-P-0073, dated November 18, 2008, concerning the bioequivalence criteria used for approval of the BIS drug product:

1. ANDA Applicants May Demonstrate Bioequivalence of Their Generic BIS Drug Products to Pulmicort Respules Through In Vitro Tests

For locally acting products, bioequivalence is generally not measured directly. Because budesonide is a locally acting drug, the typical pharmacokinetic bioequivalence study that compares the rate and extent of absorption of the drug into the systemic circulation alone would not be sufficient to demonstrate equivalent delivery of budesonide to the lungs. This type of study is less useful when used for products like budesonide that are not intended to be absorbed in the blood stream to elicit therapeutic effects. In such cases, the Agency looks to alternative ways to determine whether significant differences in rate or extent of absorption exist between two products. We may rely on other methods to assess bioequivalence. Taking into consideration the characteristics of BIS, we have concluded

that in vitro methods are capable of assessing bioequivalence of budesonide under certain circumstances.

BIS is an inhalation suspension in which the active ingredient is undissolved and the inactive ingredients are dissolved in the suspending fluid. Suspension characteristics are important for oral inhalational products and are critical in determining whether in vitro methods alone are appropriate for determining bioequivalence for BIS. Because all the inactive ingredients in BIS are dissolved, if the inactive ingredients and active ingredient are qualitatively and quantitatively the same as the reference product, the only potential difference between the test and reference product would be the properties of the suspended drug substance (active ingredient) particles in the product. In a product that is qualitatively and quantitatively the same as Pulmicort Respules, there will be no other suspended particles to interfere with a determination of the particle size distribution of the BIS drug product. If there is equivalence in particle size between generic BIS and Pulmicort Respules, then the budesonide in generic BIS can be expected to be delivered at the same rate and extent at the site of action (i.e., the lungs) as the budesonide in Pulmicort Respules. Assuming there is equivalence in particle size distribution, systemic availability would also be expected to be equivalent because the amount of budesonide absorbed into the blood stream after passing through the lungs would be expected to be equivalent. For these reasons, we believe that it is important to focus on the particle size of the active ingredient in evaluating generic BIS products.

We have identified the attributes of the particles that could potentially affect the availability of the delivered dose at the primary sites of action (i.e., in the lungs) and also the systemic availability of the delivered dose. These attributes include particle size distribution (in suspension and in the nebulized aerosol), polymorphic form of the particle, and drug particle size in the droplets. We believe that through in vitro tests, ANDA applicants can demonstrate that there is no significant difference in these properties of the drug substance (active ingredient) particles and therefore no significant difference in both the local and the systemic availability of the generic and reference drug products.

For these reasons, based on our authority under section 505G)(8)(C) of the Act and our regulations at 21 CFR 320.24(b)(6), we request that applicants for generic BIS demonstrate that their formulations are qualitatively and quantitatively the same as the reference product and conduct in vitro testing to demonstrate that they have particle size distributions equivalent to the reference product. The recommended in vitro equivalence tests are extensive and include the following:

• Unit dose content of drug in the ampules

• Mean nebulization time and mean delivered dose at the mouthpiece (% nominal dose) at the labeled flow rate of 5.5 liters/minute through such time that mist is no longer coming out of the mouthpiece.

• Particle size distribution of the active ingredient in the product and comparative particle

size distribution in the suspension (in the ampoule) and in the nebulized aerosol. The particle size distribution determination should be based on a validated method. Validation should demonstrate method sensitivity to drug particle size over the expected size range in the suspension. Drug particles and agglomerates in the suspension both in the ampoule and the nebulized aerosol should be characterized for mean size and distribution.

• Sameness of polymorphic form based on X-ray diffraction

• Sameness of shape (crystalline habit)

• Sameness of aqueous droplet size of the nebulized aerosol by a laser diffraction method[1]

If the applicant demonstrates bioequivalence through in vitro testing, we will not expect an ANDA applicant to conduct a clinical study to demonstrate bioequivalence.

Alternatively, if an applicant is unable to measure the particle size distribution, we will consider an applicant's proposal to perform the in vitro tests recommended above (with the exception of the test addressing particle size distribution) and also in vivo clinical and pharmacokinetic studies (in addition to demonstrating qualitative and quantitative sameness in formulation) to demonstrate bioequivalence. In vivo studies to establish bioequivalence would likely include (1) a clinical endpoint bioequivalence study for local delivery with demonstration of acceptable dose-response for test and reference products to assure study sensitivity and (2) a systemic exposure (pharmacokinetic) bioequivalence study. Prior to initiating such studies, applicants should submit a protocol with their proposal for both studies for our review.

Only the active ingredient is undissolved and all inactive ingredients are dissolved in the BIS suspension and particle size distribution of budesonide can be measured using in vitro methods. Therefore, an in vitro testing method may be used to demonstrate bioequivalence of generic BIS drug products.

Pulmicort Respules is supplied in sealed aluminum foil envelopes and the nebulizer devices that are used with Pulmicort Respules are commercially available separately from the suspension product. Therefore, the bioequivalence evaluation for BIS drug products does not need to include an evaluation of the device. The generic BIS labeling, like the Pulmicort Respules labeling, would bear substantively the same instructions with respect to the device used to deliver budesonide. For example, the labeling would say that BIS "should be administered via jet nebulizer connected to an air compressor with an adequate air flow, equipped with a mouthpiece or suitable face mask." To further ensure consistency between the size of droplets produced and the amount of drug delivered, we

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[1] If an applicant is proposing both a 0.5 mg/2 ml and a 0.25 mg/2ml strength generic BIS drug product and if the micronized budesonide (bulk drug) used in the lower strength product is the same as that used in the higher strength product, i.e., same particle size, particle size distribution, polymorphic form, and shape, and the comparative test and reference lower strength formulations are qualitatively and quantitatively the same, then we recommend an abbreviated testing method for the lower strength BIS drug product.

recommend that applicants for BIS conduct their bioequivalence testing using the same nebulizer described in the RLD labeling and used in the clinical trials for the RLD.

In summary, based on the characteristics of BIS, ANDA applicants for BIS products that are qualitatively and quantitatively the same as Pulmicort Respules may demonstrate bioequivalence of their drug product to Pulmicort Respules by conducting in vitro tests if they can measure particle size distribution. FDA will also consider proposals involving a combination of in vitro and in vivo tests if an applicant is unable to measure the particle size distribution.

2. The Clinical Program May Not Be Necessary To Demonstrate Bioequivalence

We do not believe that it would be appropriate to require all applicants for generic BIS drug products to conduct a comparative clinical study and pharmacokinetic study when they can use an in vitro method (assuming particle size distribution can be measured) to demonstrate bioequivalence. The in vitro method would obviate the need for human testing, and this approach is consistent with our mandate to avoid unnecessary human testing. Under the recommended in vitro bioequivalence method, we would expect the total amount of drug nebulized, the particle size distribution of drug in the droplets, and the droplet size distribution to be bioequivalent between the generic BIS drug product and Pulmicort Respules. If the criteria are met, we can reasonably expect that there would not be a significant difference in the systemic exposure and local delivery between the two drug products because of the characteristics of the suspension in which the active ingredient remains undissolved.

The in vitro bioequivalence method described above would be more sensitive to differences between two BIS products than the clinical trial that has been proposed to the Agency in the past. In order for the clinical end points to be meaningful BE response measures, the selected doses must fall within the ascending portion of the dose-response relationship and not in the flat portion, and it is difficult to establish a dose-response relationship for inhaled corticosteroids in a mild population using standard outcomes, such as FEV1 as the dose-response relationship plateaus at relatively low doses. Establishing the dose-response relationship is essential if bioequivalence is to be shown by a comparative clinical trial methodology. We note that the apparent flatness of the dose-response relationship indicates that small changes in the amount of drug delivered are not easily detectable by clinical or pharmacodynamic measures. Therefore, the clinical study proposed thus far to the Agency likely would not be as sensitive to differences between two BIS products as would the in vitro bioequivalence method previously described.

