CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-658

APPROVABLE LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-658

10/21/04

Aventis Pharmaceuticals
200 Crossing Boulevard, Route 202-206
P.O. Box 6890
Bridgewater, NJ 08807-0890

Attention: Daniel Bollag, PhD
Director, US Regulatory Affairs

Dear Dr. Bollag:

Please refer to your new drug application(NDA) dated December 22, 2003, received December 23, 2003, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Alvesco (ciclesonide) Metered Dose Inhaler ——, 80 mcg, and 160 mcg. b(4)

We acknowledge receipt of your submissions dated February 5(2), 11, 16, and 26, March 2, 4, 10, and 22, April 2, 26(2), and 29, May 27, July 7, 8, and 26, August 2(2), 4(2), 9, and 16, September 16, 22, 27, and 30, and October 6 and 15, 2004.

We have completed our review of this application, as amended, and it is approvable. Before the application may be approved, however, it will be necessary for you to adequately resolve the following deficiencies:

1. The submitted data from your clinical program do not support efficacy of ciclesonide for the proposed indication of maintenance treatment of asthma as prophylactic therapy in adult —— Specifically, the clinical data do not support the efficacy of ciclesonide for the maintenance treatment of asthma in patients with mild to moderate disease —— The clinical data also do not support a —— dosing regimen for the various proposed doses. Further, efficacy for patients below — years of age has not been demonstrated. These deficiencies may be addressed by the following: b(4)

   Provide data from adequate and well-controlled studies to demonstrate efficacy of ciclosonide for maintenance treatment of asthma that covers the full range of severity, particularly mild to moderate asthma. These studies should cover a range of doses and dosing frequencies so that an adequately supported recommendation can be made on the dosing regimen. If —— dosing is to be proposed, —— dosing frequency should be evaluated against the same total daily dose administered at different dosing frequencies (e.g., twice-daily) to determine the efficacy and safety of ciclesonide administered —— relative to administration at more frequent intervals. Efficacy of ciclesonide for patients below — years of age should also be supported by adequate b(4)

efficacy data. Such data should also establish an appropriate dosing regimen for this age range.

2. An apparent excess of cataracts was seen with ciclesonide treatment in the 12-week treatment period in study 323/324. Perform a carefully designed and conducted ophthalmic safety study of at least 12-months treatment duration to address this safety signal. While we would like the results of this study to be available with your resubmission, it is possible for these data to be submitted post-approval, though the labeling will have to describe the outstanding findings.

3. At the August 29, 2002, pre-NDA meeting, you stated that you would submit data supporting the incorporation of a dose-counter during the review cycle. It is our expectation that, in accordance with CDER's Guidance to Industry on Dose Counters, Alvesco will have a dose-indicating device incorporated at the time of approval. We highly encourage you to submit the necessary data supporting the approval of Alvesco with an integrated dose-indicating device with the resubmission that addresses the above listed deficiencies.

4. The following general comment pertains to the Package Insert.

b(5)

We remind you of the following agreements regarding CMC issues, as outlined in your October 15, 2004, submission. We request that you address these issues in your response to the deficiencies listed above.

A. The following agreement pertains to the drug substance.

> You will provide specific references to analytical procedures in the specifications for the drug substance. These analytical procedures should be linked to methods in Section S.4.2.

B. The following agreements pertain to the drug product.

1. In regard to the Pharmaceutical Development Report:

   (a) You will explain the following discrepancy in the experiments designed to measure Particle Size Distribution (PSD) at exhaustion (page 74 in Section 3.2.P.2.2.1) and the calculations that follow:

b(4)

(b) You will provide an explanation for the increase in [redacted] content on storage. You will explain whether [redacted] is [redacted]

(c) You will provide the details of the time course of the temperature cycling experiment reported in Section 3.2. P.2.2.1.8, explaining:

(1) Whether the time periods are the same for each cycle.

(2) Whether the temperatures changed suddenly or if they were ramped. b(4)

(3) If a cycle is constituted with a period at [redacted] followed by [redacted] or a period at [redacted]

(d) You will explain how it was determined that the following manufacturing process parameters (Section 3.2.P.2.3.3) were not identified as "Critical":

(e) You will provide data to justify choice of [redacted] time and temperature in the manufacturing procedure. You will provide data showing the effects of these parameters on leak rate and valve performance. b(4)

(f) You will provide the procedures used to determine the amount of [redacted] in the foreign particulates and the data resulting from this determination. You will provide the data and calculations that form the basis for the assertion that the mass per actuation of particulates is [redacted] mcg/actuation (page 18 in Section 3.2.P.2.4.4.2).