We believe that a comparative clinical study likely would not be as sensitive to differences between two BIS drug products as would the in vitro bioequivalence method previously described. As we described, applicants for generic BIS drug products who can measure particle size distribution may conduct in vitro tests to demonstrate bioequivalence. FDA will also consider applicants' proposals involving a combination of

in vitro and in vivo tests if they are unable to measure particle size distribution and we intend to evaluate the appropriate endpoints when considering such proposals.

II. ANDA Review History and Development of BE Acceptance Criteria

At this time, the Agency has received three ANDAs for generic BIS drug product: ANDAs 77-519 (Ivax; First Generic), 78202 (Apotex).and (b) (4)

1. Approval of ANDA 77-519

The First Generic ANDA 77-519 was submitted originally on December 30, 2004 by Ivax and approved on November 18, 2008. The following *in vitro* BE tests have been conducted for ANDA 77-519 to support the waiver of the *in vivo* bioequivalence testing:

- Unit Dose Content
- Mean Nebulization Time
- Mean Delivered Dose at Mouthpiece
- Particle Size Distribution in Starting Material and in Suspension
- Particle Size Distribution in Nebulized Aerosol
- Sameness of Polymorphic Form Based on X-ray Diffraction
- Sameness of Shape
- Droplet Size Distribution of the Nebulized Aerosol

The test methods for the above tests are as follows:

- Unit Dose Content: Measurement of drug content per unit dose by HPLC/UV
- Mean Nebulization Time: Nebulization and Collection by Pari LC Plus Nebulizer/Pari Master Compressor
- Mean Delivered Dose at Mouthpiece: Nebulization and collection by Pari LC Plus Nebulizer/Pari Master Compressor; assay by HPLC/UV
- Particle Size Distribution in Starting Material and in Suspension: Laser Diffraction using Malvern Mastersizer S
- Particle Size Distribution in Nebulized Aerosol: Nebulization by Pari LC Plus Nebulizer/Pari Master Compressor; Collection of aerosol samples by Next Generation Impactor (NGI), pooling of samples in excipient solution, particle sizes determined by (b) (4) Counter. Acceptance Criteria: PBE analysis of D50 and SPAN
- Sameness of Polymorphic Form Based on X-ray Diffraction: Per USP NF <941>
- Sameness of Shape: Per USP <776> Optical Microscopy
- Droplet Size Distribution of the Nebulized Aerosol: Laser Diffraction using Malvern Spraytec, Pari LC Plus/Pari Master Compressor

Acceptance Criteria for the above tests are as follows:

Test	Test Method	BE Study Measure(s)	BE Measure(s) For Statistical Evaluation	Statistical Evaluation for BE
1. Unit Dose Content	HPLC	Drug Mass per Single Dose	Same as previous column	PBE
2. Mean Nebulization Time	Timer	Mean Nebulization Time	Same as previous column	PBE
3. Mean Delivered Dose at Mouthpiece	HPLC	Mean Delivered Dose	Same as previous column	PBE
4. Particle Size Distribution in API and in Suspension	Laser Diffraction	D10, D50, D90, SPAN	D50, SPAN	PBE
5. Particle Size Distribution in Nebulized Aerosol	NGI/ (b) (4) Counter	D10, D50, D90, SPAN	D50, SPAN	PBE
6. Sameness of Polymorphic Form	X-Ray Diffraction	Powder diffraction patterns	Qualitative Form Comparison	N/A
7. Sameness of Shape	Microscopy	Drug CMD; extent of agglomerates	Qualitative Shape Comparison	N/A
8. Droplet Size Distribution of the Nebulized Aerosol	Laser Diffraction	D10, D50, D90, SPAN	D50, SPAN	PBE

2. Pending ANDA 78-202

The ANDA 78-202 was submitted originally on March 31, 2006 by Apotex and currently reviewed. The following *in vitro* BE tests have been conducted for ANDA 78-202 to support the waiver of the *in vivo* bioequivalence testing:

- Unit Dose Content
- Mean Nebulization Time
- Mean Delivered Dose at Mouthpiece
- Particle Size Distribution in Starting Material and in Suspension
- Particle Size Distribution in Nebulized Aerosol
- Sameness of Polymorphic Form Based on X-ray Diffraction
- Sameness of Shape
- Droplet Size Distribution of the Nebulized Aerosol

The test methods for the above tests are as follows:

- Unit Dose Content: Measurement of drug content per unit dose by HPLC/UV
- Mean Nebulization Time: Nebulization and Collection by Pari LC Plus Nebulizer/Pari Master Compressor
- Mean Delivered Dose at Mouthpiece: Nebulization and collection by ProNeb Ultra nebulizer with Pari LC Nebulization kit (b) (4); assay by HPLC/UV
- Particle Size Distribution in Starting Material and in Suspension: Laser Diffraction using Malvern Mastersizer S
- Particle Size Distribution in Nebulized Aerosol: Collection of aerosol samples by (b) (4) Multistage Cascade Impactor, assay by HPLC/UV
- Sameness of Polymorphic Form Based on X-ray Diffraction
- Sameness of Shape: Light Microscopic Image Analysis
- Droplet Size Distribution of the Nebulized Aerosol: Laser Diffraction using Malvern Spraytec, Pari LC Plus/Pari Master Compressor

Acceptance Criteria for the above tests are as follows:

Test	Test Method	BE Study Measure(s)	BE Measure(s) For Statistical Evaluation	Statistical Evaluation for BE
1. Unit Dose Content	HPLC	Drug Mass per Single Dose	Same as previous column	PBE
2. Mean Nebulization Time	Timer	Mean Nebulization Time	Same as previous column	PBE
3. Mean Delivered Dose at Mouthpiece	HPLC	Mean Delivered Dose	Same as previous column	PBE
4. Particle Size Distribution in API and in Suspension	Laser Diffraction	D10, D50, D90, SPAN	D50, SPAN	PBE
5. Particle Size Distribution in Nebulized Aerosol	(b) (4) Cascade Impactor	Mass Balance (MB), Impactor-Sized Mass (ISM), MMAD and GSD	Same as previous column	PBE
6. Sameness of Polymorphic Form	X-Ray Diffraction	Powder diffraction patterns	Qualitative Form Comparison	N/A
7. Sameness of Shape	Microscopy	Drug CMD; extent of agglomerates	Qualitative Shape Comparison	N/A
8. Droplet Size Distribution of the Nebulized Aerosol	Laser Diffraction	D10, D50, D90, SPAN	D50, SPAN	PBE

3. Pending ANDA (b) (4)

(b) (4)

(b) (4)

III. Decision Tree of BE Testing Recommendations

In addition to meeting the bioequivalence testing criteria, the formulations of the generic BIS and RLD drug product should be ***qualitatively (Q1) and quantitatively (Q2) the same***. As stated in the Agency's response to the Citizen Petition above concerning the current BE testing, because all the inactive ingredients in BIS are dissolved, if the inactive ingredients and active ingredient are qualitatively and quantitatively the same as the reference product, ***the only potential difference between the test and reference product would be the properties of the suspended drug substance (active ingredient) particles in the product.*** In a product that is qualitatively and quantitatively the same as Pulmicort Respules, there will be no other suspended particles to interfere with a determination of the particle size distribution of the BIS drug product. If there is equivalence in particle size between generic BIS and Pulmicort Respules, then the budesonide in generic BIS can be expected to be delivered at the same rate and extent at the site of action (i.e., the lungs) as the budesonide in Pulmicort Respules.

The attributes of the particles that could potentially affect the availability of the delivered dose at the primary sites of action (i.e., in the lungs) and also the systemic availability of the delivered dose include particle size distribution (in suspension and in the nebulized aerosol), polymorphic form of the particle, and drug particle size in the droplets.

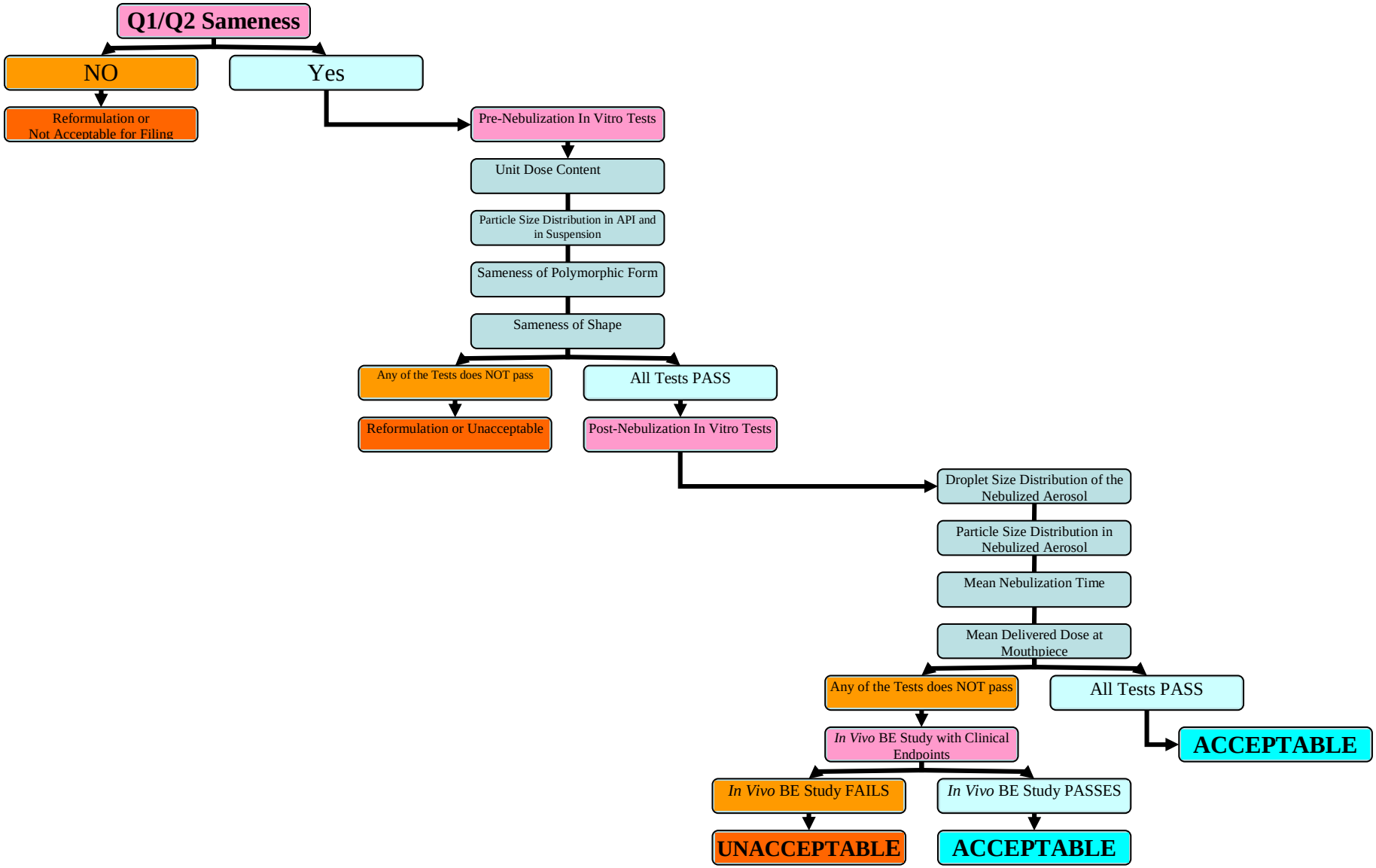
Pulmicort Respules is supplied in sealed aluminum foil envelopes and the nebulizer devices that are used with Pulmicort Respules are commercially available separately from the suspension product. Therefore, the bioequivalence evaluation for BIS drug products does not need to include an evaluation of the device, and is based only on the comparison of the single-dose drug product suspension package between a generic and the RLD products. Although we recommend that the bioequivalence testing be conducted using the same nebulizer described in the RLD labeling and used in the clinical trials for the RLD, in practice, the patients will use different nebulizing devices for the drug product as long as the following labeling use instructions are followed: The drug product *"should be administered via jet nebulizer connected to an air compressor with an adequate air flow, equipped with a mouthpiece or suitable face mask."*.

The bioequivalence testing of BIS drug products can be divided into three testing stages: (1) ***Pre-nebulization in vitro testing*** includes Unit Dose Content, Particle Size Distribution in Starting Material and in Suspension, Sameness of Polymorphic Form Based on X-ray Diffraction and Sameness of Shape; (2) ***the post-nebulization in vitro testin***g includes Mean Nebulization Time, Mean Delivered Dose at Mouthpiece and Particle Size Distribution in Nebulized Aerosol; and (3) ***in vivo bioequivalence testing with clinical endpoints***. Although failure of any of the first stage (pre-nebulization) *in vitro* tests should lead to reformulation of the generic drug product, the failure of any of the second stage (post-nebulization) *in vitro* tests would require further confirmation by the third stage *in vivo* bioequivalence testing using clinical endpoints. The first stage pre-nebulization *in vitro* testing is conducted to demonstrate the pharmaceutical equivalence between two formulations, whereas the objective of the second stage post-nebulization *in vitro* testing are to confirm the assumption that, two pharmaceutically equivalent formulations, under identical nebulization conditions, should yield the same mean

nebulization time, mean delivered dose at mouthpiece, and particle size distribution in nebulized aerosol, and droplet size distribution. Since any post-nebulization differences could potentially affect the rate and extent of the drug absorption, these differences would raise doubt in the bioequivalence between the two test products. Therefore, any failure in any of the second stage tests would prompt the need for further confirmation of bioequivalence using clinical bioequivalence studies with clinical endpoints. On the other hand, if there is no statistically significant difference detected between the two products at the second stage testing, no further *in vivo* testing should be necessary, and the two products should be deemed bioequivalent. As stated earlier, *in vitro* bioequivalence methods would be more sensitive to differences between two BIS products than an *in vivo* bioequivalence with clinical endpoints such as FEV1, and the *in vivo* bioequivalence testing should be conducted only when considered necessary.

Although suitable test methods and acceptance criteria have been established for all other pre- and post-nebulization *in vitro* tests, as seen in the in-house ANDA submissions, a test method for determination of Particle Size Distribution in Nebulized Aerosol (Test 5) has been shown to be more challenging to ANDA applicants to develop, and for the Agency to set criteria. At this time, ANDA applicants are encouraged to develop their own methods for Test 5, and any well validated test method for Test 5 will be accepted for consideration and further evaluation by the Agency. As shown above, ANDAs 77519, 78202 and (b) (4) used different test methods for determination of Particle Size Distribution in Nebulized Aerosol. Based on the validation and test data submitted the DBE has determined accordingly different but appropriate testing parameters and statistical criteria for evaluating the test results. As more data on different test methods for the Particle Size Distribution in Nebulized Aerosol test become available, the DBE may select the most appropriate test method and recommend the same method to be used by all other incoming ANDAs of the drug product.