2. In regard to the Drug Product Manufacturing:

(a) You will provide details of the manufacturing procedure for the [redacted] and [redacted] steps.

(b) You will explain why the "critical steps requiring specific processing limits," described in Section 3.2.P.3.4, Control of Critical Steps and Intermediates, do not include a number of critical controls listed in Table P3.3.1-1, e.g. "Target temperature of the [redacted] propellant" at Step [redacted] and the [redacted] control at Step [redacted]

3. In regard to the Control of the Drug Product:

(a) You will explain what will be done if a batch of Alvesco fails the tests for [redacted] and alcohol content, using the "shelf life" acceptance criteria at or before expiration. b(4)

(b) You will explain why the System Suitability Test for the weight difference for the amount of material on the filter paper in the Automated Foreign Particulate Quantification (CPS98020) is [redacted] and [redacted]. According to the Composition (Table P.1.1-2), the amount of ciclesonide delivered in ten actuations will vary with the strength.

Strength (µg/actuation ex-actuator)	Ten times microg ciclesonide/actuation
[redacted]	[redacted]
80	[redacted]
160	[redacted]

(c) You will provide results for recovery of spiked [redacted] in the validation of the Microbial Count Method b(4)

(d) Regarding the validation report for the method for determination of impurities:

(1) You will explain the following regarding the data for the "ciclesonide only" samples in the "Accuracy" experiments:

- The measured areas for ciclesonide are not proportional to the amounts of added ciclesonide.
- The measured areas for ciclesonide, which should arise as a result of overlap with the impurity peak, are not correlated with the RRT for the impurity peaks. b(4)

	[redacted]µg Ciclesonide	160 µg Ciclesonide	
	Measured area (no impurities)	Measured area (no impurities)	RRT
[redacted]			

(2) You will explain why the results for the "System Repeatability Precision" and the "Intermediate Precision" in the Validation Report for the Impurities Method were reported to be [redacted] %, when the LOQ was found to be well below this value.

(e) Regarding the justification of the specifications for the Foreign Particulates by Image Analysis, you will explain the following: b(4)

- The multiplier for sigma to set the upper limit is [redacted] for the particles in the range [redacted] µ, instead of the multiplier of [redacted] used for the [redacted] µ particles and the [redacted] µ particles.
- The back-transformation of the Proposed Specification Lim ($\log_{10}$) yields different values from those in the application:

	In NDA		FDA calculation
Particle Size Range	Proposed Specification Limit ($\log_{10}$)	Proposed Specification Limit Back-transformed (No. Particulates)	Back Transformed values
[redacted]			

b(4)

Note that, using a [redacted] sigma limit for the [redacted] µ particles, rather than a [redacted] sigma limit, the upper limit ($\log_{10}$) is [redacted], which back-transforms to be [redacted] particles.

C. The following pertain to the labeling:

1. You will explain the necessity for the sentence "[redacted]."

2. You will provide measurements to support the statement in the label that the drug product delivers "x mcg from the valve." b(4)

3. You will explain what part of the product the Container Label is applied to - the actuator of the canister.

Please be advised that the establishment inspection of the [redacted], has not yet been completed. We cannot approve this application until satisfactory establishment inspection reports have been received for all facilities involved in the manufacture, packaging, and testing of the drug product.

Labeling comments will be provided following satisfactory resolution of the above comments.

When you respond to the above deficiencies, include a safety update as described at 21 CFR

314.50(d)(5)(vi)(b). You are advised to contact the Division of Pulmonary and Allergy Drug Products regarding the extent and format of your safety update prior to responding to this letter.

Within 10 days after the date of this letter, you are required to amend this application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division of Pulmonary and Allergy Drug Products to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Colette Jackson, Regulatory Project Manager, at (301) 827-9388.

Sincerely,

{See appended electronic signature page}

Robert J. Meyer, MD
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration

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

/s/

Robert Meyer
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