The Decision Tree diagram of the BE testing recommendations below shows that the qualitative and quantitative sameness between the generic and RLD formulation, and the *in vitro* pre-nebulization testing using Tests 1,4, 6 and 7 are considered the most critical criteria for bioequivalence determination of a test formulation. If the formulation sameness and any of the pre-nebulization tests fail the acceptance criteria, the test product will not be considered bioequivalent to the RLD product, and no further testing is needed unless the test product is reformulated. On the other hand, if the above critical criteria are met, the post-nebulization tests are conducted, under example nebulizing setup conditions similar to those described in the RLD labeling and used in the clinical trials for the RLD, to explore and confirm whether additional *in vivo* bioequivalence testing with clinical endpoints is necessary. Only when a post-nebulization test fails that the DBE recommends *in vivo* BE testing with clinical endpoints.


Q1/Q2 Sameness
NO
Yes
Reformulation or
Not Acceptable for Filing
Pre-Nebulization In Vitro Tests
Unit Dose Content
Particle Size Distribution in API and in Suspension
Sameness of Polymorphic Form
Sameness of Shape
Any of the Tests does NOT pass
All Tests PASS
Reformulation or Unacceptable
Post-Nebulization In Vitro Tests
Droplet Size Distribution of the Nebulized Aerosol
Particle Size Distribution in Nebulized Aerosol
Mean Nebulization Time
Mean Delivered Dose at Mouthpiece
Any of the Tests does NOT pass
All Tests PASS
ACCEPTABLE
In Vivo BE Study with Clinical Endpoints
In Vivo BE Study FAILS
In Vivo BE Study PASSES
UNACCEPTABLE
ACCEPTABLE

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/s/

Hoainhon T. Nguyen
1/13/2009 12:03:07 PM
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Dale Conner
1/15/2009 09:35:00 AM
BIOPHARMACEUTICS

BIOEQUIVALENCE AMENDMENT

ANDA 78-202

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Apotex Inc. TEL: 954-384-3986

ATTN: Kiran Krishnan FAX: 954-349-4233

FROM: Nam J. Chun FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on March 31, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __**two**__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalence Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

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BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-202

APPLICANT: Apotex Inc.

DRUG PRODUCT: Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL

The Division of Bioequivalence has completed the review of your submission acknowledged on the cover page. The following deficiencies have been identified:

1. To validate the two new test batches (Lot # GZ2610 for 0.5 mg/2 mL, and HY9696 for 0.25 mg/2 mL) used in your Particle Size Distribution (PSD) in Nebulized Aerosol by Cascade Impaction (CI) and Mean Delivery Dose (MDD) at Mouthpiece tests, please submit the following information:

    - Statements clarifying whether these batches (Lot # GZ2610 for 0.5 mg/2 mL, and HY9696 for 0.25 mg/2 mL) were manufactured, controlled and released the same way as the previous batches (Lot # GZ7634, GZ8818 for 0.5 mg/2 mL, and GZ7632, GZ8410 for 0.25 mg/2 mL) used in the earlier *in vitro* bioequivalence studies, in terms of i) formulation, ii) manufacturing process, and iii) in-process controls.

    - Chemistry, Manufacturing and Control (CMC) information for the new batches Lot # GZ2610 and # HY9696. Please contact the Division of Chemistry for the CMC information considered necessary for acceptable validation.

2. Your repeated Particle Size Distribution test was conducted using a new Cascade Impactor. However, you did not provide method validation report for this new Cascade Impactor and/or a cross validation study between the original and new Cascade Impactors. Please submit this information. Please explain whether there are any differences between these two Cascade Impactors, whether the test method used with the new Cascade Impactor is the same as the one used with the old Cascade Impactor, and provide comparative setup parameters for both CIs.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Dale Conner
12/18/2008 01:43:27 PM

MINOR AMENDMENT

ANDA 78-202

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Apotex Corp. TEL: 954-384-3986

ATTN: Kiran Krishnan FAX: 954-349-4233
U.S. Agent for Apotex Inc.
FROM: Esther Chuh PROJECT MANAGER: (240) 276-8530

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 31, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL.

Reference is also made to your amendments dated February 20, June 11, and June 12, 2008.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (___2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

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CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 78-202

APPLICANT: Apotex Inc.

DRUG PRODUCT: Budesonide Inhalation Suspension; 0.25 mg/2 mL and 0.5 mg/2 mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiency:

(b) (4)

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Your bioequivalence information is deficient. Please respond to the deficiency communication from the Division of Bioequivalence dated July 7, 2008.

2. Your microbiological and labeling information are currently pending review. Deficiencies, if any, will be communicated separately.

Sincerely yours,

{See appended electronic signature page}

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
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/

Michael Smela
7/29/2008 09:24:11 AM
For Rashmikant M. Patel, Ph.D.

FAX – Microbiology Deficiencies Enclosed

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville MD 20855-2773 (240-276-8408)

TO: Tammy McIntire
Agent for Apotex Inc.
PHONE: (905) 508-2396
FAX: (905) 508-2359

FROM: Kun Shen
Microbiology Project Manager
PHONE: (240) 276-8722
FAX: (240) 276-8428

Total number of pages, excluding this cover sheet: __2__

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format. This will improve document availability to review staff.

Microbiology Deficiencies:

Enclosed are the microbiology deficiencies for **ANDA 78-202, Budesonide Inhalation Suspension**. The submissions reviewed were submitted on 3/31/2006, 6/20/2006, 2/21/2007, and 11/5/2007. Please respond to this communication as quickly as possible. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review. The response to this communication will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT-RESPONSE TO MICROBIOLOGY DEFICIENCIES should appear prominently in your cover letter.

Should you also have other outstanding deficiencies, for review purposes, please attempt to consolidate your responses into a single submission for this application.

If you have questions, feel free to call Kun Shen, Bonnie McNeal or Mark Anderson.

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LIST OF MICROBIOLOGY DEFICIENCIES AND COMMENTS:

ANDA: 78-202 APPLICANT: Apotex Inc.

DRUG PRODUCT: Budesonide Inhalation Suspension

A. Microbiology Deficiencies:

Regarding the comparability protocol, please clarify whether a separate [redacted] (b) (4) (other than the [redacted] (b) (4) sterilizer currently installed in line with the existing [redacted] (b) (4) filling machine) will be installed for use with the proposed filling line. In addition, please indicate the name/make of the sterilizer and its location/room number within the expanded manufacturing facility.

If the proposed filling line will be served by the same [redacted] (b) (4) sterilizer described for the existing filling line, please provide a detailed description of the relationship of Room [redacted] (b) (4) with the filling room/location of the proposed [redacted] (b) (4) filling machine within the expanded manufacturing facility, and describe sterile API transfer from Room [redacted] (b) (4) to the proposed filling line. Addition of a floor plan diagram to the description will be helpful.

If a new [redacted] (b) (4) will be installed in line with the proposed [redacted] (b) (4) filling machine, please provide a description of how sterile API will be transferred from [redacted] (b) (4) to the new filling line.

Please clearly identify your amendment to this facsimile as "RESPONSE TO MICROBIOLOGY DEFICIENCIES". The "RESPONSE TO MICROBIOLOGY DEFICIENCIES" should also be noted in your cover page/letter.

Sincerely yours,

{See appended electronic signature page}

Brenda Pillari, Ph.D.
Microbiology Team Leader
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Brenda Pillari
7/21/2008 01:57:34 PM

BIOEQUIVALENCY AMENDMENT

ANDA 78-202

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT: Apotex Inc.

TEL: (905) 508-2396

ATTN: Paul Bonnici, B.Sc.

FAX: (905) 508-2359

FROM: Nam Chun

FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on March 31, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __**two**__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

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BIOEQUIVALENCE DEFICIENCIES

ANDA: 78-202

APPLICANT: Apotex Inc.

DRUG PRODUCT: Budesonide Inhalation Suspension, 0.25 mg/2 mL & 0.5 mg/2 mL

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. Your particle size distribution (PSD) measured by Cascade Impaction (CI) test is **incomplete**. The DBE currently evaluates the test data using at least 30 samples for both test and reference products (3 batches from each product, 10 samples from each batch). Please repeat this test, and increase the sample size from 20 samples to 30 samples for both test and reference products (3 batches from each product, 10 samples from each batch). The DBE currently also evaluate the data at **each individual deposition site**. Please submit the CI data for ***both* the original and *repeat*** PSD by CI test results for **each individual deposition site** (i.e., nebulizer assembly, the induction port and inlet cone, S0 to filter), and the mass balance data. Please also submit the data in electronic format using similar data templates specified by the DBE in the April 27, 2007 letter

2. Your originally submitted Mean Delivered Dose (MDD) at mouthpiece test is **incomplete.** The MDD test results for the **0.25 mg/2ml strength product** did not meet the population bioequivalence criteria (PBE). For the PBE method and criteria currently used by the Agency to evaluate in vitro testing data, please see the Guidance for Industry: Statistical Information from the June 1999 Draft Guidance and Statistical Information for In Vitro Bioequivalence Data (issued April 11, 2003). Please repeat your MDD at mouthpiece test for the **0.25 mg/2ml strength product,** and increase the sample size from 20 samples to 30 samples for both test and reference products (3 batches from each product, 10 samples from each batch). You can measure the MDD test using one of the following two nebulization systems:

- Pari-LC-Jet Plus Nebulizer/Pari Master compressor system at the flow rate of 5.5 L/min, as stated in the Control 03-612; or,

- Repeat its MDD test using ProNeb Ultra Nebulizer with Pari LC Plus Nebulization at the flow rate of (b) (4) L/min, as specified in its method PD-188.

Please also submit the data for the *repeat* MDD test in electronic format using similar data templates specified by the DBE in the April 27, 2007 letter.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Dale Conner
7/7/2008 10:26:20 AM

RECORD OF TELEPHONE CONVERSATION

Reference is made to ANDA #78-202; Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL; Apotex, Inc.

We called Ms. Bernice Tao of Apotex regarding a couple issues regarding their ANDA:

- Apotex was previously asked to address a potential problem associated with the drug product; specifically precipitation or adhesion of the drug in the ampoule to the wall over time. The reason for this occurrence has not been determined, however, Apotex was asked to evaluate their product under various environmental conditions. Apotex submitted results of a cycle study exposing the product to alternating hot and cold temperatures, and found no drug adhesion.

  We suggested that they do additional testing of the drug product under low pressure conditions (such as that encountered during airline travel in the holds of aircraft). They could do a shipping study or do a simulation study at low pressure (we indicated that there may be some standard methods available).

  Bernice indicated that she would discuss the issue and come up with something to address the low-pressure issue.

- Apotex was asked to address the acceptance criteria for the (b) (4) [redacted] in the drug product. Apotex proposed a limit of (b) (4)% for the epimers based on comparable limits for the Nasal Spray of (b) (4)%. However, based on the Route of Administration and Dose, (b) (4)% is too high. Based on an ICH limit of (b) (4) ug/day limit for (b) (4) [redacted] compounds, we have requested that they establish a limit of (b) (4)% for the combined (b) (4) epimers, or an individual limit of (b) (4)% for each of the epimers.

  Bernice indicated that she would discuss the issue and revise the specifications within the guidelines we suggested.

We indicated that Apotex should submit a Telephone Amendment addressing the 2 issues. Bernice asked how quickly we would need the information, and we indicated that she should try to submit it within 10 business days. If, however, she could not generate the data that quickly, she should contact us.

We recommended that she FAX us a copy of the information in addition to submitting it as an amendment to the ANDA.

DATE:
May 29, 2008

ANDA NUMBER
78-202

TELECON INITIATED BY
FDA

PRODUCT NAME:
Budesonide Inhalation Suspension
0.25 mg/mL & 0.5 mg/mL

FIRM NAME:
Apotex Inc.

FIRM REPRESENTATIVES:
Ms. Bernice Tao, Ph.D.
Executive Vice President

PHONE NUMBER:
(416) 401-7889

FDA REPRESENTATIVE(S)
Ken Furnkranz
Mike Smela

SIGNATURES:

Kenneth J. Furnkranz

Michael Smela

CC: V:\Chemistry Division I\Team 2\TL Folder\Draft\78202TC05290kjf.doc

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/s/

Kenneth Furnkranz
6/18/2008 01:53:49 PM
CHEMIST

Michael Smela
6/18/2008 02:13:09 PM
CHEMIST

RECORD OF TELEPHONE CONVERSATION

Reference is made to ANDA #78-202; Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL; Apotex, Inc.

We called Ms. Bernice Tao of Apotex regarding a couple issues regarding their ANDA:

- Apotex was previously asked to address a potential problem associated with the drug product; specifically precipitation or adhesion of the drug in the ampoule to the wall over time. The reason for this occurrence has not been determined, however, Apotex was asked to evaluate their product under various environmental conditions. Apotex submitted results of a cycle study exposing the product to alternating hot and cold temperatures, and found no drug adhesion.

  We suggested that they do additional testing of the drug product under low pressure conditions (such as that encountered during airline travel in the holds of aircraft). They could do a shipping study or do a simulation study at low pressure (we indicated that there may be some standard methods available).

  Bernice indicated that she would discuss the issue and come up with something to address the low-pressure issue.

- Apotex was asked to address the acceptance criteria for the (b) (4) in the drug product. Apotex proposed a limit of (b) (4)% for the epimers based on comparable limits for the Nasal Spray of (b) (4)%. However, based on the Route of Administration and Dose, (b) (4)% is too high. Based on an ICH limit of (b) (4)ug/day limit for (b) (4) compounds, we have requested that they establish a limit of (b) (4)% for the combined (b) (4) epimers, or an individual limit of (b) (4)% for each of the epimers.

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We indicated that Apotex should submit a Telephone Amendment addressing the 2 issues. Bernice asked how quickly we would need the information, and we indicated that she should try to submit it within 10 business days. If, however, she could not generate the data that quickly, she should contact us.

We recommended that she FAX us a copy of the information in addition to submitting it as an amendment to the ANDA.

DATE:
May 29, 2008

ANDA NUMBER
78-202

TELECON INITIATED BY
FDA

PRODUCT NAME:
Budesonide Inhalation Suspension
0.25 mg/mL & 0.5 mg/mL

FIRM NAME:
Apotex Inc.

FIRM REPRESENTATIVES:
Ms. Bernice Tao, Ph.D.
Executive Vice President

PHONE NUMBER:
(416) 401-7889

FDA REPRESENTATIVE(S)
Ken Furnkranz
Mike Smela

SIGNATURES:

Kenneth J. Furnkranz

Michael Smela

CC: V:\Chemistry Division I\Team 2\TL Folder\Draft\78202TC05290kjf.doc

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/s/

Kenneth Furnkranz
6/2/2008 04:06:25 PM
CHEMIST

Michael Smela
6/2/2008 04:21:31 PM
CHEMIST

MINOR AMENDMENT

ANDA 78-202

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Apotex Corp. TEL: 954-384-3986

ATTN: Kiran Krishnan FAX: 954-349-4233
U.S. Agent for Apotex Inc.
FROM: Esther Chuh PROJECT MANAGER: (301) 827-5773

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 31, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL.

Reference is also made to your amendments dated February 21 and April 16, 2007.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (___4_ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

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III. List Of Deficiencies To Be Communicated

ANDA: 78-202 APPLICANT: Apotex Inc.

DRUG PRODUCT: Budesonide Inhalation Suspension; 0.25 mg/2 mL and 0.5 mg/2 mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Drug Master File (DMF) # (b) (4) is deficient. The holder has been notified. Please do not respond to this letter until the DMF holder has informed you that a complete response to the DMF deficiency letter has been submitted to the Agency.

2. (b) (4) is listed in the DMF as a contract facility for micronization of the drug substance, however, they have indicated that they are not performing this function. Please verify with the drug substance manufacturer and resolve this situation.

3. Regarding the specifications for Budesonide drug substance:

   a. Please provide a complete literature search to support your contention that the drug can exist in only one form. Alternatively, you will need to establish a specification for morphic form (however, once verification of the results are demonstrated, you may rely on the (b) (4) COA).

   b. The PSD specifications for the drug substance are still too lax. Please tighten the D_{50} and D_{90} specifications reflecting the data on the batches.

4. Budesonide will become official in USP 30, Supplement 1 effective 8/1/07. Please evaluate your tests and specifications to ensure compliance with the new monograph, and revise as appropriate. Please also acknowledge that the USP methods will be the regulatory methods and will rule in the event of a dispute. Please also provide a representative COA for a lot of Budesonide tested by the USP methods demonstrating compliance with the USP monograph.

5. Regarding the test, specifications and results for DSD and PSD of the drug product at release and through shelflife:

   a. Why is the PSD of the drug substance in the drug product suspension significantly larger than that for the drug substance alone, since essentially the same method is used for both samples?

   b. Why is the PSD of the drug product larger than the DSD/Agglomeration size distribution?

   c. Please submit the analytical method for DSD/Agglomeration (Method #GEN-9-004-RH). It is unclear how the method can measure agglomeration/DSD, since those parameters seem unrelated.

d. Please explain the results reported for "Particles LT (b) (4) um" for the PSD test in your stability reports. Should the results be reported in %?

6. Regarding the Degradation Products in the drug product:

   a. Please tighten the limit for the (b) (4) to (b) (4)% or qualify it at the current limit as it is a "(b) (4)" compound.

   b. Due to the potential for low level genotoxic degradants to be present, the Individual Unspecified Degradation Products limit in the drug product should be tightened to ≤ (b) (4)%. Any allowed higher should be identified and qualified.

7. Please provide retest results of the accelerated stability samples against the revised specifications.

8. As the drug product is a suspension, there is a possibility that variations in environmental conditions during storage and transport (e.g. temperature, pressure) may cause drug particles to adhere to the interior walls of the container. In such a situation, the dose delivered from the nebule may be subpotent. Please comment on this issue. An actual or simulated transportation study may be appropriate.

In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The Microbiology portion of your application is under review. Deficiencies, if any, will be conveyed to you under separate cover.

2. Please address the outstanding Labeling and Bioequivalence deficiencies which have been conveyed to you under separate cover.

3. Please submit any additional stability data available.

4. Please explain how the analyst will handle drug substance impurities that do not have limits in the drug product when they are detected during drug product testing.

5. An acceptable compliance evaluation is needed for approval. We have requested an evaluation from the Office of Compliance.

OGD is changing its CMC review process though our question based review (QbR) initiative, which is described in more detail on the OGD website: http://www.fda.gov/cder/ogd/QbR.htm.

OGD's QbR was designed with the expectation that ANDA applications would be organized according to the Common Technical Document (CTD), a submission format adopted by multiple regulatory bodies including the FDA. Generic firms are strongly recommended to submit their ANDAs in the CTD format (either eCTD or paper) to facilitate the implementation of the QbR and to avoid undue delays in the review of their applications.

Because of the increasing number of ANDA submissions OGD receives each year, the Quality Overall Summary (QOS) part of the CTD format is extremely important to making our new review process more efficient. Beginning in January 2007, all ANDA applicants are recommended to

provide an electronic copy of a QOS that addresses OGD's QbR questions. The QbR-Quality Overall Summary Outline posted on our webpage http://www.fda.gov/cder/ogd/ contains all the questions to prepare the QOS. The QOS should be submitted in both MS Word and pdf format along with the paper or electronic submission. The QOS should be provided even if the remainder of the application is not in CTD format. OGD has prepared QOS models that can be found on the OGD web site. We ask you to use these as a guide for your submissions.

If you are already submitting QbR-based applications, we would like to take this opportunity to thank you for supporting this very important initiative.

Sincerely yours,

{See appended electronic signature page}

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Michael Smela
7/27/2007 01:42:10 PM
For Rashmikant M. Patel, Ph.D.

BIOEQUIVALENCY AMENDMENT

ANDA 78-202

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Apotex Corp. U.S. Agent for Apotex Inc.

TEL: 954-384-3987

FAX: 954-349-4233

ATTN: John G. Lay B.Sc., RAC

PROJECT MANAGER: (240) 276-8782

FROM: Aaron Sigler

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on June 20, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Budesonide Inhalation Suspension, 0.25 mg/2mL and 0.5 mg/2mL.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __**6**__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

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BIOEQUIVALENCY DEFICIENCIES

ANDA: 78-202 APPLICANT: Apotex Inc.

DRUG PRODUCT: Budesonide Inhalation Suspension, 0.25 mg/2 mL & 0.5 mg/2 mL

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. You did not submit the method of particle size distribution in the nebulized aerosol using cascade impactor (method PD 102). Instead, you submitted two copies of the method validation report. Please submit the method describing the procedures of how the measurement was conducted and how data were collected and analyzed for this test. In addition, please provide the rational of using this method for the measurement of particle size of drug and agglomerates in the nebulized aerosol.

2. You did not submit the X-ray Diffraction results and the Particle Size Distribution Determination by Light microscopic Image Analysis results for the 0.25 mg/2 ml product. Please submit information to prove that "*the budesonide (bulk drug) used in the lower strength is the same as that used in the higher strength product, i.e., same particle size, PSD, polymorphic form, and shape*". Alternatively, you submit the comparison between the high strength product and low strength product.

3. Your Mean Delivered Dose values obtained for the test and reference listed drug (RLD) products ranged (b) (4) (% nominal), compared with 17(% nominal) specified in the RLD product labeling. Please explanation for the difference between your test results and the Mean Delivered Dose specified in the labeling.

4. Your mean nebulization time obtained for the test and RLD was ten (10) minutes, compared with 5 minutes or less specified in the RLD product labeling. Please provide

explanation for the difference between your test results and the mean nebulization time specified in the labeling.

5. The results of your particle size distribution (PSD) in suspension measured by two different methods are inconsistent. The PSD measured by Laser Diffraction is significantly greater than that measured by light microscopy. Please investigate your method of PSD measurement by laser diffraction. You may use other alternative particle size measurement method, such as Coulter Multisizer, to confirm the study results.

6. Please re-submit raw data for the in vitro tests (Unit Dose Content of Drug in the Ampoules, Mean Nebulization Time and Mean Delivered Dose at the Mouthpiece, Particle Size Distribution of the Active Ingredient in the Suspension, Droplet Size Distribution of the Nebulized Aerosol) of the test and reference products, in electronic SAS Transport files, in the format of recommended tables provided.

7. Please submit the batch sizes and manufacturing dates of the test product.

8. Please submit the study site information for each in vitro test.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

SAS Data Definition Tables for in Vitro Nasal Nebulized Aerosol Data

Data in these tables should be arranged in columns as shown in examples. Data sets should be submitted as SAS Transport files. Each separate table should be used for data from each strength.

Table 1. Unit Dose Content of Drug in the Ampoules

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
LOT	Lot number	Alphanumeric/ Numeric	Alphanumeric/ Numeric	Identifier for product lot
CONTAINER	Ampoule Number	Numeric	Numeric values	Identifier for ampoule. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
AMOUNT	Actual measured amount of drug mass	Numeric	Numeric values	Drug mass per ampoule
PCTLABEL	Percentage of label claim	Numeric	Numeric values	Percentage of drug mass per single actuation

Example

PRODUCT	LOT	CONTAINER	AMOUNT	PCTLABEL
TEST	1234	1		
		2		
		3		
		4		
		5		
		6		
		7		
		8		
		9		
		10		

Table 2. Mean Nebulization Time and Mean Delivered Dose at the Mouthpiece

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
LOT	Lot number	Alphanumeric/ Numeric	Alphanumeric/ Numeric	Identifier for product lot
CONTAINER	Ampoule Number	Numeric	Numeric values	Identifier for ampoule. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
DELIVERED DOSE	Dose delivered expressed in % of Nominal Dose	Numeric	Numeric values	Percent dose delivered
NEBULIZATION TIME	Nebulization time expressed in minutes or seconds	Numeric	Numeric values	Nebulized time expressed in minutes or seconds

Example

PRODUCT	LOT	CONTAINER	DOSE%	NEBULIZATION TIME
TEST	1234	1		
		2		
		3		
		4		
		5		
		6		
		7		
		8		
		9		
		10		

Table 3. Particle Size Distribution of the Active Ingredient in the Suspension

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
LOT	Lot number	Alphanumeric/ Numeric	Alphanumeric/ Numeric	Identifier for product lot
CONTAINER	Ampoule Number	Numeric	Numeric values	Identifier for ampoule. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
D10	D10	Numeric	Numeric values	D10
D50	D50	Numeric	Numeric values	D50
D90	D90	Numeric	Numeric values	D90
SPAN	SPAN	Numeric	Numeric values	SPAN calculated as ((D90-D10)/D50)

Example

PRODUCT	LOT	CONTAINER	D10	D50	D90	SPAN
TEST	1234	1				
		2				
		3				
		4				
		5				
		6				
		7				
		8				
		9				
		10				

Table 4. Droplet Size Distribution of the Nebulized Aerosol

Variable Name	Variable Label	Variable Type	Content	Notes
PRODUCT	Product Name	Character	TEST or REF	Identifier for product
LOT	Lot number	Alphanumeric/ Numeric	Alphanumeric/ Numeric	Identifier for product lot
CONTAINER	Ampoule Number	Numeric	Numeric values	Identifier for ampoule. Must be unique for each product (e.g. #1-30 for test and #31-60 for ref).
D10	D10	Numeric	Numeric values	D10
D50	D50	Numeric	Numeric values	D50
D90	D90	Numeric	Numeric values	D90
SPAN	SPAN	Numeric	Numeric values	SPAN calculated as ((D90-D10)/D50)

Example

PRODUCT	LOT	CONTAINER	D10	D50	D90	SPAN
TEST	1234	1				
		2				
		3				
		4				
		5				
		6				
		7				
		8				
		9				
		10				

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

/s/

Barbara Davit
4/26/2007 04:59:13 PM
Signing for Dale P Conner

Telephone Fax

ANDA 78-202

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North I
7520 Standish Place
Rockville, MD 20855-2773
301-827-5846

TO: Apotex Inc.

TEL: 954 - 349-4217

ATTN: Tammy McIntire

FAX: 954 -349-4233

FROM: Mrs. Angela Payne

This facsimile is in reference to your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Montelukast Sodium Tablets.

Pages (including cover): _5_

SPECIAL INSTRUCTIONS:

See attached labeling comments.

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
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REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: **78-202** Dates of Submission: 20 JUN 2006 (original)

Applicant's Name: Apotex Inc.

Established Name: Budesonide Inhalation Suspension 0.25 mg/2mL and 0.5 mg/2 mL, UNIT DOSE ampules

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Labeling Deficiencies:

1. CONTAINER- Satisfactory in draft.

2. FOIL POUCH -

a. The text is difficult to read. Please resubmit with improved readability.
b. Revise ' (b) (4) to each unit-dose ampule…".
c. Insert the term ' (b) (4)" just prior to the list of in-actives.
d. Add "Sterile unit dose ampules" to the label.
e. Increase the prominence of the strength. Increase the font size.
f. Differentiate your product strengths by the use of boxing, contrasting colors, or some other means.
g. Delete (b) (4). You can use "Inhalation via use with a jet nebulizer", if you prefer.

3. CARTON -

a. See comments under POUCH.
b. Identify number of pouches 30s (6 pouches x 5- 2 mL unit dose ampules).
c. Include the established name and strength on the fop panel.

4. INSERT-

a. GENERAL COMMENT - Please provide a patent certification for patent number. In addition to the changes below please update your labeling to be in accord with the most recent labeling approved for the reference listed drug (NDA 20-929).

b. CLINICAL PHARMACOLOGY, Pharmacodynamics, 5th paragraph - revise to read "…In the subgroup of children age 6 months to 2 years (n-21) receiving a total daily dose of budesonide inhalation suspension or placebo, the mean change from baseline in ACTH-stimulated cortisol levels show a decline…..statistically significant compare to placebo. Another study was conducted in pediatric patients 6 to 12 months of age with mild to moderate asthma or recurrent/persistent wheezing had an evaluation of serum cortisol levels…value of 500 nmol/L.

* Note: Retain most of the 5th as seen in the reference listed drug labeling but modify as instructed above.

c. CLINICAL TRIALS - Revise as follows:

i.) First paragraph - …and severity. [redacted] (b) (4)

ii.) Second paragraph, First sentence - Results of the three controlled clinical trials for recommended dosages of budesonide inhalation suspension in patients 12 months to 8 years…

iii.) Third paragraph, second sentence - Significant improvements were seen in FEV1 [budesonide inhalation suspension 0.5 mg twice daily] and morning PEF [budesonide inhalation suspension 0.25 mg twice daily; 0.5 mg twice daily] compared to placebo.

d. CLINIICAL TRIALS , [redacted] (b) (4), Revise second sentence as follows:

i.) Approximately 70% were not previously receiving inhaled corticosteroids. The changes from baseline to weeks 0-12 in night time asthma symptom scores are show in figure 2-. Budesonide inhalation…

ii.) Include the graph in this section. Delete data for once daily dosing.

iii.) Delete last paragraph ' [redacted] (b) (4)

e. PRECAUTIONS, Delete the text that you have inserted in several sections of this section ' [redacted] (b) (4) " is not necessary.

f. PRECAUTIONS, Pediatric Use subsection- Reinsert the second paragraph of the innovator's labeling. You may modify it as follows: "It has been report a study was conducted in pediatric patients 6 to 12 months of age with mild to moderate asthma or recurrent/persistent wheezing, All patients were randomized to receive either budesonide inhalation suspension or placebo. Adrenal axis function was assessed…respectively.

g. ADVERSE REACTIONS- Delete the text that you have inserted in several sections of this section [redacted] (b) (4) " is not necessary. Second paragraph- Delete [redacted] (b) (4) (b) (4) ". In addition, you must also delete the [redacted] (b) (4) mg total dose data in the charts.

h. OVERDOSAGE - Delete the text that you have inserted in several sections of this section ' [redacted] (b) (4) " is not necessary.

i. DOSAGE AND ADMINISTRATION, Patients Not Receiving Systemic (Oral) Corticosteroids, 2nd paragraph, 2nd sentence- Delete "If [redacted] (b) (4)

j. HOW SUPPLIED- "Add store in an upright position"

k. PATIENT INSTRUCTIONS -

Ensure that the patient instruction sheet is detachable. Provide a separate instruction sheet in each pouch as does the innovator. Each pouch should have a patient instruction sheet. Include the established name with the pronunciation in the title section of the patient instructions sheet. Cite the full established name (Budesonide Inhalation Suspension) in all of the section titles and paragraph rather than using "budesonide".

Revise your labels and labeling, as instructed above, and submit final printed or draft if you prefer electronically according to the guidance for industry titled Providing Regulatory Submissions in Electronic Format – ANDA.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address - http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling and the latest approved labeling for the reference listed drug (or your last submission) with all differences annotated and explained.

{See appended electronic signature page}

_____

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
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/

John Grace
3/2/2007 06:37:27 AM
for Wm Peter Rickman

MINOR AMENDMENT

ANDA 78-202

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Apotex Corp. U.S. Agent for Apotex Inc.

TEL: 954-384-3987

FAX: 954-349-4233

ATTN: John G. Lay B.Sc., RAC

PROJECT MANAGER: (301) 827-5765

FROM: Simon Eng, Pharm.D.

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated March 31, 2006, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Budesonide Inhalation Suspension, 0.25 mg/2mL and 0.5 mg/2mL.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__2__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, OR PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.
If received by someone other than the addressee or a person authorized to deliver this document to the addressee, you are hereby notified that any disclosure, dissemination, copying, or other action to the content of this communication is not authorized. If you have received this document in error, please immediately notify us by telephone and return it to us by mail at the above address.

ANDA: 78-202 APPLICANT: Apotex Inc.

DRUG PRODUCT: Budesonide Inhalation Suspension; 0.25 mg/2 mL and 0.5 mg/2 mL

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Drug Master File (DMF) # (b) (4) is deficient. The holder of the DMF has been notified. Please do not respond to this letter until the DMF holder has informed you that a complete response to the DMF deficiency letter has been submitted to the Agency.

2. Regarding the specifications for Budesonide drug substance:

   a. Please establish a control for morphic form or provide more specific information that the drug substance cannot exist in multiple morphic forms.

   b. As particle size is considered critical, please tighten your specifications reflecting the particle size distribution of your exhibit lots of drug substance.

   c. Epimer (b) (4) content should reflect the proposed PF limit of (b) (4)% or, alternatively, you should justify the (b) (4) limit with data from the RLD or other information demonstrating that the epimers are equally efficacious for the therapeutic indication.

   d. Please include a specification for (b) (4) or provide justification why the specification is not necessary.

3. Regarding the specifications for the drug product at release and on stability:

   a. Please tighten the pH limits reflecting your results or justify the wide limits.

   b. Please tighten the limits established for Assay.

   c. The Total Impurity limit for release and stability should be tightened based on the available data.

   d. Particle size testing will also need to be performed as part of the release and stability evaluation of the drug product, and appropriate acceptance criteria established reflecting the profile of particles ≤ (b) (4) um.

   e. Please establish a microscopic test for foreign particulate matter in the drug product.

   f. Osmolality and Fill Volume testing should be performed for release, and appropriate limits established.

g. A test for Color of Suspension should be added and appropriate specifications established based on the description of the drug product as a "White to off-white suspension".

h. An assessment of particle agglomeration should be included and appropriate limits established.

i. A test and specification for resuspendability should be developed.

4. We also request that you provide additional PSD data for the drug product under the long term conditions due to the trend observed in the PSD toward higher PSD values (D_{10}, D_{50} and D_{90}) under accelerated and long-term conditions as well as during cycle studies. Please also evaluate the PSD of the RLD to determine whether the RLD is similarly affected during cycle studies. Finally, please discuss why PSD was not able to be measured after Light Stress in unprotected LDPE ampoules.

5. Please clarify your designation of (b) (4) as a degradant as it does not appear to increase over time.

6. Please provide retest results of the accelerated stability samples against the revised specifications.

In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Labeling, Microbiology and Bioequivalence portions of your application are under review. Deficiencies, if any, will be conveyed to you under separate cover.

2. Please submit any additional stability data available.

3. The specification for (b) (4) residual solvent in Budesonide drug substance is pending evaluation. Since there is no limit established by ICH Q3C, we have sent the DMF holder's limit and justification for the limit for Pharm/Tox consult.

4. An acceptable compliance evaluation is needed for approval. We have requested an evaluation from the Office of Compliance.

OGD is changing its CMC review process though our question based review (QbR) initiative, which is described in more detail on the OGD website: http://www.fda.gov/cder/ogd/QbR.htm.

OGD's QbR was designed with the expectation that ANDA applications would be organized according to the Common Technical Document (CTD), a submission format adopted by multiple regulatory bodies including the FDA. Generic firms are strongly recommended to submit their ANDAs in the CTD format (either eCTD or paper) to facilitate the implementation of the QbR and to avoid undue delays in the review of their applications.

Because of the increasing number of ANDA submissions OGD receives each year, the Quality Overall Summary (QOS) part of the CTD format is extremely important to making our new review process more efficient. Beginning in January 2007, all ANDA applicants are recommended to provide an electronic copy of a QOS that addresses OGD's QbR questions. The QbR-Quality Overall Summary Outline posted on our webpage http://www.fda.gov/cder/ogd/ contains all the

questions to prepare the QOS. The QOS should be submitted in both MS Word and pdf format along with the paper or electronic submission. The QOS should be provided even if the remainder of the application is not in CTD format. OGD has prepared QOS models that can be found on the OGD web site. We ask you to use these as a guide for your submissions.

If you are already submitting QbR-based applications, we would like to take this opportunity to thank you for supporting this very important initiative.

Sincerely yours,

{See appended electronic signature page}

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

Michael Smela
2/1/2007 09:04:30 AM
For Rashmikant M. Patel, Ph.D.

APOTEX CORP.

September 11, 2006

N/NC

Mr. Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North 4 (MPN 4) HFD-600
7519 Standish Place
Rockville, MD 20855

RE: ANDA # 78-202
Budesonide Inhalation Suspension, 0.25 mg/2 mL and 0.5 mg/2 mL
- Change in Point Of Contact Information

This letter is to notify FDA (Office of Generic Drugs) that we have hired a US Director of Regulatory affairs and thus, Mr. John Lay will be the primary point of contact, effective September 11, 2006 in relation to the above-mentioned ANDA application.

The new contact information is as follows:

John G. Lay, B.Sc., RAC
Director, Regulatory Affairs
Apotex Corp.
2400 N. Commerce Parkway Suite 400
Weston, FL 33326

Telephone: (954) 384-3987
Fax: (954) 349-4233

Should you have any questions, please do not hesitate to me at the information above.

Sincerely,

Tammy McIntire

Tammy McIntire, M.S., R.Ph.
President

RECEIVED
SEP 14 2006
OGD / CDER

2400 N. Commerce Parkway • Suite #400 • Weston, Florida 33326 • Phone: 1-800-706-5575 • Fax: 1-800-706-5576

APOTEX CORP.

April 12, 2007

N/MC

Mr. Gary Buehler, Director
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA # 78-202
Budesonide Inhalation Suspension 0.25mg/2mL and 0.5mg/2mL
US Agent Change in Contact Information

We would like to notify FDA (Office of Generic Drugs) of a change in the contact information of our US Agent, effective April 1, 2007 in relation to the above-mentioned ANDA application.

The new contact information is as follows:

Kiran Krishnan, MPharm, RAC
Project Leader, Regulatory Affairs
Apotex Corp.
2400 N. Commerce Parkway Suite 400
Weston FL
33326

Telephone: (954) 384-3986
Fax: (954) 349-4233

Should you have any questions, please do not hesitate to contact myself at tel: (416) 401-7889 or fax: (416) 401-3807.

Sincerely,

for Bernice Tao
Director, Regulatory Affairs (US)

RECEIVED
APR 13 2007
OGD / CDER

Enclosure- Change in US Agent and Point Of Contact Information Letter